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ABSTRACTS

37th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 16–19 May 2017, Basel, Switzerland

1. Deltamethrin poisoning in two children following treatment of head lice with a veterinary product

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Objective: Using chemicals, including veterinary drugs not intended for human therapy, can be a serious health risk. We present two cases of severe acute deltamethrin poisoning in children following intentional treatment with a veterinary product.
Case report: The mother of two girls aged 6 (patient 1) and 12 years (patient 2) washed their hair with a veterinary ectoparasitic product for cattle and sheep containing 5% deltamethrin (Butox®) for pediculosis capitis (head lice). The product was left on for 15 minutes and on washing off it got into the eyes and mouths of the children. Within a few minutes both developed vomiting and dizziness, and on admission to hospital they had mental confusion, anxiety, excitation, pallor, acrocyanosis, cold extremities and dilated pupils. Patient 1 also had uncontrolled vomiting. Both had arterial hypertension (arterial BP 140/90 mmHg) and tachycardia (140 bpm patient 1; 120 bpm patient 2). Within a few hours superficial coma, divergent squint, upper deviation of eyeballs, reduced muscle tension, muscle spasm in distal sections of extremities and absence of tendon reflexes were noted. Clinical and biochemical blood and urine analyses were normal, except for moderate changes of acid–base balance indices: pH 7.140, pCO_2 60.5 mmHg, pO_2 29.3 mmHg, bicarbonate 20.6 mmol/L, base excess −8.5 mmol/L, oxygen saturation 38.1%, which later resolved to pH 7.396, pCO_2 39.1 mmHg, pO_2 104.7 mmHg, bicarbonate 24.0 mmol/L, base excess 0.9 mmol/L, oxygen saturation 98.0%. Radiographs showed bilateral focal-confluent shadows along all pulmonary fields. They were intubated with artificial ventilation for 10–12 hours. Local therapists consulted both the Astana Toxicological Center in Kazakhstan and Moscow Poison Information Center specialists for advice on management. Therapy was symptomatic, which also included gastric lavage, administration of activated charcoal and forced diuresis. Consciousness improved and neurologic symptoms resolved on the second hospital day in patient 2. In patient 1 neurologic symptoms resolved after 4 days. Both children recovered without complications and were discharged from hospital on the 8th day.
Conclusion: This case demonstrates the risks of using veterinary drugs not intended for human use, and the favorable prognosis in deltamethrin poisoning. It is also a good example of international collaboration of toxicological centers.

2. Polyneuropathy following fenitrothion poisoning

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Objective: Organophosphorus insecticide-induced neurotoxicity includes acute cholinergic crisis, intermediate syndrome, and delayed neurotoxicity [1]. We report a case of severe fenitrothion poisoning with an unusual polyneuropathy.
Case report: A 60-year-old female with a history of hypertension and depression, ingested approximately 100 mL of 40% fenitrothion (O,O-dimethyl-O-4-nitro-*m*-tolyl phosphorothioate) solution with 400 mL of 8% ethanol in a suicide attempt. Following an acute mild cholinergic phase for 55 hours after ingestion treated with atropine (2.0–4.0 mg/day) and pralidoxime (12 g/day), she developed respiratory muscle weakness and decreased level of consciousness, which combined with aspiration pneumonia, necessitated intubation and mechanical ventilation. Glycopyrronium (1.2–2.4 mg/day), and pralidoxime (12 g/day, every other day) were given until hospital day 36. By hospital day 16, her pneumonia was much improved. She became fully alert and maintained neck flexion against gravity. She could not, however, be weaned off the mechanical ventilator, and had reduced deep tendon reflexes, sensory change on distal upper extremities and motor weakness on upper and lower extremities. Electrophysiological studies on hospital day 21 showed polyneuropathy with the absence of a decremental response on repetitive stimulation, and a decreased amplitude of sensory (digital nerve 9.0–9.7 microvoltage) and motor action potential (median nerve 3.4–4.6 millivoltage, ulnar nerve 3.8–4.2 millivoltage, common peroneal nerve 2.3–2.9 millivoltage), which had dramatically improved by hospital day 35 with antidote therapy and conservative care. On hospital day 42, the patient was discharged in good medical condition.
Conclusion: Our patient showed organophosphorus insecticide-induced neurotoxicity with acute cholinergic crisis, intermediate syndrome, and delayed neurotoxicity. Although it was uncertain, electrophysiological findings and no progression of weakness in our patient seemed to be consistent with critical illness polyneuropathy [1,2]. One study found that prognosis of fenitrothion poisoning is related to time to presentation after ingestion, initial serum concentration, and acute lung injury [3], which was consistent with our patient. Clinicians should pay careful attention to patients with fenitrothion poisoning as delayed intermediate syndrome and acute lung injury might frequently occur, and are related to high morbidity and mortality.

Abstract 238 was originally published with errors. This version has been corrected. Please see Corrigendum (http://dx.doi.org/10.1080/15563650.2017.1322791).

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References

[1] Jayawardane P, Senanayake N, Dawson A. Electrophysiological correlates of intermediate syndrome following acute organophosphate poisoning. Clin Toxicol. 2009;47:193–205.

[2] Hermans G, De Jonghe B, Bruyninckx F, et al. Clinical review: critical illness polyneuropathy and myopathy. Crit Care. 2008;12:238.

[3] Matsuda K, Suzuki K, Ishihara S, et al. Assessment of the severity of organophosphate (fenitrothion) poisoning based on its serum concentration and clinical parameters. Clin Toxicol. 2011;49:820–827.

3. Deltamethrin acute poisoning by intravenous injection

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Objective: Deltamethrin is a class II pyrethroid insecticide. The main systemic target of pyrethroids is the axonal sodium channel, prolonging depolarization, leading to nervous hyperexcitation and eventually to seizures. This effect is rarely seen in humans due to rapid metabolism and a high dose is required to produce systemic effects. Poisoning is difficult to achieve with products registered for domestic use (concentration under 1%) but easier with agricultural formulations containing 10 times the concentration of the active substance. The solvent and the route of entry are also relevant to toxicity and clinical effects. We present the first reported case of suicide attempt by intravenous poisoning with an agricultural deltamethrin-based insecticide.
Case report: A 79-year-old farmer, without psychiatric history, was found in a post-ictal state, with loss of bladder and bowel control, collapsed in his car. During transfer to hospital he remained stuporous with fasciculations and tonic-clonic movements. Nothing of significance was detected on physical exam, laboratory tests, plain chest and abdominal X-rays, and computerised tomography (CT) scan. He was monitored for 24 hours, during which time his left arm was mildly swollen and he was discharged without a definitive diagnosis. He returned 48 hours later with a progressive oedema affecting the entire left arm. It was swollen from the wrist to the armpit and several venepunctures were discovered in the cubital region. Radial pulse was present. A Doppler exploration showed thrombosis of the balisic vein. After deeper questioning, the patient revealed he had injected himself with 15 mL of an insecticide containing 2.5% deltamethrin (375 mg) with naphtha as a solvent, prior to the first episode. Under suspicion of possible cellulitis or necrotizing infection he was admitted to the hospital and treated with broad spectrum antibiotics, pain relievers, heparin and postural therapy. In the next two days, the inflammation progressed to violaceous discoloration of the skin and blisters. The patient underwent an emergency surgical procedure which revealed compartment syndrome, partial necrosis of the biceps muscle and a collection of gelatinous material along the anterior compartment of the arm. All necrotic tissues were removed and a wide fasciotomy of the arm and forearm was performed. Microbiological tests on the extracted tissues ruled out an infectious component. Postoperative evolution was uneventful.
Conclusion: The case illustrates the systemic effects of intravenous deltamethrin, with fasciculations and seizures, which resolved quickly and spontaneously, and the local effects of the insecticide and its solvent following extravasation into the tissue around the injection site.

4. Toxicity indicator value of plasma pseudocholinesterase in hepatic patients

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Objective: A small proportion of the healthy population is lacking in plasma cholinesterase enzyme (ChE) due to a genotype aberration. Plasma (ChE) activity is therefore reduced in liver dysfunction due to reduced synthesis. We sought to measure ChE and establish its relationship with hepatic status.
Methods: A prospective cross-sectional study was carried out at Dammam Regional Poison Control Center, Saudi Arabia, in cooperation with Dammam Medical Complex Hospital to measure ChE and establish its relationship with hepatic status. Cases were divided into the following groups: Group I comprised 50 age-matched male and female subjects, not exposed to pesticides, who were recruited randomly as a control group. All participants were from the same geographical setting. Group II comprised 75 patients with chronic liver diseases of different etiologies. Fibroscan and biochemical enzyme assays including a ChE assay were performed.
Results: The activity of the ChE enzyme was significantly lower in the hepatic patients as compared to the control group (120.1 ± 69.3 and 167.1 ± 30.6 Ukat/L, respectively). There was a significant decrease in plasma ChE as the fibroscan score increased. There was also a significant decrease in ChE activity in patients with Wilson's disease and intrahepatic cholestasis due to hepatitis B and C. There was a significant decrease in plasma (ChE) activity with increase in age; a significant inverse relationship with other hepatic variables (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma glutamyl transferase [GGT]). Plasma (ChE) activity had a significant negative correlation with plasma prothrombin time and International Normalized Ratio (INR) ratio.
Conclusion: The present study clarifies the non-interpretable plasma cholinesterase activity in cases of suspected insecticide toxicity of hepatic patients.

6. Delayed and fatal toxicity of chlorfenapyr

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Objective: Chlorfenapyr is a novel pyrrole group insecticide that interferes with mitochondrial oxidative phosphorylation, resulting in disruption of adenosine triphosphate (ATP) production and eventual cellular death [1]. In animal studies, its acute oral LD_{50} is 626 mg/kg in rats and 55 mg/kg in mice. The World Health Organization (WHO) has thus classified it as a class 2 (i.e., moderately hazardous) chemical. Case reports of human chlorfenapyr poisoning are rare but fatalities due to rapid deterioration of delayed onset neurological dysfunction have been reported [2,3]. We sought to better understand the toxicity profile of chlorfenapyr.
Methods: We conducted a retrospective analysis of all chlorfenapyr exposures reported to the Taiwan National Poison Center (PCC) from January 2002 to December 2014.
Results: A total of 22 patients were reported to the Taiwan PCC during the study period. There were 15 male and 7 female patients, ranging in age from 19 to 86 years. Most exposures involved suicidal ingestions of chlorfenapyr alone (18 cases, 82%).

Eight patients were asymptomatic, while the other 14 patients manifested various toxic effects, such as gastrointestinal signs (39%) and altered mental status (17%). Although most patients recovered uneventfully, two patients succumbed after presenting with sudden onset and rapidly deteriorating neurotoxicity one week post-exposure.
Conclusion: Emergency physicians and clinical toxicologists should be alert to the likely late occurrence of severe/fatal toxicity in patients with chlorfenapyr poisoning. More studies on the pathophysiology and/or effective treatments of chlorfenapyr poisoning should be sought in the future.

References

[1] Raghavendra K, Barik TK, Sharma P, et al. Chlorfenapyr: a new insecticide with novel mode of action can control pyrethroid resistant malaria vectors. Malar J. 2011;10:16.
[2] Kang C, Kim DH, Kim SC, et al. A patient fatality following the ingestion of a small amount of chlorfenapyr. J Emerg Trauma Shock. 2014;7:239–341.
[3] Choi UT, Kang GH, Jang YS, et al. Fatality from acute chlorfenapyr poisoning. Clin Toxicol. 2010;48:458–945.

7. Poisonings involving refugees in Northern Germany during the migrant crisis, 2015–2016

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Objective: Over the past few years more than one million refugees, mostly from Syria, have arrived in Europe. Since the climax of the "migrant crisis" in September 2015, Germany has hosted approximately one million people and enquiries concerning refugees have been documented by the Poison Center (PC). The aim of this investigation was to analyse these cases and compare them to all reported human exposures in the same period in order to identify major differences.
Methods: Retrospective analysis of human exposures from 1 September 2015 to 31 August 2016 to compare those involving refugees and the general population. The following characteristics were analysed: age, sex, etiology of poisoning, product categories and severity according to the Poison Severity Score (PSS).
Results: From a total of 33,837 cases over the study period, 174 patients with a migrant background (refugees) were documented (0.51%) and 33,663 cases involved non-migrants (other). The gender proportions were almost similar in both groups. Compared to the general population exposures in refugees typically involved adults ($p < .001$), had suicidal intent ($p < .001$), involved drugs ($p < .01$) and patients were less likely to be asymptomatic or have minor effects ($p < .01$). There were no known deaths in the refugee group (Table 1).
Conclusion: The findings demonstrate an over-representation of suicidal intent in the group of refugees among the PC calls compared to the other cases. This seems to correspond well to drug overdose as the most frequent ingested product group in suicidal cases of refugees in contrast to the other inquiries reported to GIZ-Nord PC.

8. Exposures in refugees reported to the Poisons Information Centre Erfurt, 2007–2016

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Objective: According to current numbers of the Federal Ministry of the Interior, almost 890,000 refugees entered Germany in 2015. At the same time, exposures in refugees (EIR) registered by the Poisons Information Centre (PIC) Erfurt increased as well. We wanted to compare EIR with all human exposures (AHE) reported to the PIC Erfurt over a decade.
Methods: The changes in frequencies, circumstances of exposure, symptoms, symptom severity, age groups, and substance groups involved in all EIR-related enquiries to the PIC Erfurt were analysed retrospectively from the beginning of 2007 to the end of September 2016 and compared to AHE.
Results: In total, 161 and 147,686 cases of EIR and AHE, respectively, were registered. Between 2007 and 2014, the annual number of EIR cases was low (median: 2; range 0 to 14). In 2015, EIR rose to 54. In the first 9 months of 2016, 75 EIR were observed. EIR and AHE differed in circumstances of exposure

Table 1. Characteristics of enquiries concerning refugees and other inhabitants reported to the GIZ-Nord PC (2015–2016).

		Refugees ($n = 174$)	Other inhabitants ($n = 33,663$)		
Parametera	Value	*n*	Relative proportion		*p*-Value
Age class	Children <18 years	62	36%	42%	<.001
	Adults ≥18 years	108	62%	55%	
	Unknown	4	2%	3%	
Etiology (all age groups)	Accidental	66	45%	75%	<.05*
	Suicidal	75	51%	18%	
	Other	6	4%	7%	
Etiology 15–49 years old	Suicidal	69	62%	41%	<.001
	Other	42	38%	59%	
Product category	Drugs	110	63%	38%	<.01
	Chemicals	29	17%	27%	
	Plants	8	5%	9%	
	Others	26	15%	26%	
Severity (PSS)	No symptoms (0)	22	13%	42%	<.01**
	Minor (1)	61	35%	30%	
	Moderate (2)	32	18%	10%	
	Severe (3)	9	5%	3%	
	Fatal	0	0%	0.045%	
	Unknown/NR	50	29%	15%	

NR: not recorded; *"other" excluded; **PSS 0 + 1 versus 2 + 3.

(suicidal 42.2% versus 23.3%; abuse 2.5% versus 3.7%; accidental 21.7% versus 60.3%), symptom severity (none to mild 69.6% versus 79.2%; moderate 13.7% versus 7.7%; severe 3.7 versus 2.5%), age groups (adolescents 13.0% versus 3.7%; middle aged adults 49.1% versus 26.4%; babies 1.2% versus 6.3%; toddlers 11.2% versus 33.3%; seniors 0% versus 5.7%) and gender (male 57.8% versus 44.9%; female 29.8% versus 47.3%). In EIR, the main substance classes were drugs (66.7%), detergents (9.3%), and plants (3.7%) and in AHE drugs (45.4%), plants (10.1%), and detergents (9.3%). In some EIR, poisoning occurred when toxic plants were eaten in error. For example, a 32-year-old male refugee ate an unknown quantity of *Wisteria sinensis* seeds, probably in mistake for *Ceratonia*. He developed haemorrhagic diarrhoea and abdominal pain and called for an ambulance. He had elevated creatinine concentrations but showed no neurological symptoms as described in the literature [1]. After IV fluid therapy for two days, the symptoms resolved and the patient was discharged (Case 201615151).

Conclusion: In 2015 and 2016, increasing numbers of refugees in Germany and EIR reported to the PIC Erfurt were observed. EIR occurred more often with suicidal intention in male adolescents or middle aged individuals than in AHE, reflecting epidemiological data of the refugee population. Mistaking toxic plants for edible species may result in unusual and severe exposures, which has also been seen with mushroom poisoning.

Reference

[1] Rondeau ES. Wisteria toxicity. J Toxicol Clin Toxicol. 1993;31: 107–112.

9. Two cases of ayahuasca poisoning: a poison crossing borders

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Objective: To describe the clinical course of two cases of ayahuasca poisoning, a traditional brew originally from Peru and increasingly used worldwide for spiritual purposes. Ayahuasca brew is traditionally made from the ayahuasca vine (*Banisteriopsis caapi*) and chacruna (*Psychotria viridis*). *Banisteriopsis caapi* contains B-carboline alkaloids, mainly harmine, tetrahydroharmine (THH) and harmaline. *Psychotria viridis* contains the hallucinogenic drug dimethyltryptamine (DMT). The alkaloids are potent inhibitors of monoamine oxidase (MAO), allowing oral dosing and increasing toxicity of DMT. Other plants containing DMT has also been used.

Case series: Two men were admitted after attending an ayahuasca cleansing ritual. They both drank shots of the brew. Patient 1 was a 35-year-old previously healthy male, who took more than one shot of ayahuasca, and during 6–8 hours was observed by others to become increasingly disoriented with profuse vomiting. He was also very thirsty and drank lots of water. He then had 4 self-limiting generalized tonic-clonic convulsions without regaining consciousness, and was intubated before transportation to hospital. Here, serum sodium was low (113, reference 135–145 mmol/L). He had a spontaneous diuresis of 6 litres over the next 24 hours, and sodium was then 125 mmol/L. INR was increased to 1.7 (reference 0.8–1.2) on admission, indicating hepatotoxicity. After 24 hours he developed rhabdomyolysis with maximum creatine kinase (CK) 25,000 U/L and myoglobin 3200 µg/L, and was treated with forced alkaline diuresis. He was released after 5 days in good health. Patient 2 was a 21-year-old previously healthy male who took four shots of ayahuasca, and 2 hours later developed severe agitation and anxiety, and was restrained by others to stop him harming himself. He started vomiting and lost consciousness for a brief period of time. On admission, he was awake and lucid. Serum sodium was normal (144 mmol/L), but INR was slightly increased to 1.3. Serum creatinine was increased to 121 µmol/L (reference 60–105). He developed rhabdomyolysis on day 2 with maximum CK 11,000 U/L and myoglobin 6300 µg/L. He was treated with intravenous fluids only. He was released on day 3 in good health.

Conclusion: Ayahuasca rituals are also performed outside South America, and the plants are imported illegally into Europe. These cases demonstrate the features of ayahuasca poisoning, with gastrointestinal symptoms, agitation and anxiety, convulsions and rhabdomyolysis. For patient 1, hyponatremia may have contributed to the convulsions. Serotonergic syndrome was not observed. These cases highlight that spiritual use of ayahuasca can be toxic.

10. Most amatoxin poisonings in Sweden occur in persons of non-Swedish background

Bengt Carlvik and Erik Lindeman

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Objective: Ingestion of even a single mushroom of the species *Amanita virosa* or *Amanita phalloides* may lead to severe organ damage and larger ingestions can be fatal. These mushrooms are common in Sweden and may be mistaken for edible mushrooms, a risk that may be greatly amplified if the mushroom gatherer is from a part of the world where these species are rare. The aim of this study was to quantify the existing perception at the Swedish Poisons Information Center (PC) that people of non-Swedish background comprise a large proportion of the amatoxin poisonings that come to our attention.

Methods: We searched our PC database for cases of suspected amatoxin poisonings during the period January 2014 to September 2016. Only hospital calls were included. Accidental ingestions in children were excluded. The search results were examined to identify true poisonings which were defined as a history of a possible exposure and (1) a urine sample positive for amatoxin; or (2) AST/ALT >132 U/L (twice the normal value). If the PC notes stated that the patient was foreign born, the patient was considered as having a non-Swedish background.

Results: The search yielded 87 cases of possible amatoxin poisoning. Of these, 27 cases were deemed true poisonings according to the case definition. *Amanita virosa* was involved in 22 cases. Urine analysis of amatoxin was positive in 17 cases and 10 patients met the AST/ALT criteria (range 300–11,000 U/L). In 17 cases (65%) the patients had a non-Swedish background. There were no deaths from amatoxin poisoning during the study period. One person of non-Swedish background required a liver transplant.

Conclusion: This study confirms that people of non-Swedish background comprise a large proportion of amatoxin poisonings in Sweden. In the present study period the majority of cases were refugees of Middle Eastern origin. In earlier years we have seen severe poisonings in tourists from central Europe and in immigrants/tourists from South East Asia. We believe that many of these poisonings occur in people who are experienced mushroom gatherers who mistake amanita mushrooms for white button mushrooms or paddy straw mushrooms. In order to alert people of non-Swedish background to the dangers of the Swedish mushroom flora the PC has produced an illustrated

brochure with warnings translated to 27 languages (available at http://www.giftinformation.se/mushrooms), which we annually ask the Swedish immigration authority to disseminate through their network at the beginning of the mushroom season.

11. Unusual mushroom poisoning in an immigrant: a case report

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Objective: *Rubroboletus satanas* (previously *Boletus satanas*, Satan's bolete) is generally regarded as a poisonous mushroom responsible for gastrointestinal symptoms of nausea and violent vomiting when eaten raw or cooked. In Slovenia, the species is considered rare and endangered and is listed on the Red Data List. Fortunately, Slovenians are discouraged to pick it due to its odd appearance and putrid smell. What is more, its flesh turns blue when cut or bruised. We report *Rubroboletus satanas* poisoning in an immigrant.
Case report: A 42-year-old Thai woman without previous medical history was admitted at the Emergency Department due to severe gastrointestinal symptoms. The patient had accidentally ingested *Rubroboletus satanas* in a self-prepared meal, mistaking it for an edible mushroom growing in Thailand. Within 30 minutes of ingestion she developed nausea, repeated vomiting and abdominal pain and 4 hours after the meal profuse watery diarrhoea started. On arrival, she was afebrile and her physical and neurological examinations were unremarkable. The initial laboratory tests showed mild leukocytosis and marked elevation of procalcitonin (25.6 µg/L) (normal value: <0.5 µg/L). Other laboratory parameters were normal. She was treated with 0.9% sodium chloride and antiemetics. A mycologist identified the mushroom as *Rubroboletus satanas* from the picture the patient took before consuming the mushroom. Antibiotic therapy was not introduced despite increased procalcitonin concentrations. Subsequent microbiological examination of a stool sample was negative. Gastrointestinal symptoms resolved on the third day, but the increased procalcitonin concentration decreased more slowly. The patient was discharged on the fourth day, with a procalcitonin concentration of 11.6 µg/L. This was the second case of ingestion of *Rubroboletus satanas* in Slovenia by an immigrant who consumed it because of resemblance to edible mushrooms in their homeland [1].
Conclusion: In immigrants with gastrointestinal symptoms unusual mushroom poisoning should be suspected, especially including mushrooms with colouring and smell that discourage native people from picking. *Rubroboletus satanas* ingestion causes severe non-infectious inflammatory stimuli and an aseptic increase of procalcitonin that does not require antibiotic treatment [2].

References

[1] Sarc L, Jurca T, Planinc NS. Poisoning by *Boletus satanas* causes hyperprocalcitoninemia: Case report. Clin Toxicol. 2013; 51:264.
[2] Merelet A, Dauchy FA, Dupon M. Hyperprocalcitonemia due to mushroom poisoning. Clin Infect Dis. 2012;54:307–308.

12. Increased migration to Sweden and increased incidence of isoniazid poisonings

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Objective: During recent decades, published cases of isoniazid poisoning have been rare. However, the recent drastic increase of people migrating to Sweden has resulted in more patients treated with isoniazid due to tuberculosis. As a consequence, the Swedish Poisons Information Centre (PC) has been consulted in an increasing number of isoniazid poisonings, from single cases annually during most of the twenty-first century to as many as 12 cases in 2016 (until September). Most of these intoxications have been related to suicide attempts among refugees under the age of 20, likely traumatised by armed conflicts and violence. Isoniazid blocks pyridoxine synthesis leading to elevated glutamate and decreased GABA concentrations, thereby increasing the risk for multiple seizures followed by lactic acidosis and central nervous system depression. The antidote pyridoxine effectively terminates the seizures and high dose treatment in isoniazid poisonings has not caused severe adverse effects. Dialysis is generally not recommended but may be helpful at an early stage, especially in patients with impaired renal function. Here we present an illustrative case and some observations regarding isoniazid poisoning.
Case report: A 16-year-old boy from Afghanistan ingested a maximum dose of 21 g of isoniazid in a suicide attempt. He presented to the emergency department within a few hours with repeated seizures, unconsciousness and desaturation. Immediately after intubation, extreme bradycardia required a brief period of resuscitation with adrenaline to restore sinus rhythm. Laboratory tests showed pH 6.52, base excess −30 and lactate 30 mmol/L. He was given 5 g of pyridoxine intravenously and four hours after admission continuous veno-venous haemodialysis (CVVHD) was started due to persistently high lactate values. Another 10 g of pyridoxine was given in the following hours and he was extubated 13 hours after admission. Later, he developed pronounced rhabdomyolysis but recovered completely and was discharged after 8 days. In 2016, the PC was consulted in several similar cases of isoniazid poisonings including one fatality. In that case, diagnosis was initially overlooked, leading to delayed ambulance service. Consequently, the patient experienced multiple seizures and cardiac arrest at home, resulting in hypoxic brain damage.
Conclusion: Owing to the recent increase of migration to Sweden, isoniazid poisoning has shifted from being rare to common. In our experience, pyridoxine should be given generously, without delay and repeated doses are necessary if there is recurrence of seizure activity. In patients presenting with multiple seizures of unknown origin, isoniazid poisoning should be considered, especially in adolescents with a migrant background.

13. Drugs crossing borders: unexpected dosing error with identical formulation of prazepam (Lysanxia®)

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Objective: In small countries like Belgium incidents involving products from neighboring countries are common. For economic

reasons people cross borders to buy food, consumer products or medicine. We report a case where a prescription medicine available in Belgium and France under the same name, same formulation and same concentration of the active substance lead to a therapeutic error due to a difference in the dosage delivery device.
Case report: A patient was prescribed Lysanxia® (prazepam) formulated as oral drops 15 mg/mL by a French general practitioner. She bought her medication in Belgium where the product is available under the same commercial name at the same concentration. She followed the dose prescribed to her in France and felt tired and sleepy. After three weeks she contacted the Poison Center for advice. Both Lysanxia® forms are 15 mg/mL solution in 20 mL containers and look very much alike. The ingredients of both solutions are the same. The difference between the French and Belgian form of Lysanxia® is the character of the pipette. The French form needs 30 drops to deliver a volume of 1 mL while the Belgian form only needs 15 drops. It appears that the marketing authorisation holders are different in Belgium and France.
Conclusion: Liquid medication dosing errors are common. However we are not aware of other examples where an identical formulation is sold under the same name in different countries with a different delivery device. In this case the difference led to a repeated overdosage of prazepam. Lysanxia® is a widely prescribed medication and we would like to warn our colleagues, especially those working at the French border of this peculiarity.

14. Occupational inhalation poisoning with the veterinary antibiotic tiamulin

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Objective: Tiamulin is a semisynthetic pleuromutilin diterpene veterinary antibiotic, widely used in farms for the treatment of infectious diseases in poultry and swine. There are limited data regarding human toxicology, but according to animal studies on dogs, tiamulin can prolong the QT interval after a single dose [1]. We present a case with prolonged QT interval and ventricular tachyarrhythmia after tiamulin inhalation.
Case report: A 43-year-old veterinarian without previous medical history was preparing an antibiotic mixture for the first time for approximately one hour, without wearing the personal protective equipment recommended in the Summary of Product Characteristics (SPC) of tiamulin. Half an hour after exposure nausea occurred, four hours later he started to vomit and soon after that he experienced syncope. He became somnolent, dizzy and nauseous with sweating and salivation. On admittance at the Emergency Department five hours after the exposure, he was conscious, amnestic, normocardic and normotensive. Initial laboratory results including electrolytes were within the normal reference ranges. Electrocardiography showed a prolonged QTc interval of 740 ms with numerous polymorphic ventricular extrasystoles and episodes of non-sustained polymorphic ventricular tachycardia (torsades de pointes) that resolved after treatment with lidocaine and magnesium. Subsequent electrocardiography revealed gradual shortening of QTc interval with QTc interval normalization (423 ms) on the second day after tiamulin exposure. Laboratory tests, morphologic heart diagnostics (echocardiography, magnetic resonance imaging and coronarography) and genetic testing excluded other potential causes of QTc-interval prolongation. Subsequent toxicology analysis by liquid chromatography–tandem mass spectrometry confirmed the presence of tiamulin in his blood sampled five hours after exposure (500 ng/mL). No other drugs or medications were found in the patient's blood and urine samples.
Conclusion: In this patient, tiamulin inhalation provoked lengthening of the QT interval with polymorphic ventricular tachycardia that was successfully treated with lidocaine. When handling the product, inhalation of the dust must be avoided by wearing a half-mask respirator conforming to European Standard EN 149. In veterinarians and farmers presenting with prolonged QT interval, an inappropriate handling of veterinary medicines should be suspected.

Reference

[1] Woodward K. Toxicological effects of veterinary medicinal products in humans. Vol. 1, Cambridge (UK): The Royal Society of Chemistry; 2013.

15. Occupational-related fatal case of acute methyl ethyl ketone peroxide ingestion: case report and review of the literature

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Objective: Methyl ethyl ketone peroxide (MEKP), commonly used in the lamination industry, is a highly flammable substance. Reports of acute overdose or adverse effects after human exposure have been limited. We report a Taiwanese male plastic worker with MEKP poisoning.
Case report: A previously healthy 48-year-old male, working at a plastic plant was immediately brought to the primary care hospital after accidental ingestion of 2 mouthfuls of Trigonox® which had been in a tea bottle. Trigonox which was used as a catalyst in the plastic plant is a solution of 40% MEKP mixed with dimethyl phthalate. On arrival, his vital signs were blood pressure 142/78 mm Hg, heart rate 100 beats/min, respiratory rate 16/min and body temperature 37.5 °C. Arterial blood gas analysis at Fraction of Inspired Oxygen (FiO_2) 50% revealed a pH of 7.232, PO_2 31.0 mmHg, $PaCO_2$ 50.3 mmHg, and bicarbonate 21 mEq/dL. He received endotracheal intubation for airway protection and mechanical ventilation 5 hours post-ingestion. Approximately 7 hours post-ingestion, the patient developed worsening hypoxemia and metabolic acidosis, and died 18 hours post-ingestion.
Results: Our Medline search revealed 12 reports of MEKP-associated acute oral poisoning between 1958 and 2014, involving a total of 13 patients. Combined with our case these add up to a total of 14 cases with an overall mortality rate of 50% (7/14 cases). Complications in fatal cases have included gastric perforation, pulmonary hemorrhage/edema, acute renal failure, and hepatic coma. Of all 14 cases, only 5 cases were published after 2000. Most victims were males (male:female 12:2), with ages ranging from 19 months to 70 years. Chemical burns with upper gastrointestinal tract injury are common among these patients. Early gastrointestinal bleeding and perforation, and esophagitis with delayed esophageal stricture, may occur. Some victims may need repeated endoscopic esophageal dilation up to 5 years post-ingestion. Multiple organ failure was also common in these published cases. Although N-acetylcysteine and hemodialysis have been suggested as possible therapies for severe MEKP toxicity there is little clinical data to support their usage. In the acute phase, all patients with suspected MEKP ingestion should be immediately evaluated for airway compromise due to burns and associated swelling.

Conclusion: Complications associated with fatal cases have included gastric perforation, pulmonary haemorrhage and/or edema, acute renal failure, and hepatic coma in MEKP poisoning cases. Ingestion of any amount of MEKP should be regarded as potentially serious.

16. Suspected metal fume fever from domestic exposure to lead fumes while making lead sinkers in an enclosed space

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Objective: We report a case of suspected metal fume fever after prolonged domestic exposure to lead vapors.
Case report: A 26-year-old, unemployed, man presented to hospital complaining of headache, fever, retrosternal chest pain, generalized muscle aches, nausea, vomiting (×1) and diarrhoea (×6). Ten hours earlier, he melted and poured lead to make fishing sinkers, for 2 hours, in an unventilated shed without the use of personal protective equipment. He had performed the same task twice recently without any sequelae. On examination he had global headache, generalized myalgia, pulse 138 bpm, BP 138/80 mmHg, tachypnoea (respiratory rate 22/min), temperature 38.6 °C and oxygen saturation 99% (room-air). Lungs were clear to auscultation and neurological examination was normal. Hemoglobin was 156 g/L, leucocytes 8.8×10^9/L (normal $4.0–11 \times 10^9$/L), electrolytes and liver function tests were unremarkable. A 12-lead electrocardiogram (ECG) showed sinus tachycardia. C-reactive protein was initially 33 mg/L and 88 mg/L (normal <5) the following day. Metal fume fever was suspected, however, given the presence of headache, and concern for inhalational lead toxicity, succimer was commenced until a whole blood lead could be performed the next day. This was less than 0.10 µmol/L and succimer was ceased after 4 doses. Chest X-ray was normal. He remained febrile and tachycardic for 24 hours. Blood and urine cultures were all negative. Symptoms fully resolved after 24 hours. The patient remains well post-discharge.
Conclusion: Metal fume fever presents as a transient, flu-like illness after prolonged exposure to metal oxide fumes. Zinc oxide fume inhalation during industrial welding is the most common cause [1]. The precise pathophysiology is unknown. Theories include delayed hypersensitivity from repeated exposure to fumes and direct pulmonary inflammatory mediator-release. Lead has been suggested as a potential cause [1,2], but currently there are no documented cases reporting this. Management is supportive and includes eliminating infective causes of fever. Based on the history of repeated exposure to lead fumes, the temporal relationship between exposure and onset of a febrile illness with non-specific rise in inflammatory markers, negative blood and urine cultures, and spontaneous resolution, we theorise that metal fume fever was the cause of his presentation. Due to the ease of melting and inadvertently vaporising lead, this case suggests that lead should be considered as an uncommon precipitant of metal fume fever.

References

[1] Greenberg M. Metal fume fever and polymer fume fever. Clin Toxicol. 2015;53:195–203.
[2] Mueller EJ. Metal fume fever – a review. J Emerg Med. 1985;2:271–274.

17. Descriptive study of an urban academic toxicology consultation service, 2012–2016

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Objective: In 2012, a toxicology registry database was constructed within the Research Electronic Data Capture (REDCaps) database by our toxicology department as a surveillance tool to better elucidate trends in demographics, toxic exposures, interventions, and outcomes at an institutional level. In this study, we provide a descriptive analysis of the over 2400 consultations performed by our department from 2012 to 2016.
Methods: A descriptive analysis was performed on all consultations entered into the REDCaps database for the four-year period from July 2012 to July 2016 for the six hospitals covered by our service. Frequency statistics were used to report distributions of age, gender, year and month of consult, site, category of exposure, decontamination and treatment methods used, and disposition status.
Results: A total of 2421 consultations were entered into the REDCaps database during the study period. Gender distribution was roughly equivalent between females (48.7%) and males (51.1%). Patients ranged from 2 weeks to 107 years old, with a mean age of 29 years. Patients aged 26–45 years (27.8%), 46–65 years (21.3%) and 0–5 years (19.9%) accounted for the majority of consultations. The most common exposures were analgesics (15.4%), sedative-hypnotics/ethanol (12.9%), street drugs (10.1%), antidepressants (10.0%), antipsychotics (9.6%), and household and environmental toxicants (9.6%). In the cases where the exposure was known, 1919 cases (79.3%) involved exposure to a single substance, 276 cases (11.4%) involved exposure to two substances, and 143 cases (5.9%) involved exposure to three or more substances. Of gastrointestinal decontamination procedures, gastric lavage was performed on three patients (0.1%), activated charcoal was administered to 82 (3.4%) patients, and whole bowel irrigation was performed on 38 (1.6%) patients. The most commonly administered antidotes included naloxone (4.5%) and N-acetylcysteine (3.3%). Sodium bicarbonate was used in 1.4% of cases. Enhanced elimination interventions were uncommon. Multi-dose activated charcoal (MDAC) was used in 14 (0.6%) patients. Only 7 patients (0.3%) underwent hemodialysis, and one patient received extracorporeal membrane oxygenation (ECMO). The proportion of patients admitted (1110, 45.8%) versus discharged (1001, 42.3%) were similar. Only two deaths were recorded in the database.
Conclusion: We report descriptive statistics for toxicological consultations seen at our institution. Characteristics of exposures seen by our consultation service were similar to those reported in the National Poison Data System Annual Reports. Descriptive analysis of exposures at the institutional level may help identify target populations for interventions and guide resource management.

18. Acute digoxin overdose and response to antibody (DORA study)

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Objective: There are controversies regarding the use and dose of digoxin specific antibody (digoxin Fab) in acute digoxin poisoning. This study aims to investigate the pharmacokinetics and dynamics of digoxin and response to digoxin Fab in acute poisoning.
Methods: This is a prospective cohort study of patients recruited through the New South Wales Poisons Information Centre (NSWPIC) and 3 toxicology centres from September 2013 to September 2016.
Results: Nineteen patients had acute digoxin poisoning, 13 were treated with digoxin Fab (Table 1) and this appeared to be effective in all 13 patients with an improvement in bradyarrhythmia, and in one case reversion of ventricular tachycardia. All survived the initial poisoning but one died 5 days after Fab treatment from urinary sepsis. Five patients received a single dose while 8 patients received staggered doses of digoxin Fab within the first 24 hours of admission (range 1–47 hours). Free digoxin concentrations dropped to zero within an hour of Fab administration. When a large dose of digoxin Fab was used, there was an excess of free digoxin Fab but it disappeared from the central compartment quickly. The free digoxin concentrations rebounded in all patients within 10–40 hours, but many patients did not develop recurrent toxicity. Six patients were not treated with digoxin Fab. One patient died from asystole when digoxin Fab was unavailable. Another patient showed minimal digoxin toxicity and was treated conservatively due to metastatic cancer. Four had bradycardia, managed conservatively without problems.
Conclusion: Digoxin Fab appeared to be effective for cardiac complications of acute digoxin poisoning, the only death occurring when digoxin Fab was not available. The recommended full neutralising dose resulted in an excessive amount of free digoxin antibody. Digoxin Fab may be given in staggered doses in the first 24–48 hours, titrated against electrocardiogram (ECG) changes and clinical response.

19. Prevention of lethal colchicine toxicity by colchicine-specific Fab treatment in a porcine model

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Objective: Colchicine poisoning results in high case fatality. Fragment antigen-binding (Fab) fragments have been shown to alter distribution and increase urinary clearance of colchicine in a rodent model. Administration of goat colchicine-specific Fab to one patient resulted in a good outcome. We aimed to develop a porcine model of single-dose colchicine toxicity and test novel ovine colchicine-specific Fab fragments.
Methods: We established a model of colchicine poisoning, with continuous and extensive monitoring, in 30 kg Gottingen minipigs. Serial blood samples were taken for clinical chemistry, haematology, and colchicine and Fab pharmacokinetics (PK). Animals were euthanised if the mean arterial pressure fell to <45 mmHg, without response to fluid resuscitation, or at study end.
Results: Preliminary studies indicated that oral dosing with 0.5 or 1.0 mg/kg colchicine gave variable colchicine PK and time to death. We then administered colchicine IV over one hour. The first two animals (0.25 and 1.0 mg/kg) developed cardiotoxicity and required euthanasia at 26.1 and 14.5 hours, respectively. A second pair (both 0.25 mg/kg) required euthanasia at 20.1 and 21.3 hours. Poisoning was associated with acute liver, renal, and muscle injury. Colchicine PK at 0.25 mg/kg was highly consistent and this dose was considered an appropriate challenge for evaluation of colchicine-specific Fab. Two pigs were given Fab from 6 hours after the end of the colchicine infusion with a full-neutralising equimolar dose, split 50% over the first hour and 50% over the next 6 hours (to reduce renal loss of unbound Fab). The animals showed similar toxicity to untreated animals and required euthanasia at 26.7 and 31.5 hours. However, PK analysis showed a complete absence of free colchicine during the Fab infusion, together with a large increase in total blood colchicine. The equimolar Fab dose was then given over 1 hour to two animals, 1 hour after the end of colchicine infusion; these animals survived to 48 hours without marked toxicity. Delay in Fab dosing to 3 hours post-colchicine infusion was similarly associated with moderate toxicity and survival to 48 hours. PK analysis showed

Table 1. Biochemistry profile of 19 patients treated for acute digoxin poisoning with and without digoxin Fab.

Parameter	Patients treated with digoxin Fab ($n = 13$)	Patients not treated with digoxin Fab ($n = 6$)
Median age (years)	63 (range 34–94)	58.5 (range 18–88)
Male (%)	7 (54%)	5 (83.3%)
Median dose ingested (mg)	14.3 (range 3.6–37.5)	12 (range 4.7–19.3)
Median time since ingestion (h)	3.5 (IQR2.5–11; range 1–20)	7 (IQR 5.8–13.6, range 5–18.5)
Initial median heart rate per min	39 (IQR 35–48; range 15–80)	65 (IQR 39–85; range 20–95)
Initial median digoxin concentration (nmol/L)	16.9 (IQR 13.6–28.2; range 6.6–52)	12 (IQR 5.1–17.3; range 4.7–19.3)
Initial median K concentration (mmol/L)	5.1 (range 4.4–6.7)	5 (range 4.7–6.9)
Initial median creatinine (μmol/L)	79 (range 60–230)	93 (range 69–135)
Median digoxin Fab dose (number of vials, 40 mg per vial)	8 (2–25)	0
Fatality (number of patients)	0	1

substantially larger amounts of intravascular Fab-bound colchicine associated with a decrease in the unbound colchicine concentration.
Conclusion: Intravenous colchicine 0.25 mg/kg produced a reliable model of colchicine poisoning consistent with human experience. In this model of toxicity, colchicine-specific Fab given early, in equimolar dose, prevented severe colchicine toxicity associated with extraction of colchicine from the tissues into the blood. Subsequent clinical development may provide a safe and effective antidote for colchicine poisoning.

20. Acute hypersensitivity reaction to Crotalidae polyvalent immune Fab (CroFab) initially presenting as galactose-alpha-1,3-galactose (alpha-gal) allergy

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Objective: Crotalidae polyvalent immune Fab (CroFab), commonly used for the treatment of symptomatic North American crotalinae envenomation, is generally well-tolerated; the most common reported adverse events are urticaria and rash [1]. A novel form of anaphylaxis due to an IgE antibody response to the mammalian oligosaccharide galactose-alpha-1,3-galactose (alpha-gal) has been established following red meat consumption as well as IV administration of cetuximab, which contains the alpha-gal epitope [2]. This allergy is associated with prior tick bite and is reported throughout the world. We present a case of alpha-gal allergy discovered after acute hypersensitivity reaction to CroFab.
Case report: A 61-year-old healthy female was bitten on her left ankle by *Agkistrodon contortrix*. Within 20 minutes, she developed ecchymosis and swelling of the left ankle. She had ecchymosis and edema extending proximally 13 cm up the calf and distally to the midfoot. Given the patient's rapid progression of pain and swelling, she was given CroFab. She denied any known allergy to papaya. During infusion of CroFab, she developed bilateral palmar and groin itching as well as hives on her right thigh and abdomen. Within 10 minutes, she developed diffuse hives over her entire body and worsening itching. She denied respiratory or gastrointestinal symptoms. Her vital signs remained stable; other than urticaria, she developed no signs of anaphylaxis or angioedema. The CroFab was immediately discontinued and she received intravenous diphenhydramine and famotidine with gradual resolution of hives and itching. On further discussion, she denied a history of alpha-gal allergy but admitted to rarely eating red meat and having sustained frequent tick bites. Subsequent antibody testing was significant for an alpha-1,3-galactose IgE concentration of 4.5 kU/L (normal <0.35 kU/L), confirming alpha-gal allergy.
Conclusion: To our knowledge, this is the first report of CroFab hypersensitivity associated with an underlying alpha-gal allergy. Over 1000 patients with alpha-gal allergy have been identified globally, and this number continues to grow [1]. Clinicians should be aware of the possible cross-reactivity and should incorporate the query of red meat allergy into the decision making process prior to CroFab administration.

References

[1] Schaeffer T, Khatri V, Reifler L, et al. Incidence of immediate hypersensitivity reaction and serum sickness following administration of Crotalidae polyvalent immune Fab antivenom: a meta-analysis. Acad Emerg Med. 2012;19:121–131.
[2] Commins S, Platts-Mills T. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,2-galactose (alpha-gal). Curr Allergy Asthma Rep. 2013;13:72–77.

21. Infant botulism in Italy: antidote treatment consideration from 8 years' experience

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Objective: Infant botulism (IB) results from absorption of neurotoxins produced *in situ* by *Clostridium* colonizing the intestinal lumen in infants less than one year. To date, IB remains an underdiagnosed disease due to insidious clinical onset and despite the typical "floppy baby" picture. Severe IB cases may require specific treatment, but antidote type varies in several countries (even if specific neutralizing capability is comparable) and the appropriate dose is not yet internationally standardized. For US-BAT (heptavalent) formulation, a paediatric dosage is proposed. In Italy and the EU, a 500 mL standard dose of Trivalent-Equine-Antitoxin (750 IU-anti-A, 500-anti-B, 50-anti-E/mL) (TEA) is indicated for all forms of botulism. The optimal dose should be related to the circulating toxin concentrations, which in IB are known to be low, so TEA requires a dose adjustment in IB.
Methods: All laboratory-confirmed and treated IB cases collected from 2009 to date were evaluated concerning demographics, clinical manifestations, toxin-type, antitoxin administered dose, adverse reactions, and outcome.
Results: Thirteen cases of IB were collected (mean age 16 ± 7.59 weeks, body-weight from 679 to 3.744 g). History for honey ingestion was positive in 3 cases but no other definitive sources of spores were identified. Constipation (starting 2–3 weeks before) was the first symptom in the majority of cases. Due to rapid progressive worsening of neurological symptoms, 9 patients (69%) were treated with TEA (6/9 were breastfed). The administered dose was progressively reduced during the study period from 40 to 10 mL/kg. No acute or delayed adverse reactions were registered. After TEA administration clostridiocidal antibiotic therapy and whole bowel irrigation were started. The main clinical manifestations were severe hypotonia (7/9; 77.7%), dysphagia (6/9; 66.6%), difficulty in feeding (sucking) (6/9; 66.6%), mydriasis (6/9; 66.6%), constipation (6/9; 66.6%) and ptosis (5/9; 55.5%). Four patients had a "surgical abdomen" (only in 1 was exploratory laparotomy was needed). Four babies required intubation and respiratory support. All patients fully recovered (length of hospital stay ranged from 15 to 57 days). *Clostridium botulinum* type A (1 case), type B (5 cases), type Bf (1 case) and *Clostridium butyricum* type E (2 cases) were isolated from stool samples. In one case type B toxin was detected in blood (4000 minimal lethal dose).
Conclusion: Equine-antitoxin is safely used to treat IB in several countries. The optimal dose of TEA remains a challenge; 10 mL/kg was safe and effective to counteract the circulating toxin in cases of IB. This dose is bigger than those used in Argentina and US, and a further reduction can be evaluated.

22. *Vipera ammodytes* bites treated with antivenoms Viperfav® and ViperaTAb®

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Objective: Clinically *Vipera berus* and *Vipera ammodytes* envenomation are difficult to differentiate. In the past this was not a concern, but due to the current shortage in European viper venom antiserum availability, *V. ammodytes* venomous bites have recently been treated with Viperfav™ and ViperaTAb®. Viperfav contains polyvalent equine $F(ab')_2$ fragments as an active principle against *V. aspis, V. berus* and *V. ammodytes*, while ViperaTAb contains monospecific ovine Fab fragments against *V. berus*. ViperaTAb's and Viperfav's therapeutic convenience for use against *V. ammodytes* venom-induced toxicity in humans has not been described, although protective efficacy has been proved preclinically. The aim of this study was to evaluate Viperfav and ViperaTAb in *V. ammodytes* envenomations.

Methods: A prospective case series of consecutive patients envenomed by *V. ammodytes* treated with Viperfav and/or ViperaTAb in the University Medical Centre Ljubljana in 2015 and 2016. *V. ammodytes* venom, neurotoxic ammodytoxins, and $F(ab')_2$ and/or Fab fragments concentrations were determined in serum samples with a pharmacokinetic analysis of the antivenoms.

Results: Ten patients bitten by *V. ammodytes* were treated using Viperfav and/or ViperaTAb; 5 received Viperfav, 4 ViperaTAb, and 1 patient received both. *V. ammodytes* venom and antivenom concentrations were measured in 5 patients. *V. ammodytes* venom was detected in serum of all 5 patients, but ammodytoxins were detected in only the most severely envenomed patient who developed neurological symptoms. Viperfav (4 mL) promptly reduced local swelling and improved systemic pathological signs, except recurrent thrombocytopenia. ViperaTAb (8 mL) reduced moderate swelling and temporarily improved systemic effects as well. However, this dose of ViperaTAb had no effect on neurological signs. ViperaTAb and Viperfav administration induced a decrease in *V. ammodytes* venom serum concentrations, but only Viperfav affected the serum ammodytoxins concentration. Viperfav's systemic clearance and elimination half-life were 1.64 (mL/h)/kg and 97 hours, while ViperaTAb's were 4.3–13.4 (mL/h)/kg and 14.1–55.4 hours, respectively.

Conclusion: In patients bitten by *V. ammodytes*, both Viperfav and ViperaTAb reduce local swelling and temporarily improve systemic effects. ViperaTAb did not affect neurological symptoms or the serum concentration of neurotoxic ammodytoxins. The recommended dose of Viperfav and ViperaTAb may be inadequate in serious cases of *V. ammodytes* bites, therefore duplication and repetition of the treatment, with an adjustment of administration timing, should be considered. However, it should be pointed out that this study was the result of *V. ammodytes* antivenom shortage and it emphasises the importance of the specific antivenom availability.

23. Discontinuation of N-acetylcysteine in patients meeting certain criteria: outcomes in a retrospective review

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Objective: Repeated supratherapeutic ingestion (RSTI) and unknown times of ingestion of acetaminophen are recognized as an important risk of morbidity and mortality. Experience using N-acetylcysteine (NAC) as therapy for each of these clinical scenarios is vast, however, outcomes after the discontinuation of NAC after 12 hours for RSTI and unknown times of ingestion has not been reported. This study describes the characteristics and clinical course of patients with RSTI and unknown times of ingestion of acetaminophen after meeting criteria for and having discontinuation of NAC therapy after 12 hours.

Methods: A multicenter, retrospective chart review of patients treated with IV and/or oral N-acetylcysteine for acetaminophen poisoning from 2006 to 2015. Inclusion criteria included all subjects coded as RSTIs as well as unknown times of ingestion. With convention, we defined RSTI as ingestion of greater than 4 g of acetaminophen per 24 hours over a period longer than 8 hours and unknown times of ingestion in which the clinician could not identify a time of ingestion. Each of the patients in the analysis received NAC. Discontinuation criteria were APAP <20 µg/mL, decreasing AST and ALT or within 5% of the presenting values, and clinically well after 12 hours of NAC. Data collected and analyzed include demographics, relevant coingestants, preexisiting comorbidities, presenting laboratory data, and outcomes.

Results: In total 722 patients were identified that presented to one of the study hospitals after either acute, RSTI, or unknown time of ingestion acetaminophen overdose. Of these, 203 (28.1%) were RSTI and 227 (31.4%) were unknown time of ingestion. The mean age was 35.2 years. Of these, 70.7% of the patients were females, 21.5% carried a diagnosis of chronic alcoholism, 8.6% had viral hepatitis, and 5% had a disease state associated with malnourishment. Opioids were the most common coingestant (34.6%) followed by ethanol (22.4%). Among the group meeting criteria for discontinuation of NAC at 12 hours (71 patients), 36 patients had NAC discontinued at 12 hours. After discharge, 33 patients returned to one of the study hospitals for medical care more than one week after overdose without evidence of hepatic failure. Three patients were lost to follow up.

Conclusion: Discontinuation of NAC at 12 hours for patients meeting certain criteria after RSTI and unknown times of ingestions appears to be safe. Patient-tailored NAC dosing for acetaminophen overdose should be considered going forward.

24. Fewer adverse effects with a modified 2-bag intravenous acetylcysteine protocol compared to the traditional 3-bag protocol in paracetamol overdose

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Objective: Acetylcysteine (NAC) is an effective antidote for paracetamol poisoning. However, NAC side effects are common and may be related to the rapid initial infusion rate of the traditional 3-bag protocol, the first bag at 150 mg/kg over 1 hour. A protocol change at our institution occurred in February 2015 to a modified 2-bag infusion: 1st bag 200 mg/kg over 4 hours (50 mg/kg/h) and 2nd bag 100 mg/kg over 16 hours. We hypothesized that a modified 2-bag NAC protocol will result in fewer side effects.
Methods: A retrospective cohort study. We reviewed our service patient database from August 2010 to September 2016 for paracetamol overdose requiring NAC treatment. Data was extracted on demographics, details of paracetamol overdose and NAC infusion, as well as adverse effects. Patient cohorts before and after protocol change (3-bag versus 2-bag NAC infusions) were compared for adverse effects using chi-squared testing.
Results: Over the study period 1011 paracetamol poisonings presented to our toxicology service, of which 468 required NAC infusions (2-bag = 156 and 3-bag = 312). Demographic characteristics of the 2 groups were similar. Fewer anaphylactoid reactions (itch, rash, swelling) occurred in the 2-bag group 13.1% versus 4.5%, $p = .004$), an absolute reduction of 8.7%. Similarly, there were fewer prescriptions of anti-allergy medications in the 2-bag group (10.3% versus 3.8%, $p = .017$). No differences were found in rates of hypotension (9.3% versus 7.1%) or vomiting only after NAC (13.8% versus 12.8%) or hepatotoxicity (4.5% versus 3.8%, $p =$ NS). Hypotension was mild in only 5 patients (1%), defined as a systolic blood pressure under 90 mmHg. Post-NAC vomiting and hypotension is likely multi-factorial due to vagal stimulation and the presence of co-ingestants. There were no transfers to a liver unit or requirement for transplant.
Conclusion: Adverse reactions to NAC were reduced with the simplified 2-bag infusion protocol, with a 66% reduction in anaphylactoid reactions. Other advantages include less preparation time for nurses and potentially fewer medication errors. Our study adds to a growing body of evidence that a modified 2-bag NAC infusion protocol results in fewer adverse effects, and that reconsideration of guidelines for treating paracetamol poisoning is required.

25. Palatability of tablets and capsule forms of N-acetylcysteine and methionine and associated adverse events in healthy volunteers

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Objective: To evaluate the palatability and adverse events associated with tablets and capsule forms of N-acetylcysteine (NAC) and methionine in healthy volunteers to guide the provision of cost-effective antidotes.
Methods: Forty healthy students were enrolled in this single blind randomized control study. Each volunteer was randomly assigned to receive therapeutic doses of NAC (70 mg/kg) in capsules (NAC_cap), NAC tablets (NAC_tab), methionine (2500 mg) capsules (Meth_cap), methionine tablets (Meth_tab) and folic acid as a control over five weeks. Volunteers were kept isolated in 5 rooms of a tertiary care hospital and were asked to rate the taste, smell, ability to swallow, after taste and overall acceptability in a Visual Analog Scale (VAS) from 0 to 5 (100 mm) and any adverse events that occurred within 1 hour. VAS scores were analyzed by Friedman's non-parametric and Wilcoxon sign rank tests.
Results: Forty students were enrolled but only 33 (9 females and 24 males) completed all 5 dosage forms. Median age was 23 (IQR 23–22) years. Palatability ratings (Table 1) for taste, smell and "ease to swallow" were similar (Friedman's 4.7, $p = .19$, Friedman's 2.6, $p = 0.46$, Friedman's 6.5, $p = .09$). However, there were significant differences in after taste (Friedman's 9.8, $p = .02$) and overall acceptability (Friedman's 10.2, $p = .02$). The rank order of overall acceptability was NAC_cap, NAC_tab, Meth_tab and Meth_cap with statistically significant differences ($p < .01$) between Meth_cap and Meth_tab, NAC_cap and Meth_cap, NAC_tab and Meth_cap. NAC_cap had a more acceptable after taste than Meth_cap ($p = .001$). There were no reported adverse events with Meth_tab. Five reported mild nausea and two abdominal discomfort with Meth_cap. Mild nausea was also reported with NAC_cap ($n = 2$) and NAC_tab ($n = 2$).
Conclusion: NAC capsules were the preferred preparation, but all were palatable and tolerated sufficiently well to be used in resource poor settings. Nausea was infrequent with any preparation.

Table 1. Acceptability of N-acetylcysteine and methionine tablets and capsules with folic acid control in volunteers (using a Visual Analog Scale in millimetres).

Parameter		Folic acid	Meth_tab	Meth_cap	NAC_cap	NAC_tab
Smell	Mean	97	82	75	81	87
	SD	6	13	24	22	18
	IQR (Q3–Q1)	100–91	90–70	97.5–60	100–80	100–80
Taste	Mean	98	87	80	87	82
	SD	3	15	19	15	20
	IQR (Q3–Q1)	100–100	100–80	100–69	100–80	100–80
After taste	Mean	97	88	78	90	86
	SD	6.4	15.3	19.9	10.63	16.12
	IQR (Q3–Q1)	100–97	100–80	98–60	100–80	100–80
How easy to swallow	Mean	96	66	61	73	69
	SD	10	23	28	23	26
	IQR (Q3–Q1)	100–98	80–47	85–45	88.5–62.5	90–60
Overall acceptability	Mean	97	80	71	83	82
	SD	5	13	21	17	17
	IQR (Q3–Q1)	100–93	90–75	85–60	99–80	90–80

26. Efficacy of isosorbide dinitrate as an antidote in cyanide poisoning in a swine model

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Objective: To evaluate the efficacy of intravenous and oral sprayed isosorbide dinitrate (ISDN) in cyanide poisoned swine, following a previous study that demonstrated ISDN benefit in cyanide-poisoned rabbits [1].
Methods: A comparative animal study using 24 swine, randomized into 6 study groups. Animals were poisoned intravenously with potassium cyanide (2 mg/kg). The first group received no further treatment. The second, third and fourth groups were treated intravenously with ISDN: 50 µg/kg within 1 minute post-poisoning, 50 µg/kg within 4 minutes, and 100 µg/kg within 1 minute, respectively. The fifth and sixth groups were treated with an ISDN oral spray: 3.75 mg (3 spray actuations) within 1 minute post-poisoning and 5 mg (4 spray actuations) within 4 minutes, respectively. The measured outcomes included a clinical score (0 = dead to 5 = fully alert and mobile), mean blood pressure, pulse, blood pH, lactate and methemoglobin concentrations. The animals were observed continuously up to 30-minutes after poisoning.
Results: All animals collapsed within 20 seconds after cyanide injection and developed signs of severe poisoning including respiratory distress, generalized convulsions, loss of consciousness, a marked decrease in blood pressure and pulse and profound lactic metabolic acidosis. Starting 10 minutes after poisoning, the clinical scores of the treated animals (groups 2–6) were significantly better compared to the untreated animals. The average clinical score at the end of the observation period was 3.5 for the untreated animals and 4.33–5 for the treated ones. One out of 4 untreated animals died during the observation, while none of the treated animals died. Mean blood pressure returned to baseline more rapidly in the treated animals than in the untreated, within an average time range of 5–19 minutes compared to 27 minutes, respectively. Laboratory results showed better improvement of the blood pH and lactate in the treated animals starting 5 minutes after poisoning. At the end of the observation period, the average blood pH and lactate were 7.15 and 20 mmol/L, respectively, in the untreated animals and 7.23–7.37 and 12–14.2 mmol/L, respectively, in the treated ones. There were no statistically significant differences in the study endpoints between the different treatment groups. Methemoglobin concentrations remained below 1% after ISDN administration in any dose, route or timing.
Conclusion: Intravenous and oral sprayed ISDN improved clinical and metabolic status of cyanide poisoned swine without any formation of methemoglobin. ISDN shows potential as a novel antidote against cyanide, both intravenously and through an oral spray.

Reference

[1] Lavon O. Early administration of isosorbide dinitrate improves survival of cyanide-poisoned rabbits. Clin Toxicol. 2015;53:22–27.

27. Risk factors for mortality after caustic ingestion

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Objective: Caustic injury remains an important medical problem worldwide despite various educational and regulatory efforts to reduce its occurrence. A large number of post-corrosive exposures result in serious chemical injuries and high mortality. The purpose of our study was to identify the risk factors for mortality in patients with acute caustic ingestion.
Methods: We performed a retrospective study of all caustic substance exposures that were the subject of enquiries to the National Toxicological Information Centre (NTIC) in Slovakia during an 18-year period (1998–2015). Only patients who underwent an endoscopic evaluation within 24 hours and whose medical reports were forwarded to the NTIC were included in the study. Data were evaluated for demographic and clinical factors. Endoscopic findings were classified according to the Zargar's classification [1].
Results: We analyzed medical reports of 316 patients. The median age was 27 years (1–87 years); 202 (63.9%) males and 114 (36.0%) females. Most of the exposures were accidental ($n = 245$, 77.5%). Intentional ingestion occurred in 66 (20.9%) patients. The median length of hospital stay was 3 days (1–45 days). Ingested caustic substances were mainly alkalis ($n = 92$), bleaches ($n = 87$) and acids ($n = 80$), followed by cationic detergents ($n = 21$), paraquat/diquat ($n = 9$), potassium permanganate ($n = 8$) and glyphosate ($n = 8$). The majority of the patients ($n = 271$, 85.6%) had positive initial endoscopic findings. Grade I was present in 108 patients (34.2%); grade IIa in 94 (29.7%); grade IIb in 10 (3.2%); grade IIIa in 28 (8.9%) and grade IIIb was found in 25 cases (7.9%). The overall mortality was 8.2% (26/316). Causes of death were ingestion of strong acids ($n = 22$), paraquat ($n = 3$) and glyphosate ($n = 1$). High mortality was significantly associated ($p < .001$) with strong acid ingestion (22/80, 27.5%) including hydrochloric acid (14/26, 53.8%), suicidal intent (21/66, 31.8%), grade IIIb caustic injury (17/25, 68.0%) and age ≥55 years (17/79, 21.5%).
Conclusion: According to our results ingestion of strong acids, grade IIIb caustic injury, age over 55 years and suicidal intent seem to be the risk factors for fatal outcome after caustic ingestion.

Reference

[1] Zargar SA, Kochhar R, Mehta S, et al. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. Gastrointest Endosc. 1991;37:165–169.

Table 1. Characteristics of patients ingesting solid bars of soap.

Population (*n*)	Mean age	Symptomatic cases	Medical consultation/hospital admission	Severity (PSS 2 and 3)	Fatalities
Patients with dementia (220)	83 (±9 years)	74% ($n = 162$)	21% ($n = 46$)/22% ($n = 48$)	8% ($n = 17$)	2
Patients without dementia (333)	9 (±20 years)	34% ($n = 114$)	7% ($n = 25$)/0.8% ($n = 3$)	0% ($n = 0$)	0
p	<.001	<.001	<.001/<.001	<.001	.15

29. Soap bars oral poisoning: are patients with dementia at risk?

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Objective: Most household or toilet soaps have an alkaline pH (9–12). In addition to their foaming effect, they are irritating to the skin [1]. This study aims to describe symptoms following oral exposure to bars of soap and their potential severity.
Methods: A retrospective study of accidental or deliberate oral exposure to solid soaps reported to the Grand Ouest Poison Control Center between 1 January 2000 and 1 April 2015. Severity of poisoning was reassessed for each case according to the Poisoning Severity Score (PSS).
Results: In total 553 cases of exposure were recorded (including 201 household soaps and 352 toilet soaps). In over 40% of cases ($n = 226$), exposure occurred in community homes (e.g., retirement homes, nursing homes). Patients had a history of dementia in 220 cases (40%), autism in 14 cases (2.5%) and other psychiatric history in 21 (4%). The most common symptoms were lip edema (28%, $n = 153$), oropharyngeal irritation (10%, $n = 56$), salivation (10%, $n = 53$), vomiting (9%, $n = 48$) and cough (8%, $n = 45$). Among symptomatic patients ($n = 276$), two died after developing aspiration pneumonia (male, 9 years old, half a toilet soap) or by cardiovascular shock following pulmonary edema, as a result of oropharyngeal edema, vomiting, cough and bronchial obstruction (male, 82 years old, 2 solid soaps). The intended use of the soap (household, toilet) had no influence on the poisoning severity ($p = .4$). Mildly severe (PSS2, $n = 14$), highly severe (PSS3, $n = 1$) and fatal (PSS4, $n = 2$) poisonings were observed only in patients with dementia (Table 1).
Conclusion: Ingestion of soap bars is potentially serious, especially in patients with dementia. This type of soap should not be available to individuals in community homes and close monitoring should be considered in the event of oral exposure.

Reference

[1] Baranda L, González-Amaro R, Torres-Alvarez B, et al. Correlation between pH and irritant effect of cleansers marketed for dry skin. Int J Dermatol. 2002;41:494–499.

30. Unusual administration route of an antiparasitic product: a case report

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Objective: Neostomosan® is an antiparasitic product used in veterinary medicine; it is for external use in horses, cats and dogs and contains two pyrethroids (transmix and tetramethrin). Pyrethroids work by keeping open the sodium ion channels in the axon. Human poisoning with pyrethroids is very rare. We present a case of pyrethroid poisoning after parenteral administration.
Case report: A 54-year-old male accidentally injected a 5 mL ampoule of Neostomosan® (total dose transmix 0.25 g, tetramethrin 0.025 g) in the gluteal area. His medical history revealed partially controlled asthma. The patient was admitted to the Intensive Care Unit Toxicology Department two hours after the intramuscular injection. On admission the patient presented with headache, tremor of the upper extremities, paresthesia in the lower limbs, sialorrhoea, nausea, vomiting, wheezing with respiratory effort, and stable hemodynamic status. Laboratory results revealed leukocytosis (17,200/µL). Soft tissue ultrasound identified small fluid accumulation up to 1 mm, but no collection was discovered. We initiated electrolyte rebalancing therapy, gastroprotectants, diuretic therapy, corticosteroids, broad-spectrum antibiotics, vitamin supplementation, antihistamines and aerosols for management of an asthmatic episode. Initial symptoms persisted for 48 hours with improvement in clinical signs. The patient was discharged after 4 days, with complete remission of symptoms and a follow-up of the neurological toxicity was recommended.
Conclusion: This case presents a rare case of human pyrethroid toxicity. Although the administration route of this product in veterinary use is topical application of a diluted solution, it is worth noting that the intramuscular injection of the undiluted substance resulted in rather weak toxic manifestations. The pyrethroids triggered an asthma attack in our patient, but prompt intervention improved his prognosis.

31. Dramatic improvement of poisoned patient survival in Southern province, Sri Lanka

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Objective: To identify the epidemiological features of poisoned patients and to compare the epidemiological data from 2012 to 2015 with 2002 to 2006.
Methods: A retrospective study was conducted on patients with intentional self-poisoning admitted to The Teaching Hospital, Karapitiya (THK). Data were obtained from a review of hospital records. The cases were identified by manual search through the hospital records room. The poison was identified from the history, containers, transfer letter, and/or clinical toxidrome. Previous studies have shown that the poison stated on history is confirmed to be present in more than 80% of cases [1].
Results: We determined the substances ingested and the demographic data of 4790 admissions from 2012 to 2015 and 5490 admissions from 2002 to 2006. The 5-year age band with the highest number of cases was 16–20 years in both women and men. Self poisoning was more common in males (51%) than females between 2012 and 2015. The most common type of poison ingested was medicines (44%) and this was even higher in females (56%). Paracetamol poisoning was reported in 64% of

medicinal poisonings. Overall case fatality was 2.8% ($n = 134$), which was higher in males (3.1%) than females (2.5%); 36.5% of all deaths were due to pesticides. From 2002 to 2006, a total of 578 patients died of self poisoning. The case fatality was 8.6% and 3.6% of deaths were due to medicines while 83.4% were due to pesticide. Of the 1056 patients admitted due to pesticide poisoning from 2002 to 2006, 422 deaths were reported (39.9%). The average number of patients admitted due to poisoning per year between 2012 and 2015 was 1198 and from 2002 to 2006 it was 1098.

Conclusion: The percentage of cases involving pesticide ingestion has declined. Drug poisoning (most commonly paracetamol) and other poisons have become more popular, especially among females. Deaths are rare since the medicines commonly taken are of low toxicity or easily treated and mortality rates were almost equal to that of developed countries. There was not much difference between poisoning incidences between the two time periods. Even though the mortality rates have declined due to effective measures taken by the health authorities, more effort is need to decrease the incidence of self poisoning.

Reference

[1] Eddleston M, Gunnell D, Karunaratne A, et al. Epidemiology of intentional self-poisoning in rural Sri Lanka. Br J Psychiatry. 2005;187:583–584.

32. Patients with acute chemical exposure seen in Emergency Departments (ED) in Spain: results of the Spanish Toxic Surveillance System (STSS) 2015

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Objective: The STSS, designed in 1999 by the Spanish Ministry of Health and a group of Clinical Toxicologists working in the ED of public hospitals, aims to report the cases of acute poisoning by chemical products in their ED to evaluate the risks of exposure to these substances under current EU regulations. This Program has been managed since 2010 by the Spanish Foundation of Clinical Toxicology (FETOC). We present the results of the Program in 2015.

Methods: The participating hospitals report all cases of intoxication due to household, agricultural or industrial chemicals treated in their ED. An online questionnaire is accessible through the FETOC website around the clock by means of an encrypted system. The files are downloaded on a regular basis to a database (File Maker 9.0®) making it possible to produce a final yearly report to be presented to the Health Ministry.

Results: In 2015 the Program collected 1117 cases from 21 hospitals covering a population of about 6 million. Mean age was 38 ± 24 years, with 564 (51%) men (age 37 ± 23 years) and 543 (49%) women (age 39 ± 25 years). There were 222 patients under 16 years (20%). Domestic accidents were significantly prevalent (78%) followed by occupational accidents (11%) and suicide gestures (9%) ($p < .05$). The main chemicals involved were: toxic gases (44%), caustics (20%), solvents (10%), irritant gases (10%), detergents (8%) and pesticides (5%). The main routes of entry were respiratory (56%) and oral (34%). Ocular (10%) and cutaneous contact (4%) were much less frequent ($p < .05$). In total 74% of patients were symptomatic at admission, presenting with neurological (28%), digestive (25%), respiratory (24%) and ocular (11%) symptoms, most of them mild. Only 10% were defined as severe cases. Overall 78% of cases received treatment, mainly symptomatic (48%). In 38% of cases an antidote was used: oxygen in 416 carbon monoxide exposures, 8 in association with hydroxocobalamin, ethanol was used in 4 ethylene glycol and 2 methanol cases, and atropine and oximes in 3 cases of organophosphorous insecticide poisoning. Only 13% required hospital admission for 24 hours observation and 13 (1%) were admitted to the intensive care unit (ICU). The mortality rate was 0.7%; 4 cases due to suicide gestures and 4 due to domestic accidents by inhalation of gases.

Conclusion: Acute poisoning by chemicals in Spain are low-risk events, caused mainly by domestic accidents involving toxic gases (particularly carbon monoxide) and caustic cleaning agents.

33. Increases in pediatric vitamin D exposure calls to the US National Poison Data System

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Objective: In 2008 the American Academy of Pediatrics increased its recommended dose for vitamin D supplementation to at-risk children. In 2010 the US Food and Drug Administration released a bulletin alerting to possible medication errors with vitamin D. We evaluated the American Association of Poison Control Centers' National Poison Data System (NPDS) with respect to reported vitamin D exposures among young children and infants over a 10-year period spanning the policy change.

Methods: All calls to certified US poison control centers get coded and then compiled by the NPDS. We queried the NPDS for all reported human vitamin D exposures, via generic code (#0046000), among children aged less than or equal to five years, during the years 2005–2014. We also examined cases recorded as being due to "unintentional therapeutic error."

Results: In 2005 there were 123 human exposure calls to US poison control centers concerning vitamin D exposures in young children. This number remained relatively stable pre-2008, with 117 exposures in 2006 and 169 in 2007. Subsequent to 2007 a rise in pediatric vitamin D exposures was noted: 2008 $n = 391$; 2009 $n = 957$; 2010 $n = 1885$; 2011 $n = 2521$; 2012 $n = 2721$; 2013 $n = 2823$; and 2014 $n = 3041$. Reports due to unintentional therapeutic error rose similarly during this time period.

Conclusion: Pediatric exposures to vitamin D, as reported to US poison control centers, rose 25-fold between the years 2005 and 2007 compared to 2014. The upward trajectory of vitamin D-related poison center calls was temporally associated with a policy change, emphasizing vitamin D supplementation, by the American Academy of Pediatrics. This data should inform future policy considerations with respect to childhood vitamin D supplementation. Further evaluation of the data will focus upon the circumstances of the exposures, detail the severity of clinical outcomes, and explore the role of bias within this voluntary reporting system.

34. Elimination half-life and chronic health impairment 50 years after 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) exposure

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Objective: In 1965–1968, eighty workers developed signs of poisoning with 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) during production of the herbicide trichlorophenoxyacetic acid [1]. The back-calculated group mean TCDD plasma concentration of 6000 pg/g fat classifies this intoxication among the most severe TCDD mass poisoning. Our objective was to study the long-term consequences of this occupational intoxication with TCDD in the last survivors, TCDD elimination half-life and possible mechanism of intoxication.
Methods: Examination of 8 men (72.1 ± 1.5 years) in 2016 included measurement of TCDD in plasma, densitometry of the body fat, internal, neurological, neuropsychological examination, single photon emission computer tomography (SPECT) of the brain, visual evoked potentials (VEP), Lanthony test of acquired visual impairment, nerve conduction study (NCS), and ultrasonography of the carotid artery. The following markers of oxidative stress were analysed in exhaled breath condensate (EBC) using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS): malondialdehyde, 4-hydroxy-trans-hexenal, 4-hydroxy-trans-nonenal, 8-iso-prostaglandin F2α, 8-hydroxy-2-deoxyguanosine, 8-hydroxyguanosine, 5-hydroxymethyl uracil, *o*-tyrosine, 3-chlorotyrosine, and 3-nitrotyrosine.
Results: The mean TCDD concentration was 180 ± 110 pg/g blood lipids; median 112 pg/g (12 pg/g was found in the control cumulative sample). All patients had chloracne scars, abnormal SPECT of the brain (50% had progression since 2010), and plaques in the carotid arteries. Mild polyneuropathy was found in 75% of subjects, confirmed by nerve conduction velocity (NCV) studies in 50% cases. VEP was abnormal in 62.5% patients. Lanthony test demonstrated acquired dyschromatopsia in 75% patients. Neuropsychological examination found impairments in 50% subjects; 75% of patients were treated for hyperlipidaemia, 75% for hypertension, 62.5% for diabetes type II, 45% for ischaemic heath disease, and 36% for psychological disorders. The level of all markers of oxidation of lipids, nucleic acids and proteins measured in EBC confirmed elevation compared to a control group (already found in 2010, $p < .05$).
Conclusion: In these subjects, 50 years after intoxication, the TCDD plasma concentration is still more than 10-fold that of the general population and TCDD may promote long-term neurological, vascular and metabolic impairments. Total TCDD content in the body fat decreased slightly from an average 5.058 µg in 2010 to 4.620 µg in 2016 (median 3.602–3.154 µg). The elimination half-life 5 decades after exposure is 13–20 years. Elevated markers of oxidation of lipids, proteins and nucleic acids support the hypothesis that TCDD may induce cardiovascular and neurological damage via oxidative stress.
Acknowledgements: P25/1LF/2, P28/1LF/6.

Reference

[1] Pazderova-Vejlupkova J, Lukas E, Nemcova M, et al. The development and prognosis of chronic intoxication by tetrachlordibenzo-p-dioxin in men. Arch Environ Health. 1981;36:5–11.

35. National vitamin D intoxication outbreak among infants due to a manufacturing error of vitamin D droplets: challenges for the healthcare system

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Objective: The Danish Health Authority (DHA) recommends vitamin D supplementation for children up to 2 years with 10 µg (400 IU)/day, equal to five droplets of 2 µg/droplet. An erroneous manufactured vitamin D product was identified in July 2016 after an infant developed severe vitamin D intoxication, despite a daily dose of the recommended five drops. We describe the first 10 days of the outbreak and identify risk assessment and risk communication between physicians from the Danish Poisons Information Centre (DPIC), the Danish Paediatric Society (DPS) and DHA.
Case series: Laboratory analysis performed by the Danish Veterinary and Food Administration showed that the specific vitamin D product contained 150 µg/droplet instead of the intended 2 µg/droplet. Infants dosed as recommended therefore received 750 micrograms (30,000 IU) daily. There was no concentration stated on the label. The manufacturing company claimed the production of 500 bottles (each 10 mL) due to a human error in the manufacturing process. The product was immediately withdrawn. A total of 340 bottles were already sold from March 2016. Nine days after withdrawal of the product the DHA had identified 150 children <2 years of age at risk of intoxication. Of those, 87 children had already been diagnosed with serum 25-hydroxy vitamin D concentrations >150 nmol/L. Serum ionized calcium >1.35 mmol/L was detected in 76 infants, and 18 infants had severe hypercalcemia with ionized calcium of >1.49 mmol/L. Symptoms included reduced appetite, vomiting, irritability and failure to thrive. A few patients had severe symptoms. We developed an urgent national tracing, diagnosis and treatment algorithm for vitamin D intoxication. Warnings and public emergency announcements were issued from the DHA and a strategy for keeping the media attention on the matter was made between DPIC, DPS and DHA to ensure identification and management of all exposed infants.

Conclusion: The outbreak occurred in the summer holiday and our collective risk assessment drew attention to the importance of thorough medical examination of all exposed patients, preferably in a hospital setting. Errors in distribution of important information regarding triage and treatment according to new guidelines within the healthcare system were seen in numerous situations in the first days. This case series illustrates the legislation challenges by categorization of potentially toxic substances as food supplements instead of registered pharmaceuticals and the need for well-established routes of communication between health authorities and the healthcare system.

36. Dosage regimen of biperiden to treat haloperidol-induced severe facio-troncular dystonic syndrome in children

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Objective: In 2015, Médecins Sans Frontières (MSF) had to face an outbreak of facio-troncular dystonic syndrome (FTDS) in North-East Congo, resulting from counterfeit pills sold as diazepam, but containing 10 mg of haloperidol. Initial treatment was based on diazepam which relieved FTDS but resulted in long-lasting sedation. Owing to the definitive diagnosis, a shift to a more specific antidote was chosen and we evaluate these cases.
Methods: In total 925 individuals were admitted for 1021 episodes of FTDS. Biperiden was used in 223 cases including 84% of the pediatric cases. Treated children presented with severe dystonia as evidenced by inability to swallow. We initially used the dosage regimen recommended in the Swiss pharmacopeia to treat drug-induced dystonic syndrome in children. Initially, biperiden administration was administered under medical supervision by the MSF referent at the scene.
Results: There was no pediatric preparation of biperiden and therefore, the adult preparation was used in children. The preparation contained 5 mg of biperiden in one milliliter of solvent. The initial planned dose for children of 1 year and less and those up to 5 years were 1 and 2 mg, respectively. However, the one 1 mg dose was either of limited efficacy or associated with signs suggestive of an adverse reaction to biperiden. A dilution of 0.5 mg of biperiden/mL saline was used. A 0.5 mg dose was administered IV as a bolus dose, followed by observation for 15 minutes. In the absence of improvement in facial dystonia, a second bolus dose of 0.5 mg was administered and a third dose could be considered 15 minutes later if the FTDS did not resolve. The cumulative initial dose did not exceed 2 mg. In addition to the reversal of facial dystonia, the therapeutic effect of biperiden included return of swallowing allowing giving further doses of biperiden by the oral route. The first oral dose was administered no less than 12 hours after the last initial dose at a dose equal to the effective initial cumulative dose. The following doses were halved every 12 hours. No adverse drug reactions to biperiden were reported using this dosage regimen. The mean duration of hospitalisation was 3.4 ± 0.8 days.
Conclusion: The dosage regimen of anticholinergic drugs in children are poorly documented. The dosage regimen recommended by the pharmacopeia resulted in frequent and severe adverse reactions but titration of biperiden resulted in an efficient and safe treatment of haloperidol-induced FTDS in children.

37. (Il-)legal psychoactive ingredients of recreational drugs or dietary supplements: recent findings in a regional toxicology laboratory

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Objective: Recreational drugs as well as dietary supplements are increasingly used and are easily available via the Internet in many countries. Manufacturers and retailers often remain unknown and declaration of ingredients is often incomplete, sometimes promising "traditional manufacturing". In addition, some of the active compounds do not meet national controlled substances legislation.
Methods: Drug samples were requested in all cases reported to two poisons centers in Northern and Eastern Germany in 2015 where patients developed clinical symptoms after consumption of recreational drugs or dietary supplements. Untargeted analysis by gas chromatography/mass spectrometry (GC/MS) was performed for all samples.
Results: In total 66 samples were collected containing 26 active substances including cannabinoids, stimulants, medical drugs, active substances, impurities and precursors. Adulterated herbal and cannabis products, approved pharmaceuticals, not approved pharmaceuticals with limited toxicity dataset and recently synthesized substances without any toxicological dataset, as well as chemical precursors and impurities were identified (Table 1). In 60 products no or misleading ingredients were indicated on the label. The amount of active ingredients varied considerably.
Conclusion: Systematic chromatographic toxicological analysis by GC/MS was able to disclose active components in almost all products. A wide variety of psychoactive substances are hidden in recreational drugs, including pharmaceuticals reported in the 1960s or very recently in the literature, especially new synthetic cannabinoids, new high potency designer benzodiazepines, several kratom alkaloids, 3-fluorphenmetrazine and new fentanyl derivatives. Product labels are often incomplete and misleading. Some ingredients are covered by the narcotics act in Germany, and until now, some are not.

Table 1. New drugs detected in drug samples from patients developing clinical signs after use of recreational drugs or dietary supplements (caffeine [in high doses], cannabis, amphetamines, cocaine and therapeutic opiates are not listed).

Stimulants	Cannabinoids	(New) Benzodiazepines	Others	"Traditional substances"	Degradation products
2-Aminoindane	5F-ADB, 5F-AKB48, 5F-AMB	Flubromazepam	Acetylfentanil	Woodrose (*Argyreia nervosa*, d-lysergic acid amide, ergine)	8-Hydroxy-quinoline
MDPV	5F-PB22, AB-FUBINACA	Flubromazolam	3-Methoxyphen-cyclidine	Cathine	Heptaphenone
3-Fluorophen-metrazine	MDMB-CHMICA	Diclazepam	Diphenidine, Methoxy-phenidine	Synephrine	
PV8, alpha-PHP, alpha-PVP	ADB-CHMINACA EG-2201, XLR-11, MAM-2201	Clonazolam		Kratom alkaloids	

38. Clinical and analytical aspects of quetiapine ingestion: a case report

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Objective: Quetiapine is an atypical antipsychotic drug. There are few data in the literature on acute quetiapine overdose in which clinical aspects and analytical data are reported. We report a case of quetiapine overdose with determination of drug concentrations in body fluids.
Case report: A 59-year-old woman in treatment with quetiapine (50 mg/day) intentionally ingested 1.4 g (56 tablets of 25 mg). She presented to hospital comatose (Glasgow Coma Scale 8 [E2V1M5]), with severe depression of the gag reflex. No typical symptoms associated with quetiapine intoxication such as hypotension, tachycardia or seizures were present; the QTc interval and blood glucose (96 mg/dL, normal 70–110) were normal. She was immediately transferred to the Intensive Care Unit (ICU). On admission to ICU, approximately 4.5 hours after ingestion, she was intubated and gastric lavage was performed (no pill fragments were recovered). She was treated with supportive care and serial samples of blood, urine and gastric fluid were taken. Gas chromatography mass-spectrometry confirmed quetiapine overdose and the absence of other drugs. The quetiapine serum concentration at admission was 1.21 mg/L (toxic concentration >0.4 mg/L) and rapid decline of quetiapine concentrations were observed: 0.87, 0.46, 0.32 and 0.10 mg/L 1, 2, 4 and 8 hours later, respectively. This decline was associated with progressive improvement of consciousness. Cardiac status was stable and she was extubated 12 hours after admission. The woman confirmed the amount of ingested quetiapine. The following day she was transferred to the psychiatric ward without residual symptoms. Gastric lavage removed 326 mg of quetiapine. The total amount of drug found in urine during the first 24 hours was 2.1 mg. No quetiapine was found in serum and urine 24 hours post-ingestion.
Conclusion: A retrospective analysis of 14 cases of quetiapine poisoning reported ingested doses of 1.2–18 g and serum concentrations ranging from 1.1 to 8.8 mg/L, and it was suggested that the severity of clinical symptoms in quetiapine overdose is associated with neither a high serum concentration nor the amount ingested of quetiapine [1]. In our case the effect was dose-dependent but atypical (coma without cardiac symptoms with a relatively low peak serum concentration). Gastric lavage, performed 4.5 hours post-ingestion, removed 23% of ingested drug, suggesting partial benefit of the intervention in this case.

Reference

[1] Hunfeld NG, Westerman EM, Boswijk DJ, et al. Quetiapine in overdosage: a clinical and pharmacokinetic analysis of 14 cases. Ther Drug Monit. 2006;28:185–189.

39. Disintegration and possible bezoar formation of large sized extended release tablets: an *in vitro* study

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Objective: Pharmaceuticals in extended release formulations are becoming increasingly common and many contain drugs that can cause serious symptoms in overdose. After massive intake of highly toxic substances, gastric lavage may be considered. Many extended release formulations are large in size and remain in their original shape throughout the gastrointestinal passage. In addition, pharmacobezoars may occasionally be formed in the ventricle. Gastric lavage will then be ineffective, since the tablets or bezoars will not pass through the holes of standard lavage tubes (inner diameter usually <8 mm). In the present study, selected extended release tablets, with different disintegrating characteristics, were incubated in simulated gastric fluid (SGF) to investigate disintegration and potential pharmacobezoar formation.
Methods: Common extended release formulations available on the Swedish and Danish markets of carbamazepine (Tergretol® Retard 200 mg), quetiapine (Seroquel® XR 50 mg), and verapamil (Isoptin® Retard 240 mg) were chosen as examples. The tablets were incubated for 48 hours in SGF, either separated from each other or close together. The formation of pharmacobezoars and the size/shape of the tablets were inspected visually and by light microscopy. The release of active pharmaceutical ingredient was quantified spectrophotometrically or by liquid chromatography–high-resolution mass spectrometry (LC-Orbitrap-HRMS).
Results: Tergretol® Retard disintegrated into small coated granules within 30 minutes. Separated tablets of Isoptin® Retard were intact after 48 hours. Seroquel® XR tablets were intact after 24 hours but fully disintegrated after 48 hours. When positioned together, Seroquel® XR and Isoptin® Retard both formed pharmacobezoars that were stable for more than 4 hours. The release of active substance from the bezoars was reduced by approximately 40% for up to 8 hours compared with separated tablets. Light microscopy showed that contact with SGF transformed the coating of Seroquel® XR and Isoptin® Retard to a diffusing controlling swelled gel-layer and a rigid and slow-releasing matrix, respectively. Neither formed pharmacobezoars, nor would they, as single tablets, pass through the lumen of a standard gastric lavage tube.
Conclusion: The tendency of many, but not all, extended release tablets to maintain their size/shape and form bezoars in contact with gastric fluid renders gastric lavage ineffectual for removing these tablets. Due to delayed release of active substance from pharmacobezoars, administration of activated charcoal might be of value several hours after intake of an overdose of extended release tablets. Whole bowel irrigation may be a preventive option to avoid serious symptoms, but is probably useless once a bezoar already has formed.

40. Enzalutamide (Xtandi®) and analytical interference during the determination of digoxin

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Objective: Enzalutamide (Xtandi®), competitively inhibits binding of androgens to androgen receptors and is indicated in the treatment of metastatic prostate cancer. We report the case of elevated digoxin plasma concentrations in a patient receiving enzalutamide.
Case report: An 84-year-old man treated with digoxin (125 µg/day) and enzalutamide (160 mg/day) was hospitalized for deterioration of his general condition. The plasma concentration of digoxin was 2.8 mg/L. Despite the immediate cessation of treatment, increased digoxin plasma concentrations were observed at days 3 and 7 (3 and 3.6 mg/L, respectively). There was no clinical or paraclinical element suggesting an overdose: serum potassium (4.5 mmol/L) and the renal function (creatinine 65 mmol/L) were normal, and the patient was asymptomatic. The electrocardiogram (ECG) was unchanged. The hypothesis of a possible analytical interference was mentioned after consultation with a poison center, advising a control in a second laboratory. Plasma digoxin was assayed by chemiluminescence microparticle immunoassay (CMIA®, Abbott) in two different laboratories. The interference study was made by adding enzalutamide to control plasma at different concentrations (1, 10, 20, 40 mg/L) from a soft capsule of Xtandi® (40 mg) diluted in 10 mL of methanol. Plasma enzalutamide of patient 2 was measured by high-performance liquid chromatography coupled with an ultraviolet diode-array detection (HPLC-UV-DAD). The digoxin concentration at day 7 for the patient was the same in both laboratories (3.5 and 3.6 mg/L). Enzalutamide was detected in the plasma of the patient but not quantified. Additions of enzalutamide to the blank plasma show positivity for the concentrations 40, 20 and 10 mg/L with pseudo-digoxin respectively equal to 2.73, 1.57 and 0.71 µg/L. The result was null (<0.3 g/L) for the overload of 1 mg/L.
Conclusion: Our results highlight an analytical interference of enzalutamide on digoxin measurement with the CMIA® method. Measurement of the digoxin concentration in patients treated with enzalutamide (therapeutic concentration 23–28 mg/L) is not interpretable and cannot be used for monitoring treatment. It is necessary to consider this interference before introducing digoxin in these patients.

41. Is semi-quantitative toxicological screening in serum using mass spectrometry helpful in triaging intoxicated patients at the Emergency Department? The TOXIC study

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Objective: Triaging intoxicated patients at the Emergency Department (ED) can be challenging. Patients can exaggerate or underreport the number (or dose) of exposures. This study investigated the potential role of broad toxicological screening in serum in the triage of intoxicated patients.
Methods: Patients presenting to the ED of the University Medical Center Utrecht (UMCU), due to the intoxication, with a left-over serum sample, were included in this study from 1 January to 18 October 2015. Data on reported exposures was collected from electronic patient files. A broad semi-quantitative toxicological screening was performed retrospectively in serum using liquid chromatography-tandem mass spectrometry (LC-MS/MS) combined with a compound library (approximately 300 substances). By comparing reported and measured exposures, the reliance of the medical history was established. We corrected for reported exposures that were not included in the library, for prescription drugs, and for medication administrated by paramedics.
Results: We included 146 patients; 61% of all patients who were presented to the ED due to an intoxication. The median age was 36 years (range 14–70), and slightly more women than men (56% versus 44%) were involved. A third of the intoxicated patients reported only 1 exposure, while the median number of reported exposures was 2 (range 1–9). Reported and measured exposures were comparable in 20% and 11% for reported mono- and multi-intoxications, respectively. Underreporting occurred in 69% of the patients; one or more exposures were detected in serum that were not reported. Exaggerating the number of exposures occurred in a quarter of patients; ≥1 exposure was reported that was not detected in serum. In 55% of the patients, ≥1 exposure was measured at toxic concentrations. Slightly more than half of those patients did not report at least one of these exposures, mainly involving acetaminophen, mirtazapine, cocaine, amphetamine and quetiapine. Of the patients with toxic serum concentrations that did or did not report this exposure, 81% and 63% were admitted, respectively.
Conclusion: Underreporting of exposures among intoxicated patients at the ED is high (69%), while exaggerating the number of exposures is less common (approximately 25%). Thus, a broad toxicological screening would often provide additional information on exposures. This can be very helpful in triaging intoxicated patients at the ED, especially if toxic blood concentrations are measured or if specific antidote treatment is indicated, such as for acetaminophen overdose.

42. On-site oral fluid detection for ketamine

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Objective: Ketamine has been the most frequent drug abused by adolescents and young adults for years in Taiwan. The government has implemented multiple strategies to prevent and counter drug abuse. Under the aegis of the Minister of Science and Technology, an oral fluid device to detect abused drugs in saliva has been developed for drug testing in a clinical setting, workplace and possibly roadside. We report a clinical study to assess the effectiveness of a newly developed on-site oral fluid (OF) ketamine detection device verified by liquid chromatography-tandem mass spectrometry (LC-MS/MS).
Methods: From September 2015 to August 2016, seventy-three cases of ketamine abusers were enrolled voluntarily when they attended a public rehabilitation program, and 30 mL of urine and 3–5 mL of saliva were collected for testing. The oral fluid 0.5 mL

was assayed using an on-site device immediately and the residue oral fluid and urine sample were stored at −25 °C until assayed by mass spectrophotometry later. The detection limit of on-site device for oral fluid is 25 ng/mL.
Results: Overall 26 oral fluid samples tested positive using the device and 4 of them were not confirmed by LC-MS/MS; 47 samples were negative and only one was found to be greater than 25 ng/mL. The sensitivity of the device was calculated to be 95.7% (95% CI 78.05 to 99.89) and 92.0% of specificity (95% CI 80.77–97.78%). In cases where the saliva ketamine concentration was greater than 25 ng/mL, 20 of them (87%) also had positive urine (the summation of ketamine and non-ketamine concentration greater than 100 ng/mL detected by LC-MS/MS).
Conclusion: According to this preliminary result, the oral fluid drug detective device fulfils the performance criteria of point-of-care set by ROadSIde Testing Assessment (ROSITA-2), and might be a suitable device for prevention of driving under the influence of drugs (DUID).

43. Plasma metformin concentration as a diagnostic and prognostic tool for metformin-associated lactic acidosis (MALA)

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Objective: Metformin is a widely used antidiabetic drug. In recent years its usage and overdosage has increased, as well as the number of cases with life-threatening lactic acidosis, designated as metformin-associated lactic acidosis (MALA). The exact mechanism of MALA is still unclear and symptoms are non-specific with tachycardia, hypotension, tachypnea and mental status changes which are often not associated with a severe, life-threatening condition. Having a reliable laboratory test to diagnose the condition and assess its severity will be a valuable tool for toxicologists and physicians working in emergency settings.
Methods: We analyzed cases of acute metformin poisoning in 2015 in the Military Medical Academy, Sofia. The metformin concentration was measured after direct protein precipitation with acetonitrile and using sodium 1-octanesulfonate as ion-pairing agent in the mobile phase (10 mM triethylamine/phosphoric acid, pH 2.7/acetonitrile; 85:15) on Agilent 1260 Infinity high-performance liquid chromatography with diode-array detection (HPLC-DAD) system equipped with an octadecyl-silica (ODS) column.
Results: A total of 10 patients with acute metformin poisoning were assessed; the age range was 47–81 years. There were 2 males and 8 females. Two cases were suicide attempts. Five patients had impaired renal function; 7 cases were fatal. In all cases symptoms of MALA were observed. Laboratory analysis showed: serum lactate concentration higher than 5 mmol/L, arterial pH less than 7.35, extremely high metformin concentration >30 µg/mL (therapeutic range 0.1–1 µg/mL; toxic range 5–10 µg/mL) [1].
Conclusion: Metformin is excreted unchanged via renal filtration. In elderly patients the renal function is often affected and when metformin is prescribed the creatinine clearance, as well as kidney function have to be monitored frequently. The plasma metformin measurement is another diagnostic tool for control and prevention of MALA. In cases of severe lactic acidosis (arterial pH lower than 6.9, serum lactate higher than 16 mmol/L, creatinine concentration higher than 500 µmol/L) and plasma metformin concentration higher than 30 µg/mL a fatal outcome can be expected.

Reference

[1] Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie. 2003;58:447–474.

44. Potential pharmacobezoar formation of extended-release tablets and their dissolution: an *in vitro* study

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Objective: Pharmaceuticals in extended-release formulations are becoming increasingly common on the market and they are often large sized and may retain their original shape during their gastrointestinal passage. Extended-release tablets ingested in multiple numbers are prone to form pharmacobezoars and such conglomerates increase the risk for unexpected, late-appearing toxic effects and prolonged symptoms. Knowledge of the ability of common extended-release tablets to form pharmacobezoars and their dissolution are often lacking.
Methods: A simple reproducible standardized *in vitro* model mimicking the physical effects on pharmaceutical preparations in gastric fluid was developed. Two formulations of paracetamol, an immediate-release (Panodil® 500 mg) and an extended-release product (Pinex® Retard 500 mg) were used as model substances. Both are coated with hydroxypropyl methylcellulose (HPMC), but the composition of the polymer differs. Tablets were placed in mesh bags for three experimental setups (2 tablets in one bag, 30 tablets in one bag, or 30 tablets in separate bags), immersed in 1 L of simulated gastric fluid, and incubated at 37 °C for 48 hours. The amount of paracetamol released was spectrophotometrically quantified at 1, 4, 8, and 48 hours. The disintegration of the tablets was inspected by light microscopy.
Results: Disintegration and dissolution of Panodil® was complete within 1 hour. Light microscopy showed fully soaked matrix within minutes. Pinex® Retard tablets formed a firm pharmacobezoar strong enough to hold its own weight on a stick after 4 hours incubation. The pharmacobezoar remained at 8 hours, and was partly disintegrated at 48 hours. At 48 hours the 30 separated extended-release tablets were eroded into smaller tablets. Light microscopy inspection showed that the coating of the extended release tablets was transformed into a swelled gel layer surrounding the tablet forming the diffusion controlled release mechanism. The release of paracetamol from the pharmacobezoar was reduced by 40% for up to 8 hours compared with the separated extended-release tablets; at 4 hours the release was 13% and 21% for 30 collected and separated extended-release tablets, respectively; at 8 hours the numbers were 19% and 33%, and at 48 hours 55% and 74%.
Conclusion: This *in vitro* model showed reproducible results and could be useful to study pharmacobezoar formation and

disintegration of pharmaceutical formulations. The development of a firm and lasting pharmacobezoar of Pinex® Retard tablets was demonstrated and drug release was prolonged within the pharmacobezoar. Although this model cannot be extrapolated directly to humans, the findings challenge existing gastrointestinal decontamination guidelines after massive tablet ingestion.

45. Red blood cell acetylcholinesterase (RBC-AChE) assay as a first indicative marker in organophosphate poisoning

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Objective: Organophosphate (OP) poisoning results from exposure to OP-insecticides or nerve agents and is one of the most common causes of poisonings worldwide. The cholinergic toxidrome is characteristic and indicative in those cases, but assessment of severity of poisoning requires estimation of poison potency in human body. Detection of parent OPs is a difficult and time-consuming analytical procedure with low quantitative potential as OPs are unstable in an aqueous medium. The routine laboratory assay of plasma cholinesterase is an unspecific parameter which does not correlate with the severity of OP poisoning. The RBC-AChE is a more specific biomarker which is not affected by liver function and can be used as a marker of the effectiveness of treatment.
Methods: A modified Ellman's method was used (phosphate buffer, acetylthiocholine iodide, 5,5′-dithiobis(2-nitrobenzoic acid)) and K_2EDTA blood (lavender cap tube). A 1 mL sample of whole blood was washed 3 times in saline and hemolyzed using 100 µL 1% Triton X-100. The time-course kinetic of Ellman's reaction was measured at 420 nm for 5 min using spectrophotometry. Five to ten normal blood samples (hemoglobin content 120–160 g/L) were measured as a "normal" control. The AChE activity in the tested sample was presented as a percent of inhibition.
Results: The assay is very sensitive to OP exposure even in absence of clinical symptoms. Contrary to the unspecific plasma cholinesterase, the RBC-AChE is more specific to OP intoxication. Usually, inhibition higher than 40% (60% residual activity) corresponds to detectable clinical symptoms. RBC-AChE values lower than 25% usually corresponds to the need for mechanical ventilation. The assay could be adapted for use in each clinical laboratory and used to monitor the course of therapy, even when blood product infusions are used. In the present study we demonstrate the applicability of the assay in the diagnosis and treatment course of four cases of severe OP intoxication in parallel with plasma cholinesterase activity and poison elimination from the body.
Conclusion: The RBC-AChE assay is a fast screening method for detection of OP exposure. It can also be used to monitor therapeutic effectiveness in cases of OPs poisoning. The assay is simple and can be performed in laboratories using routine laboratory equipment to confirm contact with highly potent OPs as well as to monitor the recovery of enzyme function.

46. A case report of vasoplegic shock treated with methylene blue

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Objective: Management of severe vasoplegic shock in overdose can be challenging. We describe severe refractory vasodilatory shock secondary to a large polypharmacy overdose successfully treated with methylene blue.
Case report: A 15-year-old (70 kg) male presented 1.5 hours post-ingestion of quetiapine 13.5 g (immediate and extended release), desvenlafaxine extended release 5.6 g, venlafaxine 1.05 g, amlodipine 290 mg, ramipril 100 mg, fluoxetine 560 mg, promethazine 500 mg and an unknown amount of lithium. This was on a background of essential hypertension and depression. On arrival his systolic blood pressure was 80 mmHg, heart rate 130/min and a Glasgow Coma Score 8. He was resuscitated and intubated, requiring rapidly escalating boluses of metaraminol to maintain a mean arterial pressure of 50 mmHg. Vasopressor doses were quickly escalated to 2 µg/kg/min noradrenaline and 7 units/h vasopressin with no improvement. Bedside transthoracic echocardiogram showed a hyperdynamic heart with good global contractility. A bolus of methylene blue 1.5 mg/kg was given 6.5 hours post-ingestion followed by an infusion of 1.5 mg/kg/h for 12 hours, then 0.75 mg/kg/h for 12 hours. Within 60 minutes of the infusion, his BP increased from 65/40 mmHg to 120/45 mmHg. A PiCCO (Pulse index Contour Continuous Cardiac Output) catheter inserted post-commencement of methylene blue infusion showed a cardiac output of 8 L/min and systemic vascular resistance (SVR) of 300 dyns. Haemodynamics stabilised and the vasopressors reduced to noradrenaline 0.6 µg/kg/min and vasopressin to 2.4 units/h. At 12 hours post-overdose he developed fixed dilated pupils with temperature over 38.5 °C. He was paralysed, given levetiracetam and actively cooled but developed progressive hyperthermia with increasing rigidity in the lower limbs, progressing to difficulties in ventilating. Computerised tomography (CT) brain scan and electroencephalography were unremarkable. He was diagnosed with severe serotonin syndrome requiring active cooling and ongoing paralysis for 5 days. This was thought to be precipitated by methylene blue in conjunction with selective serotonin re-uptake inhibitor and serotonin-norepinephrine reuptake inhibitor poisoning [1]. He developed ventilator-acquired pneumonia, was extubated on day 7 and made a complete recovery.
Conclusion: This patient had severe vasodilatory shock unresponsive to noradrenaline and vasopressin. As he had a hyperdynamic heart on echocardiogram, it was felt his hypotension was related to a decrease in SVR. Methylene blue improves blood pressure by decreasing vascular smooth muscle relaxation and in this patient resulted in almost immediate improvement in haemodynamic status, but precipitated severe serotonin syndrome.

Reference

[1] Ng BK, Cameron AJ. The role of methylene blue in serotonin syndrome: systematic review. Psychosomatics. 2010;51:194–200.

47. Acute ethylene glycol poisoning and methemoglobinemia after engine coolant ingestion treated with fomepizole and methylene blue

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Objective: Ingestion of engine coolant is known to cause an elevated anion gap metabolic acidosis and acute renal toxicity due to the metabolism of the active ingredient ethylene glycol into its toxic metabolites. Less known are the side effects of the various additives in addition to ethylene glycol. We report a case of acute ethylene glycol poisoning with concomitant methemoglobinemia secondary to intentional ingestion of an engine coolant containing a sodium nitrite additive. The patient was successfully treated with fomepizole and methylene blue.
Case report: A 24-year-old male presented to the emergency department intoxicated after ingesting 2 L of a commercially available engine coolant. He empirically received 15 mg/kg IV fomepizole for presumed ethylene glycol poisoning. Presenting vital signs were notable for a heart rate of 126 bpm, a blood pressure of 114/59 mmHg, and an oxygen saturation of 96% on 100% oxygen via a non-rebreather mask. Arterial blood gas analysis showed a pH of 7.4 and a partial pressure of oxygen of 220 mmHg. Approximately one hour after presentation, oxygen saturation decreased to 88% despite supplemental oxygen. Due to the degree of hypoxia despite maximal oxygen therapy coupled with an elevated paO_2, methemoglobinemia was suspected with a subsequent methemoglobin concentration found to be 23.7%. We administered 1.5 mg/kg IV methylene blue and a repeat methemoglobin concentration was 0.3%. Ethylene glycol was elevated at 199.8 mg/dL. He continued to receive IV fomepizole until ethylene glycol was undetectable; hemodialysis was not performed due to normal pH. Review of the engine coolant material data safety sheet (MSDS) revealed that the product included sodium nitrite in addition to ethylene glycol.
Conclusion: Nitrites are known to cause an inducible methemoglobinemia and are a critical component of heavy duty diesel engine coolant as they bind to the metal components of the cooling system to form a protective layer and prevent metal corrosion. While sodium nitrite-induced methemoglobinemia is well reported in the literature, methemoglobinemia secondary to engine coolant ingestion is rare [1]. While ethylene glycol is the main ingredient in most antifreeze formulations, the erudite healthcare provider can facilitate a timely diagnosis and treatment for methemoglobinemia if nitrites are known additives in the engine coolant product.

Reference

[1] Sohn CH, Seo DW, Ryoo SM, et al. Life-threatening methemoglobinemia after unintentional ingestion of antifreeze admixtures containing sodium nitrite in the construction sites. Clin Toxicol. 2014;52:44–47.

48. An academic hospital's reassuring experience with flumazenil

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Objective: Although flumazenil is a standard part of treatment for benzodiazepine overdose, experience demonstrating that it can precipitate seizures has resulted in significant hesitation to use it. However, recent studies, including poison center data [1–3] and a small sample of emergency room patients [4], have demonstrated its safety, showing a very low incidence of complications with its use. This suggests apprehension toward flumazenil is out of proportion to the severity of its adverse effects. However, a larger survey of hospital data would afford a more robust analysis.
Case series: In this retrospective review, we searched the electronic medical record for all patients treated inpatient with flumazenil from 2011 to 2015. Cases were examined individually, and excluded only if the patient was less than 18 years old. Overall 463 separate administrations of flumazenil were given to 291 patients. The mean and median age of patients was 55 years, many of which had significant disease burden, including drug or alcohol abuse; 57% of patients were treated in the Emergency Department, while 34.5% received it while inpatient. Only 6% received it in the setting of an operation. There were 2 instances of minor emesis following administration, and one case of a 7-second period of heart block that was asymptomatic. The only seizure was in an 18 year-old who was undergoing treatment for a known intracranial mass.
Conclusion: In this hospital-based study, complications from flumazenil use were exceedingly rare, even when given by non-toxicologists to patients with significant comorbidities. This suggests that assiduous patient selection by clinicians is more than adequate; at current use patterns, flumazenil should not pose the threat that it is often made out to be. Research efforts aimed at the potential reduction in secondary measures, such as length of hospital stay and use of critical care resources, would be useful in restoring a more balanced approach to an underutilized antidote.

References

[1] Kreshak AA, Cantrell FL, Clark RF, et al. A poison center's ten-year experience with flumazenil administration to acutely poisoned patients. J Emerg Med. 2012;43:677–682.
[2] Kreshak AA, Tomaszewski CA, Clark RF, et al. Flumazenil administration in poisoned pediatric patients. Pediatr Emerg Care. 2012;28:448–450.
[3] Veiraiah A, Dyas J, Cooper G, et al. Flumazenil use in benzodiazepine overdose in the UK: a retrospective survey of NPIS data. Emerg Med J. 2012;29:565–569.
[4] Nguyen TT, Troendle M, Cumpston K, et al. Lack of adverse effects from flumazenil administration: an ED observational study. Am J Emerg Med. 2015;33:1677–1679.

49. Balancing the publication bias: 45 cases of failed lipid rescue

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Objective: Numerous case reports claim the successful use of intravenous lipid emulsion (ILE) and suggest earlier and increased use for various toxicities. The Lipid Emulsion Workgroup noted a publication bias towards both positive results and heterogeneous patient scenarios. The primary aim of this study was to identify fatal cases in the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) where ILE was administered. By definition, these cases represent failure of lipid rescue. Secondary aims include demographic data of cases, description of the substances involved, correlation with reported or predicted lipid solubility and the timing of administration of ILE therapy.
Methods: Published fatality abstracts from NPDS for the years 2005–2014 were systematically searched for the words "lipid", "fat", and "Intralipid". Fatalities for which the poisoning was attributed as "undoubtedly" or "probably responsible" as the cause of death were abstracted for predefined variables on a standardized tool.
Results: Forty-five published narratives were obtained. The mean patient age was 39 years, with four under the age of two, without a gender difference (22 males, 24 females). Twenty-four unique substances were involved, with the most common categories being calcium channel blockers ($n = 11$), bupropion ($n = 6$), other antidepressants ($n = 6$), and flecainide ($n = 5$). Of the 45 cases, 87.5% involved a primary toxicant with known or predicted log D <3.0, indicating lower lipophilicity. Two cases involved parenteral local anesthetics; all others were oral exposures. ILE therapy was given in 14 cases of cardiac arrest, 6 cases as a last resort, and only twice as first line therapy. In all other cases, ILE was associated with transient return of spontaneous circulation (ROSC) in four cases and no response in 13. In all other cases ILE was given along with other therapies. Possible adverse reactions to ILE included asystole during the bolus in one case and adult respiratory distress syndrome (ARDS) in six cases. Many reports were unclear or did not specifically report the response to ILE therapy.
Conclusion: This study demonstrates that over a 10-year period a large number failures of ILE were reported to poison centers in the US. For pending controlled studies in humans, further analysis of the unpublished narratives of ILE fatalities is needed to explore factors associated with treatment failure and overall efficacy of ILE therapy.

50. Chemical injury: 4 years' experience with an advanced approach

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Objective: Chemical burns are a specific kind of injury requiring customized therapy. A radical change in skin pH results in tissue damage, sometimes with potentially life-threatening effects. Water is still considered to be the gold standard in emergency rinsing of chemical injuries but there are additional options involving hypertonic solutions based on amphoteric and chelating molecules (Diphoterine®, Hexafluorine®). In March 2012 we started applying these products in the emergency management of chemical injuries. One product is specifically intended for decontamination of hydrofluoric acid splashes (Hexafluorine®). The other solution is indicated for all other kinds of acid or alkaline splashes (Diphoterine®).
Methods: We retrospectively compared the emergency treatment of chemical injuries admitted in our hospital between 2008 and 2015. In the control group only water was used. In the advanced approach group, the previously described hypertonic solutions were applied, according to indication and possibly preceded by rinsing with water. Both groups were statistically compared for composition (gender, age, burn cause, triage), need for surgery and days of hospitalization. Statistics were performed by means of SPSS 23.
Results: Overall 112 patients were included for statistical analysis, 66 in the control group and 46 in the advanced approach group. As far as composition is concerned, the groups were comparable. Statistics revealed significantly less surgery ($p < .0001$) and a significantly shorter hospital stay ($p = .031$) in the advanced approach group compared to the control group.
Conclusion: In our hospital, patients with chemical injury clearly benefited from the application of an advanced approach, involving hypertonic solutions based on amphoteric and chelating molecules, in the emergency management of this kind of trauma. In general, this adapted approach of chemical injuries could result in a reduction of costs.

51. Novel use of sodium thiosulphate: the treatment of calciphylaxis

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Objective: Calciphylaxis is a severe condition with 45–55% mortality occurring in chronic dialysis patients [1]. Sporadically, the disease may develop in patients with normal renal function, e.g., in the presence of chronic renal inflammation [2]. Sodium thiosulphate (STS) therapy is a treatment modality of calciphylaxis, but the mechanism of its action is unknown, as well as an optimal dosage regimen [3]. STS is typically applied as an antidote for the treatment of cyanide poisoning [4]. Its therapeutic effect is not associated with decreased serum calcium or phosphorus concentration. We describe new cases of calciphylaxis and provide new knowledge on the use of sodium thiosulfate (STS) therapy in this condition.
Case series: We report four cases of calciphylaxis treated with STS. The patients were treated in three different hospitals in the Czech Republic. The data was provided by the patients' clinicians. The administration of STS resulted in the survival of 75% of patients with documented complete or partial remission of the disease. Treatment with massive doses of STS (25 g per dialysis session) led to favourable short-term and long-term outcomes in most cases. Sodium thiosulphate was well tolerated in all patients with no adverse effects reported.
Conclusion: Calciphylaxis remains a life-threatening condition with only 50% survival during the first 3.3 months after the start of treatment [1]. In our case series, STS therapy resulted in the survival of 75% of patients. More studies are needed to clarify the mechanism of action of STS and its dosage in the management of calciphylaxis. It is also worth noting that the pattern of use of STS has changed considerably. In 2015 all thiosulphate released from the Czech Toxicological Information Centre went

to dialysis centres for the treatment of calciphylaxis and none of the stock was used for patients with cyanide poisoning.

References

[1] Zitt E, König M, Vychytil A, et al. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. Nephrol Dial Transplant. 2013;28:1232–1240.

[2] Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. J Am Acad Dermatol. 2008;58:458–471.

[3] Yu Z, Gu L, Pang H, et al. Sodium thiosulfate: an emerging treatment for calciphylaxis in dialysis patients. Case RepNephrol Dial. 2015;5:77–82.

[4] Zakharov S, Vaneckova M, Seidl Z, et al. Successful use of hydroxocobalamin and sodium thiosulfate in acute cyanide poisoning: a case report with follow-up. Basic Clin Pharmacol Toxicol. 2015;117:209–212.

52. Characterizing the administration of fomepizole by medical toxicologists

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Objective: Fomepizole is used as antidotal therapy for poisonings involving ethylene glycol (EG) and methanol. The decision to administer fomepizole may precede confirmatory serum toxic alcohol concentrations. We queried the Toxicology Investigators Consortium (ToxIC) Registry to determine the characteristics of poisoned patients who received fomepizole by a medical toxicologist.

Methods: A retrospective search of the ToxIC Registry was performed for the time period January 2010 to July 2016 for patients who received fomepizole. Demographic and clinical parameters were collected and analyzed using descriptive statistics. Logistic regression analysis was used to determine if associations existed between serum EG or methanol concentrations and endotracheal intubation, use of vasopressors, or hemodialysis.

Results: A total of 533 patients received fomepizole during the timeframe of this study. The majority of patients were 19 years or older (90%) and the most common age range was 19–65 years (83%). Most cases were reported in males (68.6%). The most common toxic alcohol exposures were EG (48%) and methanol (9.7%). Most exposures were intentional (66.9%) and involved a single substance (61.9%). Hypotension (12.5%) was the most common vital sign derangement. Acid-base laboratory abnormalities were recorded in 66.6% of cases including metabolic acidosis (pH <7.2, 51%; anion gap >20, 46.9%; osmolar gap >20, 32.4%). Central nervous system depression was present in 49.5% of cases. Therapeutic interventions included intubation (24.9%), use of vasopressors (11%), and hemodialysis (22.8%). No toxic alcohol exposure was identified in 36.9% of cases. An acid-base abnormality was present for 72% of these cases. Only 34% of the 32 total deaths reported involved a toxic alcohol. Logistic regression did not demonstrate a significant relationship between serum EG or methanol concentrations and use of intubation, vasopressors, or hemodialysis.

Conclusion: Fomepizole was most commonly administered for EG and methanol exposures. In cases where no toxic alcohol exposure was ultimately identified, it was usually given in the presence of an acid-base abnormality. Fomepizole's favorable safety profile, delay in readily available measurement of serum toxic alcohol concentrations, and high morbidity/mortality of untreated EG or methanol poisonings likely also contributed to its empiric use. The serum toxic alcohol concentration did not predict use of therapeutic interventions.

53. Arsenic at breakfast, lunch and dinner

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Objective: To report a case of inorganic arsenic exposure from a common food source.

Case Report: The patient was a 43-year-old female who was noted to have elevated urinary concentrations of inorganic arsenic (42 µg/g creatinine; reference <25 µg/g creatinine) on routine workplace testing. Her employment of 15 years involved the use of inorganic arsenic in the manufacture of silicon wafers. The patient reported using personal protective equipment as directed and there were no reports of elevated arsenic on workplace environmental monitors and no other co-workers had elevated urine arsenic concentrations. Her only physical complaints were lethargy, occurring several times per week for the preceding 2–3 years that was unchanged at the time of the test. She was given instructions to avoid foods known to contain arsenic and a repeat test 40 days later showed a urine inorganic arsenic concentration of 34 µg/g creatinine. She was removed from her usual work environment for three weeks. Repeat testing showed a urinary inorganic arsenic concentration of 90 µg/g creatinine and it was determined that her arsenic exposure was not work-related. She was returned to her usual work area, and referred for further evaluation. On close questioning, the patient revealed that she had continued eating rice during her previous urine tests, and that she consumed rice at almost every meal. She reported two sources: (1) a warehouse retailer; and (2) an Asian market. These were collected from the patient and tested for inorganic arsenic. The warehouse rice contained 130 ppb and the Asian market rice 90 ppb of inorganic arsenic. The patient was instructed to discontinue eating rice for ten days. Repeat urine inorganic arsenic was 23.6 µg/g creatinine. She was advised to limit her rice intake to one meal per day.

Conclusion: Inorganic arsenic may be present in a number of foods, including rice, with inorganic arsenic concentrations in US rice ranging from 90 to 160 ppb. This patient's practice of eating rice at every meal resulted in elevated urinary inorganic arsenic concentrations despite typical inorganic arsenic concentrations in the rice. Urine inorganic arsenic concentrations were below concentrations usually associated with acute clinical effects, but there are conflicting studies regarding potential chronic health risks, particularly of cardiovascular disease and cancer. Daily, excessive intake of rice containing permissible concentrations of inorganic arsenic may result in chronically elevated urinary inorganic arsenic concentrations.

54. Attempted suicide with intravenous copper sulphate: a case report

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Objective: Acute copper sulphate poisoning (ACuSP) usually results from oral ingestion with suicidal purpose, rarely from parenteral exposure; only a few cases of parenteral ACuSP have been reported [1,2]. We report a case of severe copper poisoning following intravenous injection of copper sulphate.
Case report: A 37-year-old man was admitted to the Emergency Department 3 hours after an attempted suicide by self-injecting an unknown quantity of a copper sulphate solution intravenously. The patient had a history of heroin and cocaine abuse. On admission, he was conscious, Glasgow Coma Scale (GCS) 15, temperature 36.5 °C, respiratory rate 18 breaths/min, oxygen saturation 96% (room air), blood pressure 105/75 mmHg and heart rate 120 beats/min. He presented tremors and diffuse myalgia. Biochemical tests were normal. One day later, the serum copper concentration reached 263 µ/dL (normal range 70–140 µ/dL). On day 3, he was oriented and febrile (38 °C). Physical examination revealed pallor, jaundice, brown to red urine, signs of extravasation by the antecubital area of both arms and he complained of epigastric pain. Laboratory findings showed normochromic normocytic anaemia (haemoglobin 7.40 g/dL) with signs of intravascular haemolysis, methaemoglobin 6.3% and rhabdomyolysis. The patient received fluid therapy, electrolyte correction, and transfusion of 4 units of packed red blood cells. N-acetylcysteine (150 mg/kg over 120 minutes +300 mg/kg/day) and D-penicillamine (30 mg/kg/day) were started. Piperacillin/tazobactam and clindamycin were administered for peri-injection cellulitis. As his critical condition persisted therapeutic plasma exchange (TPE) was performed on days 5 and 6. On day 7 he was transferred to the intensive care unit, and then to the surgery unit for wound cleaning. On day 12 he was moved to the psychiatric unit, on day 13 D-penicillamine was discontinued due to increasing liver function tests. On day 32 he was discharged asymptomatic with normal laboratory values.
Conclusion: ACuSP is uncommon and insidious. The clinical picture is mainly characterized by massive haemolysis associated with slight extracellular methaemoglobin formation. The management is symptomatic and supportive. Chelation therapy is safe and effective and haemodialysis is indicated only in cases of persistent renal failure. TPE should be considered as an additive measure, if required.

References

[1] Oldenquist G, Salem M. Parenteral copper sulfate poisoning causing acute renal failure. Nephrol Dial Transplant. 1999;14:441–443.
[2] Behera C, Rautji R, Dogra TD. An unusual suicide with parenteral copper sulphate poisoning: a case report. Med Sci Law. 2007;47:357–358.

55. Lead poisoning screening in children: an example from France, 2002–2013

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Objective: Lead exposure in infants may be responsible for neurological, haematological and renal dysfunction. Children younger than six years are more vulnerable than adults to lead poisoning due to increased digestive absorption associated with the immaturity of central nervous system, and hand-to-mouth behaviour. Screening of lead poisoning has been a priority for the French Public Health Agency since 2004 [1]. This study aimed to describe lead poisoning in minor children in an area of France from 2002 to 2013.
Methods: A retrospective study was carried out from January 2002 to December 2013, focusing on primary blood concentrations of lead in Midi-Pyrénées. These data were collected by the Greater Paris Lead Poisoning Monitoring System (Système de Surveillance du Saturnisme en Ile-de-France [SSSILF]), supplied by data from the nine French poison control centers. A blood lead level (BLL) 10 µg/dL defines a new case of lead poisoning in a minor child in accordance with a ministerial decision. Statistical analyses were conducted using Stata Version 12.0 software (StataCorp LP, College Station, TX).
Results: Overall 1321 blood lead levels (BLLs) were determined from 2002 to 2013. Most of them were done between 2003 and 2008, during a major screening period in France. The mean age was 5.6 ± 4.5 years (range 1–17 years). Overall 56 blood lead levels revealed a new case of lead poisoning (4.2%), with a mean level of 13.5 µg/dL. Risk factors associated with children's BLLs were living in an old house (26.7% versus 9.9%, $p < .001$), with lead-based paints at home (12.5% versus 4.2%, $p < .001$) and in a family where another child had an elevated BLL (23.2% versus 3.8%. $p < .001$).
Conclusion: Physicians should be aware of the risk of lead poisoning and should identify exposed children. French poison control centers have an important role to play as they receive the lead monitoring datasheets leading to improved toxicovigilance of such intoxication.

Reference

[1] Tararbit K, Carré N, Garnier R. Risque de survenue d'une intoxication par le plomb lors du suivi d'enfants à risque dont la plombémie de primodépistage est inférieure à 100 µg/L [Occurrence of lead poisoning during follow-up of children at risk with initial screening lead blood levels below 100 microg/L]. Rev Epidemiol Sante Publique. 2009;57:249–55. (French).

56. Lead poisoning in a family due to incense burning

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Objective: Exposure to lead can occur from contaminated air, water, dust, food, or consumer products. In Taiwan, incense burning at home is a common traditional religious activity. One study has demonstrated incense burning is a significant factor contributing to lead exposure [1], and we report a family with lead poisoning due to incense burning.
Case series: The family comprised 7 members, aged 5–69 years. As part of their religious beliefs they burnt a large number of incense sticks every day and this occurred for more than 40 years. Initially, the grandmother (Patient 2) developed dizziness, abdominal pain and unexplained anemia (hemoglobin 7.3 g/dL). Her blood lead concentration was 57.2 µg/dL. Details of the other family members are shown in Table 1. They all stopped burning incense and received antidote therapy. Their blood lead

Table 1. Basic data, symptoms, blood lead concentration and haemoglobin in a family exposed to lead from incense burning.

Patient	Age (years)	Sex	Medical history	Symptoms	Antidote	Blood lead concentration (μg/dL)		Haemoglobin (g/dL)
						Before treatment	After treatment	
1	69	Male	Gout, hypertension and diabetes	Both lower limb soreness; numbness over four limbs for 2 years.	1. $CaNa_2EDTA$ 2. Oral DMSA	80.2	22.4	13.2
2	67	Female	Nil	Fatigue and dizziness, back and abdominal pain for several months.	1. DMPS 2. $CaNa_2EDTA$	57.2	43.0	7.3
3	38	Male	Nil	Nil	1. DMPS 2. $CaNa_2EDTA$	62.2	48.0	13.9
4	14	Male	Nil	Nil	1. $CaNa_2EDTA$	34.0	3.6	14.9
5	13	Male	Nil	Nil	1. $CaNa_2EDTA$ 2. Oral DMSA	49.5	13.6	13.1
6	7	Male	Nil	Nil	1. $CaNa_2EDTA$ 2. DMPS 3. Oral DMSA	43.6	32.7	12.7
7	5	Female	Nil	Nil	1. $CaNa_2EDTA$ 2. DMPS	38.9	10.7	13.1

$CaNa_2EDTA$: calcium sodium edetate 500 mg/10 mL amp, 1000 mg/5mL/vial Chelagen Injection 200 mg/mL; DMPS (unithiol) 250 mg/amp; DMSA (dimercaptosuccinic acid, succimer).

concentrations decreased but Patient 1, Patient 2 and Patient 3 then refused to continue treatment.
Conclusion: Incense burning is a source of lead poisoning in Taiwan and there are still many temples and families that burn incense. Reducing exposure to lead in the environment is the best way to prevent lead poisoning.

Reference

[1] Hwang YH, Lin YS, Lin CY, et al. Incense burning at home and the blood lead level of preschoolers in Taiwan. Environ Sci Pollut Res. 2014;21:13480–13487.

57. Mercury vapor poisoning associated with home gilding

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Objective: Acute mercury vapor poisoning is an uncommon but potentially fatal toxicological emergency. The compound unithiol (2,3-dimercapto-1-propane sulfonate, DMPS) is a synthetic amino acid chelating agent of toxic heavy metals, which is an effective antidote of mercury. Here, we report two incidents of acute mercury vapor poisoning due to home gilding.
Case reports: Incident 1: A 33-year-old man performed mercury gilding at home for one week. He developed sore throat, generalized soreness, pain, fever, and skin rash over the whole body. He was admitted to our hospital 4 days later. His initial blood and spot urine mercury concentrations were 461 μg/L and 209 μg/L, respectively. His wife (26 years old) developed similar symptoms and was admitted the next day. Her initial blood and spot urine mercury concentrations were 115 μg/L and 75 μg/L, respectively. The husband also developed mild interstitial lung disease. After management with unithiol (DMPS), N-acetylcysteine and antihistamine, they recovered without sequela. The chelation regimen for husband was intravenous unithiol 250 mg every 6 hours for 3 days, then every 12 hours for 2 days. The regimen for the wife was intravenous unithiol 250 mg every 6 hours for 2 days, then every 12 hours for 2 days, followed by oral unithiol 200 mg three times daily for 2 days. The initial post-chelating urine mercury concentrations were 4319 μg/L (husband) and 3097 μg/L (wife), respectively. Incident 2: A 43-year-old man heated mercury for gilding in a bedroom. On the second day, all four family members exhibited symptoms of acute mercury vapor poisoning with weakness, fatigue, diarrhea, sore throat, anorexia, generalized soreness, cough and dyspnea. Two dogs and four pet mice died later. All patients had high urinary mercury concentrations of 2381–5396 μg/L and blood mercury concentrations of 120–391 μg/L upon referral, after 3 days of unithiol. The children (19-month-old girl, 10-month-old boy) developed coma, acute respiratory distress syndrome and pneumothorax, which necessitated mechanical ventilation and intensive care. The parents were hospitalization for 14 days and the children for 32 (girl) and 117 days (boy).
Conclusion: Exposure to mercury vapor during gilding in an enclosed environment is dangerous and may lead to a variety of adverse health effects, including severe pulmonary toxicity [1]. Diagnosis of acute mercury vapor poisoning is based on history, clinical manifestations and high mercury concentrations in urine and blood. Children may be at increased risk of adverse pulmonary effects following mercury vapor exposure.

Reference

[1] Vahabzadeh M, Balali-Mood M. Occupational metallic mercury poisoning in gilders. Int J Occup Environ Med. 2016;7:116–122.

58. Severe elemental mercury poisoning managed with selenium and N-acetylcysteine supplementation

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Objective: Recent evidence suggests the mechanism of toxicity of mercury involves the selenium-based proteins thioredoxin reductase and glutathione peroxidase. We report a patient with severe mercury poisoning unchanged by chelation who later achieved significant improvement related to selenium and N-acetylcysteine (NAC) supplementation.
Case report: Without informing his family a healthy 15-year-old athletic male spilled elemental mercury, contaminating his garage, bedroom and personal items. Over the next 6 weeks of continued vapor exposure, worsening muscle pain, new onset hypertension, mood changes, abdominal pain, anorexia and a 14 pound (6.35 kg) weight loss led to admission at tertiary care facility to rule out pheochromocytoma (ruled out). He had emotional lability, profound insomnia, delirium and delusions. Abdominal CT, renal ultrasound and blood work were normal. He was started on lisinopril and clonidine, evaluated by psychiatry, and discharged with no clear diagnosis. One week later he was admitted to a second facility for worsening abdominal pain, continued weight loss, auditory hallucinations, persistent tachycardia, hypertension, palmar desquamation, diaphoresis, tremor of his hands and ataxia. Multiple analyses revealed elevated mercury concentrations in blood (23 µg/L) and urine (330 µg/L). Succimer (DMSA) chelation for 21 days was initiated on the second hospitalization day 9 but he continued to deteriorate and on day 18 was transferred to the intensive care unit due to autonomic instability and respiratory muscle weakness. A feeding tube was placed. Three weeks post-chelation he was considered for transfer to a long-term care facility due to lack of improvement. On arrival to our facility, his exam was unchanged. He could not stand or feed himself unassisted. He was started on selenium 500 µg/day and NAC 50 mg/kg/day. By day 3 of these supplements, he showed noticeable improvement, by day 14 (discharge) delusions, delirium, tachycardia and abdominal pain had resolved. Muscle strength, weight gain, speech, unassisted ambulation and emotional liability also improved. After five months of continued supplementation 1) he had regained 45 pounds (20.5 kg), 2) was restored to premorbid emotional, academic and athletic performance (active football) and 3) tachycardia, hypertension, rash, palmar skin changes, tremor and insomnia had resolved.
Conclusion: Several important features of this case include 1) significant improvement of neurologic, cardiovascular, dermatologic and skeletal muscle function after initiation of selenium and NAC supplementation; 2) this contrasted with continued multisystem deterioration after a 21 day course of succimer chelation and 3) selenium supplementation at >9 times the US recommended daily amount (RDA) did not result in elevation of serum selenium concentrations.

59. Fatal ingestion of copper sulfate

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Objective: Copper sulfate is a soluble copper salt with fungicide, algicide, bactericide, herbicide, molluscicide, and insecticide properties. It is a strong irritant to skin and mucous membranes, and can be corrosive. Systemic exposure can lead to gastrointestinal effects as well as haemolysis, coagulopathy, methemoglobinemia, metabolic acidosis, acute organ failure, hypotension, tachycardia, seizures, coma, shock, and death. We report a case of fatal ingestion of a large amount of copper sulfate.
Case series: Between June 1996 and June 2016, a total of 83 exposures to copper sulfate were reported to the Poisons Information Centre Erfurt. Of these, 60 cases (72.3%) were accidental ingestions and 10 cases (12%) were suicide attempts. Most cases (84%) resulted in no ($n = 32$) or minor ($n = 38$) gastrointestinal symptoms, in 8 cases (9.5%) moderate to severe symptoms occurred, in 5 cases symptoms were unknown, and there was one fatality. A 50-year-old male ingested 150 g of copper sulfate in a suicide attempt. He only reported to hospital after 7 days and at this point already showed severe symptoms including prolonged nausea and vomiting (not hemorrhagic), metabolic acidosis, acute renal failure (glomerular filtration rate 20 mL/min per 1.73 m^2), elevated transaminase concentrations, and hyperkalemia. The following day, gastroscopy was performed and showed distinct necrosis of gastric mucosa without perforation or bleeding. Serum copper concentrations were 15 µmol/L (day 7) and 12.3 µmol/L (day 8), respectively (normal range 11.8 to 23.6 µmol/L). In the course of the next 3 days, the patient developed haemolysis, multiple organ failure, and respiratory failure. Treatment with penicillamine was attempted, and the patient´s condition temporarily improved, however he died on the 21st day after ingestion due to multiple organ failure.
Conclusion: Copper is an essential trace dietary mineral due to its role in several enzymatic processes. Yet, ingestion of large amounts of copper salts (10–100 g) can result in severe symptoms and even death. Excess copper in the blood is immediately deposited in the liver, which explains the elevated transaminase concentrations and severe symptoms despite "normal" serum copper concentrations in this case. Moreover, as penicillamine can only remove free copper from the blood, delayed administration could not prevent the fatal outcome in this case [1].

Reference

[1] Naha K, Saravu K, Shastry BA. Blue vitriol poisoning: a 10-year experience in a tertiary care hospital. Clin Toxicol. 2012;50:197–201.

60. "Hemp oil" ingestion: the dangers of alternative therapies

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Objective: Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive component of marijuana. We describe a case of a child who ingested up to 450 mg of THC, after the parents thought they had purchased hemp oil.
Case report: An 11-month-old female (8.6 kg) presented to hospital, as her parents noted she was irritable. This was on a background of infant acute lymphoblastic leukaemia post-allogeneic transplant and her parents were informed she was likely to relapse. The child was fed via a nasogastric tube due to slowly resolving post-transplant feed aversion. On examination observations were within normal limits, however she appeared irritable and intermittently in pain. Due to concerns she may have sepsis, intussusception or a relapse, a full septic screen, head computerised tomography (CT) scan and abdominal ultrasound were performed and all returned negative. She had ongoing irritability and was managed with a morphine infusion commencing at 10 µg/kg/h, which was increased up to 50 µg/kg/h. At 12 hours post-presentation, she was noted to be unresponsive with upper

airway obstruction. A venous blood gas revealed a pH 7.18 and pCO_2 68. This was followed by a brief respiratory arrest that responded to naloxone and bag and mask ventilation. Her parents subsequently revealed they had commenced an alternative therapy consisting of 0.5 mL daily of hemp oil per rectum but because of concerns it was not being absorbed, 9 hours prior to presentation the hemp oil was administered via nasogastric tube. It was after this that she started to became unwell. When reviewed the "hemp oil" was labelled "100% THC". Whole blood THC and delta-9-THC acid concentrations 9 hours post-ingestion were 9 µg/L and 140 µg/L, respectively. The child improved over the next 24 hours with nil deficits but full consciousness was not achieved for 3 days.

Conclusion: 100% THC oil can contain 700–900 mg THC/mL. Therefore, in this child up to 450 mg of THC could have been ingested. A study of healthy volunteers, ingesting 20 mg of THC (a typical recreational dose), resulted in peak plasma concentrations of 4.4 to 11 µg/L at 60–90 minutes [1]. In this case at 9 hours post-ingestion THC concentrations were still at these concentrations. In this case the respiratory arrest was likely from the combination of THC and opioid toxicity. Her irritability was the result of high THC concentrations, which was interpreted as pain, resulting in treatment with opioids, and together this resulted in respiratory arrest.

Reference

[1] Ohlsson A, Lindgren JE, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980;28:409–416.

61. A delicious meal!

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Objective: Collective food poisoning episodes are usually due to viral or bacterial infection. Sometimes a toxic aetiology must be discussed. We present a case of food-related poisoning in 9 people.

Case report: Two female family members (49 and 65 years) were hospitalized with symptoms of dizziness, headache, nausea, loss of consciousness, cyanosis and grey complexion. The symptoms started 1 hour after a family meal with a "baeckeoffe", a traditional dish from Alsace, with marinated meat, vegetables, white wine and aromatic herbs. Methemoglobin concentrations in the two patients at 2 hours were 27.3% and 16%. After calling the Poison Center, 7 other people who had eaten the same meal prepared by the grandmother were identified. Six of them showed the similar but minor clinical symptoms. People noted that the dish looked grayish. All victims were sent to the hospital. The methemoglobin concentrations at 4 hours were between 1.8 and 6.3%. All the patients received normobaric oxygen and the first two women also received methylene blue. There were no other cases reported in the town and intoxications by nitrates or nitrites were suspected. After contacting the grandmother, the hypothesis was raised that the source of the intoxication might have been the salt added to the dish, which had been stored at home since the grandfather was a butcher 25 years ago. Analysis of the meal, wine and salt with spices by the Department of Public Protection showed concentrations of nitrites above the allowable limits: meal (1956 mg/kg) and salt (3773 mg/kg).

Conclusion: Nitrite salts used for the preservation of charcuterie products interact with haemoglobin, causing the oxidation of iron and therefore producing methaemoglobin. European legislation limits the concentration of nitrites in food to 0.01 mg/kg [1]. The acceptable daily intake of nitrites is 0.07 mg/kg/day (European Food Safety Authority) [2]. We estimate that each patient ingested about 1 mg/kg of nitrites in the food. As with plant protection products, some professional products kept at home for a very long time can lead to intoxications in particular circumstances.

References

[1] Règlement (CE) N° 1333/2008 du Parlement Européen et du Conseil du 16 Décembre 2008 sur les additifs alimentaires [online] [cited 2016 Oct 20]. Available from: http://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/1333_2008_fr.pdf.

[2] EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Scientific opinion. Statement on nitrites in meat products. EFSA J. 2010;8:1538.

62. Carbon monoxide: a hidden threat in Shisha bars

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Objective: Shisha smoking has become popular in western countries in recent years, and is commonly claimed to be less harmful than smoking cigarettes. In contrast, research showed multiplication of harmful substances e.g., carbon monoxide (CO) in shisha smoke [1], and several cases of CO intoxications after Shisha smoking have been reported [2,3]. This study evaluates cases of shisha exposure reported to a Poisons Centre (PC).

Methods: Retrospective analysis (1995 to September 2016) of the PC database for shisha-related exposures. Cases involving additional agents were excluded.

Results: There were 49 mono-exposures (mostly accidental or abuse), involving predominantly young people aged 15–25 years (52.2%); the follow-up (FUP) rate was 24.5%. Most (95.9%) were indoor exposures, notably 38.8% in shisha bars. Symptoms were mainly non-specific: sickness/vomiting (40.1%), dizziness (34.7%), headache (32.7%), syncope (32.4%) or impaired consciousness (16.3%). Overall 38.8% of cases had minor (Poison Severity Score [PSS] 1) and 51.0% pronounced symptoms (PSS2). Hospital admission was required in 71.4% of cases and 38.8% were admitted to the intensive care unit (ICU). Carboxyhaemoglobin (COHb) values were available in 31 cases (63.3%), 93.5% of these were toxic (41.9% >10% COHb, 51.6% >20% COHb, with a maximum value 37.5% COHb). In one case the COHb was elevated (12.5%) after outdoor exposure. For 11 patients transfer to a hyperbaric oxygen (HBO) facility was initiated, in at least 3 of these cases HBO therapy was actually performed according to FUP. Outcome in 93.9% of patients remained unknown (partly loss of follow-up due to transfer of patients).

Conclusion: Increasing use of shishas in Germany is reflected by increasing numbers of PC enquiries, mainly involving adolescents and young adults. Symptoms were mostly non-specific. COHb measurement was predominantly >20%. This underlines the necessity of performing COHb measurement in all symptomatic cases following contact with shisha smoke. The majority of cases were classified PSS2, therefore the risk potential of these scenarios should not be underestimated. Doctors should be aware of

risk for CO intoxication following shisha smoking and should not hesitate to perform COHb measurement in these cases, even if symptoms are non-specific. Further education of consumers is essential. Reassessment of FUP strategy may improve information about outcome.

References

[1] El-Zaatari ZM, Chami HA, Zaatari GS. Health effects associated with waterpipe smoking. Tob Control. 2015;24;i31–i43.
[2] von Rappard J, Schönenberger M, Bärlocher L. Carbon monoxide poisoning following use of a water pipe/hookah. Dtsch Arztebl Int. 2014;111:674–679.
[3] Veen M. Carbon monoxide poisoning caused by water pipe smoking: a case series. J Emerg Med. 2016;51:e41–44.

63. Cold gel packs: harmless or not?

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Objective: We describe two cases, involving the same cold gel product with different formulations, with potentially fatal outcome.
Case report: Our first patient, a 95-year-old woman from a nursing home, presented to the emergency department due to suspected intoxication. She had poor eye sight together with type 2 diabetes and moderate kidney impairment. Prior to admission she had accidentally eaten a plate full of gel from a hot/cold package (Ice power® Hot/Cold) mistaking it for pudding. The ingested amount was less than two-thirds of the package. Four hours after exposure she seemed drunk and drowsy. Upon admission no ethanol was detected in expired air. Blood gas analysis showed an uncompensated metabolic acidosis (pH 7.27, base excess -11, pCO_2 4.4 kPa). The point-of-care analyzer showed significantly elevated blood lactate of 17.4 mmol/L, which was out of proportion to the clinical state of the patient and acid-base measurements. This suggested a cross reaction with something in the patient's blood, e.g., glycolic acid. Accordingly, toxic alcohol concentrations 6 hours post-ingestion tested positive for ethylene glycol (6.3 mmol/L). As fomepizole was unavailable, oral ethanol was initiated 14 hours post-ingestion (20% solution 7.5 dL over 6 hours). She received fluids and bicarbonate to compensate for the acidosis (pH 7.20–7.27), which resolved 40 hours post-ingestion. No dialysis was needed. During 10 days of hospitalization her serum creatinine concentration rose to 209 µmol/L. She recovered without sequelae and the creatinine returned to baseline 3 months after the accident. Our second patient was an 83-year-old male with Alzheimer's disease living at a nursing home. After similarly mistaking the product for pudding, he ingested 2 tablespoons of the gel (approximately 30 mL). In this case no ethylene glycol was detected upon blood analysis and the asymptomatic patient was discharged.
Conclusion: Before 2009 this product contained up to 40% of ethylene glycol but since then, it has been reformulated and is now harmless containing mainly glycerol which is compatible with the outcome of patient 2. In the first case it turned out, however, that the package was many years old. Cold gel packs are long-lasting and reusable. It is difficult to determine the contents of old packages. These products, despite similar package, can have different ingredients which vary from harmless to dangerous, and vigilance is required. Symptomatic patients need assessment even though the current content of the package is harmless.

64. Four fatalities after ingestion of vinegar essence

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Objective: Commercially available vinegar contains up to 25 g acetic acid per 100 g (25%). Highly concentrated vinegar essence (up to 80%) is used industrially. Despite legal regulation this is still commercially available and can also be found in households. The Austrian Poisons Information Centre documented 72 cases of oral intake of vinegar essence from 2002 to 2015. In total 45 adults and 27 children and adolescents were affected. One third ($n = 14$) of the adults ingested vinegar essence in suicide attempts, whereas the children and adolescents were exposed accidentally ($n = 25$). We present 4 cases with fatal outcome.
Case series: Case 1: A 57-year-old woman was admitted to hospital after ingestion of 100–200 mL of vinegar essence in order to commit suicide. The main symptoms were vomiting, laryngeal and gastrointestinal corrosive lesions, haemolytic anaemia, macrohaematuria, thrombocytopenia and metabolic acidosis. Despite early intubation and supportive therapy she died after 3 days due to multiple organ dysfunction syndrome. Case 2: A 63-year-old woman ingested an unknown amount of vinegar essence in order to commit suicide. Symptoms were vomiting, somnolence, gastrointestinal ulcerations, haemolytic anaemia, coagulopathy, acute liver and kidney failure. Despite treatment in the intensive care unit she died after 2 days. Case 3: An 85-year-old woman with dementia accidentally drank an unknown amount of vinegar essence. Her symptoms were vomiting, stridor and corrosive lesions in the area of the throat. Gastroscopy was not performed. She died after 2 days following metabolic acidosis, coagulopathy, haemolysis, respiratory and cardiovascular insufficiency. Case 4: A 71-year-old woman was admitted to the emergency ward after intake of approximately 100 mL vinegar essence in order to commit suicide. Her symptoms were massive mucosal oedema of the oropharynx, necrotic areas in the distal oesophagus, stomach and duodenum with signs of perforation in the abdomen, aspiration pneumonia, coagulopathy, haemolytic anaemia, acute renal and liver failure. She died after 4 days.
Conclusion: Ingestion of vinegar essence must be taken seriously since the symptoms are dramatic, leading to severe systemic effects. The mortality rate for adult patients who ingested vinegar essence in order to commit suicide is high (4/24, 29%). Treatment is symptomatic and supportive, including parenteral administration of proton pump inhibitors, antibiotics in case of infection; correction of metabolic acidosis, anaemia (blood transfusion), and coagulopathy (fresh frozen plasma, prothrombin complex, fibrinogen); early intubation, haemodialysis, and haemodiafiltration.

65. Iatrogenic medication errors in residential and care homes

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Objective: The Poisons Information Centre Erfurt frequently receives calls from care home personnel about medication errors in patients. The aim of this study was to show how often medication errors happened in residential and care homes for the elderly or those with disabilities, and children. Additionally, the potential risk of toxicity in patients was evaluated.

Methods: In a retrospective study, cases involving medication errors in residential and care homes were analysed by the Poisons Information Centre Erfurt from 2011 to 2015. Data were categorized into age groups, drugs involved, need for treatment, and estimated risk of toxicity.
Results: In total, 324 cases of medication errors in residential and care homes were reported (0.4% of all exposures). Over five years, enquiries from residential and care homes have increased by 65.3% from 49 per year (2011) to 81 (2015), corresponding with an increase from 0.34% to 0.48% of all exposures reported to the Poisons Information Centre Erfurt. The largest group were adults (91.7%), 18.2% of them seniors. Most frequent drug classes involved were antipsychotics (26%), antiepileptics (23.8%), and antidepressants (5.1%). The most common substances were valproic acid, carbamazepine, and risperidone. A little more than half of the patients were assessed to be at minor risk of toxicity (56.2%), 4.6% to be at moderate to severe risk of toxicity, and in 22.8% the risk was unpredictable, whereas in just 14.2% of the cases no adverse effects were expected. Consequently, medical treatment was recommended in 82.1% of all cases. Of those, 28.1% had to be observed in hospital immediately after exposure, and in 30.5% hospital treatment was recommended for patients if they subsequently developed symptoms.
Conclusion: This analysis shows a constant increase in calls from residential and care homes for the elderly or those with disabilities, and children. Patients may develop symptoms due to high therapeutic doses of drugs whose dose normally has to be increased gradually, such as most psychotropic drugs. The study demonstrates a need for effective measures to avoid medication errors, and consequently hospitalisation. Therefore, nursing personnel and especially non-medical personnel in these institutions have to be strictly instructed in the handling and effect of drugs.

66. Intravenous lipid emulsion: interference with laboratory analyses

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Objective: Intravenous lipid emulsion (ILE) is increasingly used to treat poisonings. The resultant lipaemia affects measurements of various biochemical analytes *ex vivo*. Erroneous or missing laboratory values could impact treatment of the poisoned patient, but the effects of ILE on biochemistry analyses in a clinical setting have not been explored. In a randomized clinical trial we therefore investigated how ILE affected measurements of relevant analytes.
Methods: Two healthy male participants each completed two trial days with ILE and two trial days with saline (placebo). In randomised order, ILE 20%/placebo was administered as 1.5 mL/kg over 1–3 minutes from time 0 minutes, followed by 0.25 mL/kg/min infusion to time 15 minutes. At baseline, 15 and 45 minutes, blood samples were collected and analysed on a standard Cobas-8000 analyser (Roche Diagnostics). Percentage change in plasma concentrations from baseline was assessed on days with ILE and placebo. Statistical significant between-group changes from baseline to 45 minutes were calculated using the Mann–Whitney *U*-test.
Results: On ILE days, analyses of plasma bilirubin, calcium, alanine aminotransferase, aspartate aminotransferase and albumin were interfered by lipaemia leading to no reporting of results. Analyses of creatine kinase, lactate dehydrogenase and potassium were interfered by haemolysis on ILE days also leading to no reporting of results. Plasma creatinine, sodium and alkaline phosphatase were reduced, whereas plasma cholesterol was increased on the ILE days (Table 1), but all reported results were within normal ranges. All changes and between-group differences were below 10%.
Conclusion: A range of analyses yielded no reported results due to lipid interference or haemolysis. ILE did not affect concentrations of sodium, cholesterol, alkaline phosphatase and creatinine to a clinically relevant degree. The exact interference of ILE on analyses (which can be extracted manually via Cobas IT Middleware) and the mechanism behind ILE-induced haemolysis needs further exploration.

67. Nationwide survey to evaluate the differences in resources, implementation and treatment strategies for management of the alcohol withdrawal syndrome (AWS) in England and Wales

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Objective: In the UK there are approximately one million hospital-admissions per year due to alcohol-related harm, with alcohol withdrawal syndrome (AWS) occurring in many of these.

Table 1. Plasma concentrations of analytes on days with intravenous lipid emulsion (ILE) and saline in volunteers.

Analyte	Baseline concentration (median)	Plasma concentration (median change from baseline in percent) after 15 minutes	Plasma concentration (median percent change from baseline) after 45 minutes
Sodium (mmol/L)			
Placebo	140.7	141.8 (+0.7)	141.9 (+0.6)[a]
ILE	140.7	137.1 (−3.1)	138.2 (−1.9)[a]
Creatinine (µmol/L)			
Placebo	78.8	77.2 (−1.8)	76.7 (−5.8)
ILE	76.7	72.4 (−7.5)	72.8 (−4.2)
Cholesterol (mmol/L)			
Placebo	3.6	3.3 (−8.3)	3.4 (−6.9)[a]
ILE	3.5	3.4 (−1.7)	3.6 (+1.7)[a]
Alkaline phosphatase (U/L)			
Placebo	51.7	47.8 (−9.1)	48.8 (−6.9)
ILE	52.0	46.3 (−9.6)	49.2 (−4.7)

[a]Denotes statistically significant differences in changes from baseline at 45 minutes between the two intervention groups ($p < .05$).

In this study we undertook a survey of all acute hospitals in England and Wales to determine local approaches to the assessment and management of patients with AWS.
Methods: A survey was developed to collect the following data: whether there was a dedicated alcohol care team (ACT); assessment scores used for the management of AWS; and pharmacological regimes used for the treatment of AWS. This survey was delivered using a web-based system between October 2015 and July 2016 to all 137 acute-care NHS Trusts (hospitals) in England and Wales.
Results: Data was available from 86 (63%) hospitals. Of these, 72 (83.7%) had an alcohol care team (ACT). The ACTs comprised a median (IQR) of 3 (1–4) members, with the majority being nurses (66%) and physicians (30%). The scores used to identify patients at risk of AWS were: the alcohol-use disorders identification test (AUDIT) 43 (50%), the original AUDIT in 12 (14%) and a revised version in 31 (36%); the fast alcohol-screening test (FAST) 5 (6%); CAGE 4 (5%) and the severity of alcohol-dependence questionnaire (SADQ) 4 (3.6%). Data on the tool used to guide treatment was only available from 74 hospitals: 49 (66.3%) used the Revised Clinical Institute Withdrawal-assessment (CIWA-Ar); 6 (8.1%) used the Glasgow modified alcohol-withdrawal (GMAW) scale; 5 (6.7%) used no specific score, and 14 (18.9%) used a different individualised tool. The majority of hospitals (73, 84.8%) reported chlordiazepoxide as the agent of choice for the management of AWS, with 9 (10.5%) using diazepam. Most used a fixed-dosing regimen with symptom-trigger (39, 45.3%), with others using a symptom-trigger for the first 24–48 hours followed by a reducing course (17, 19.8%), symptom-trigger only (10, 11.6%) or fixed-dosing only (9, 10.5%). Many hospitals had no formal policy regarding treatment recommendation for AWS in those with alcohol-related liver disease (34, 39.5%), in pregnancy (48, 55.8%) or in the elderly (42, 48.8%).
Conclusion: There are significant variations in the identification, assessment and management of AWS in England and Wales. These data suggest an urgent need for development of a nationwide consensus, and uniform implementation of evidence-based assessment and management guidelines for AWS.

68. Nosocomial transmission of *Clostridium butyricum* type E responsible for two cases (one outbreak) of infant botulism

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Objective: Botulism may develop if a preformed toxin is ingested or if clostridia producing botulinum neurotoxins grow in the intestines or wounds, and toxin is released. Person-to-person transmission does not occur and poisoned patients do not required isolation. We reported two cases (one outbreak) of nosocomial transmitted infant botulism (IB).
Case series: Case 1: A 12-week-old infant (5 kg) was admitted to the intensive care unit (ICU) because of feeding difficulties, weak cry, poor head control, mydriasis, generalized weakness, hypotonia, and acute/tympanic abdomen. The mother reported the presence of constipation associated with abdominal colic (from 2 weeks) unsuccessfully treated with cimetropium bromide. Due to the rapid neurological worsening with a floppy-baby hallmark, IB was suspected. Laboratory testing confirmed type E botulism. Considering the serious condition, the baby was intubated, treated with antitoxin and, subsequently, with clostridiocidal antibiotic (metronidazole) and whole bowel irrigation by gavage. The clinical condition progressively improved and the infant was transferred, 5 days after antitoxin administration, to the paediatric ward. Faeces were negative 12 days after antibiotic treatment. Case 2: An 8-week-old infant hospitalized from birth in the same ICU, presented a clinical picture of botulism 15 days after the case 1 admission. This baby was born at the 26th week of gestation with a birth weight of 679 g. During hospitalisation it received supplemented human milk, vitamin D, probiotics and caffeine. Laboratory investigations confirmed type E botulism. The patient was intubated with respiratory support, and treated with antidote and antibiotic. The clinical condition gradually improved with complete return to spontaneous respiration 7 days after antitoxin administration. He excreted *C. butyricum* type E from faeces for 15 days. Whole genome sequencing revealed that *C. butyricum* type E isolated from the specimens of the 2 patients were indistinguishable. No *C. butyricum* type E was detected in the ICU environmental samples collected after the second case was confirmed by laboratory investigations.
Conclusion: We report the first description of nosocomial transmission of *C. butyricum* type E responsible for two cases of IB. The two families and the two patients came from different geographical areas and never had any contact previously. Although isolation of these patients is not necessary, particular care should be taken to avoid nosocomial transmission of spores. The same procedures adopted to prevent nosocomial transmission of *Clostridium difficile* colitis could be successfully implemented to reduce spreading of neurotoxin-producing clostridia spores.

69. Pre-workout supplements: an analysis of their chemical content and pharmacodynamic interactions with monoamine transporters

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Objective: Pre-workout supplements (boosters) are poorly regulated and available to increase "focus and duration" to successfully complete challenging body building weight training. Generally, a mixture of caffeine, creatine, amino acids, vitamins, and plant-extracts are contained in these products, according to their labeling. However, some providers "upgrade" their body building powders with largely unknown amounts of pharmacological stimulants and/or other uncontrolled or prohibited chemical compounds. The use of these products may be in conflict with doping regulations and pose a health risk for users [1]. We selected four pre-workout supplements marketed via the Internet and with a proprietary blend labeling including several phenethylamine-derivatives. We pharmacologically tested the products for stimulant-like properties, especially their potential to inhibit the monoamine reuptake for norepinephrine (NE), serotonin (5-hydroxy tryptamine [5-HT]), and dopamine (DA).
Methods: We assessed *in vitro* monoamine reuptake inhibition for NE, DA, and 5-HT in human embryonic kidney (HEK) 293 cells, stably expressing the respective human monoamine transporter (NET, norepinephrine transporter; DAT, dopamine transporter; SERT, serotonin transporter) [2]. Selected pure chemicals labeled on the products were tested at a screening concentration of 100 µM and data were calculated using Prism (GraphPad, San Diego, CA).

Results: Phenethylamine-derivatives contained in the pre-workout products (2-phenethylamine [PEA], N-methyl-PEA, beta-methyl-PEA, N-benzyl-PEA, vonedrine and methylsynephrine) inhibited the NET and DAT and weakly also the SERT. Norepinephrine reuptake was also strongly inhibited by 1,3-dimethylbutylamine (DMBA or AMP citrate), whereas yohimbine and 2-dimethylethanolamine (deanol or DMEA) showed only very weak interaction with this transporter.
Conclusion: The transporter inhibitor profile of phenethylamine-derivatives sold to body builders is similar to the stimulants amphetamine and methamphetamine. Thus, depending on their metabolic stability and/or the co-use of enzyme inhibitors, these stimulants may carry cardiovascular and addictive risks.

References

[1] Lee J, Venhuis BJ, Heo S, et al. Identification and quantitation of N,alpha-diethylphenethylamine in preworkout supplements sold via the Internet. Forensic Toxicol. 2014;32:148–153.
[2] Simmler LD, Buser T, Donzelli M, et al. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol. 2013;168:458–470.

70. Wound botulism in Italy (1979–2016)

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Objective: Wound botulism (WB) occurs mainly in traumatic wounds and in injecting drug users as the consequence of *in situ* growth and toxinogenesis of *Clostridium botulinum* spores. The clinical syndrome is indistinguishable from that of food-borne botulism except for the absence of gastrointestinal symptoms. Fever can be present. Although this form of botulism was first recognised in 1950, it remains a manifestation of botulism that is rare and commonly underdiagnosed. Improvement in physician awareness is essential for an early diagnosis and prompt therapeutic measures. We evaluate the prevalence of WB in Italy and the frequency of the signs and symptoms in this condition.
Case series: In Italy, the first case of WB was recognised in 1976. From 1976 to 2016, a total of eight cases were reported to the national register. Except for one (in a drug user), all cases were due to traumatic injuries. All patients were adults, only one was female. Neurological symptoms appeared on average 10.3 days after the injury. Ptosis, mydriasis, diplopia, and dysphagia were reported. Three patients developed constipation and respiratory failure; fever occurred in two cases. As therapeutic measures antibiotics were administered to six patients, while botulinum antitoxin was given to five. Hyperbaric oxygen treatment was applied to two injuries. Two patients died. All cases were laboratory confirmed through the detection of botulinum toxins in serum or by the isolation of *Clostridium botulinum* in the infected wound. Six of the seven cases were due to type B toxin.
Conclusion: In Italy, WB is mainly underdiagnosed because of its rarity and difficulties in the formulation of clinical suspicion. WB should be considered in patients presenting with typical symmetrical descending flaccid paralysis when epidemiological investigation suggests that foodborne botulism is unlikely and where there is history of injecting drugs (skin popping). The lack of clinical suspicion is probably the main reason why only one case in a drug user was recognised. In other countries (e.g., USA, UK) the highest incidence of WB is associated with contaminated drug usage rather than traumatic injuries. Another aspect is that the onset of symptoms is gradual, subtle and can occur during the post-operative phase in a surgical ward (e.g., orthopaedics). A common error is the correlation of typical neurological symptomatology of botulism only to a history of consumption of canned food and not to traumatic injuries or wounds.

71. Accidental ingestion of nicotine solution for e-cigarettes: a case report

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Objective: The safety of e-cigarettes has been a topic of intense debate since they were introduced on to the market. In particular, intentional or accidental exposure to nicotine solutions ("e-liquids"), used for refilling the devices, may result in great toxicity and even fatality, given the high nicotine concentration (up to 72 mg/mL) [1].
Case report: A 14-year-old boy was brought to the local medical facility following an accidental ingestion of about 10 mL of a nicotine-containing e-liquid. His parents reported that 10 minutes earlier the grandfather had inadvertently administered the solution instead of a multivitamin dietary supplement. Abdominal pain and repeated emesis quickly followed, and persisted upon arrival. As the label on the refill bottle indicated an 18 mg/mL solution, the estimated dose of nicotine ingested was 180 mg (3.3 mg/kg). Vital signs were unremarkable, with blood pressure 125/75 mmHg, heart rate 70 beats/min, blood glucose 95 mg/dL, oxygen saturation 98% (room air) and normal pupil size. The Poison Control Centre suggested gastroprotectants, and while nausea and vomiting were present advised against the use of activated charcoal. The patient was then transferred to the nearest hospital where he received support therapy with ranitidine and fluids. Two hours later physical and laboratory parameters remained stable and the symptoms gradually resolved. He was discharged the following morning with no additional therapeutic intervention.
Conclusion: The lethal dose of nicotine is usually considered to be 0.5–1 mg/kg in adults, although studies based on post-mortem concentrations suggest higher thresholds (6.5–13 mg/kg) [2]. In this case, the absence of severe signs and symptoms of intoxication following the acute ingestion of 180 mg of nicotine could be explained by: (i) the age and body weight (55 kg) of the subject; (ii) the low oral bioavailability, and (iii) the rapid onset of emesis that limited absorption. Nicotine refill bottles may be indistinguishable from other product bottles commonly present in the home environment. Considering the extreme toxicity of nicotine, regulatory measures should be implemented to avoid unintentional exposure, especially in children, that could result in serious or lethal poisonings.

References

[1] Cameron JM, Howell DN, White JR, et al. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. Tob Control. 2014;23:77–78.
[2] Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88:5–7.

72. Clinical and social features in acute organophosphate pesticide poisoning in school children: a 5-year retrospective study

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Objective: To highlight the clinical picture and social consequences in acute organophosphate pesticide poisoning in school children.
Methods: We performed a 5-year retrospective study of the medical records of children with acute organophosphate poisoning admitted in our hospital. The following criteria were taken into consideration: age, implicated product, route of exposure, clinical manifestations, length of hospitalization and number of missed school days.
Results: In total, 58 students with acute accidental organophosphate pesticide poisoning were admitted in our hospital between January 2011 and September 2016. The distribution by age was 7–12 years old ($n = 31$, 49.2%) and 13–18 years old ($n = 27$, 42.8%). Dimethoate was implicated in 43 patients (74.1%), fenthion in 6 patients (10.3%) and malathion in 4 students (6.9%). The route of exposure was inhalation in 45 patients (77.5%) and ingestion in 13 students (22.4%). The poisoning was accidental in all cases. Of the total number of 58 patients, respiratory and digestive signs occurred in 18 cases (31%), respiratory, digestive and neurological signs (hallucinations, seizures) in 34 patients (58.6%) and cardiovascular signs in 2 patients (3.4%). The treatment was guided by the clinical picture because it was not possible to determine serum pseudocholinesterase activity. All the patients survived without sequelae. The length of hospitalization was 7.4 ± 0.55 days and the period of absence from the school was 18.7 ± 0.8 days, meaning about 93 school class days. The costs of epidemiologic and investigational research and decontamination of premises where the poisoning occurred but except medical transport and hospitalization could not be measured.
Conclusion: Although the clinical manifestations in acute accidental organophosphate poisoning in children are varied and severe, early and adequate treatment, even in absence of serum pseudocholinesterase determination can lead to the patients' recovery. Material, social and intellectual costs except those of hospitalization and medical transport are difficult to measure in situations.

73. Different clinical courses for poisoning with World Health Organization hazard class Ia organophosphates

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Objective: Based on animal studies, extremely hazardous pesticides are classified by the World Health Organization (WHO) as hazard class Ia [1]. However, data describing the clinical course of WHO class Ia organophosphate (OP) insecticide poisonings in humans are very scarce. We compared the clinical features of patients who ingested three different OPs classified as Ia (extremely hazardous pesticides).
Methods: This retrospective observational case study included patients with a history of ingesting ethyl p-nitrophenol thio-benzene phosphonate (EPN), phosphamidon, or terbufos. The patients were divided according to the chemical formulation of the ingested OP. Data on mortality and the development of complications were collected and compared among groups. The study design was approved by the Institutional Review Board of Chonnam National University Hospital, Gwangju, South Korea.
Results: The study included 75 patients with a history of ingesting EPN, phosphamidon, or terbufos. There were no differences in the baseline characteristics and severity scores at presentation between the three groups. No fatalities were observed in the terbufos group. The fatality rates in the EPN and phosphamidon groups were 11.8% and 28.6%, respectively. Patients poisoned with EPN developed respiratory failure later than patients poisoned with phosphamidon (6.0 [3.6–14.0] hours in EPN patients versus 3.0 [1.6–6.5] hours in phosphamidon patients, $p = .024$) and also tended to require longer mechanical ventilatory support than phosphamidon patients (19.0 [7.0–31.0] days for EPN versus 8.0 [2.5–10.5] days for phosphamidon, $p = .057$). The main cause of death was pneumonia in the EPN group and hypotensive shock in the phosphamidon group. Death occurred later in the EPN group than in the phosphamidon group (21.0 [4.5–30.8] days for EPN versus 2.0 [2.-4.3] days for phosphamidon, $p = .007$).
Conclusion: Even though all three insecticides are classified as WHO class Ia, the clinical course following ingestion and cause of death in humans varied. Consequently, the treatment protocols for poisoning and predicted outcomes should also be different and based on the particular OP involved.

Reference

[1] Dawson AH, Eddleston M, Senarathna L, et al. Acute human lethal toxicity of agricultural pesticides: a prospective cohort study. PLoS Med. 2010;7:e1000357.

74. In-hospital outcome and delayed neurologic sequelae of seizures in patients with endosulfan poisoning

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Objective: Endosulfan is an organochlorine insecticide and seizures are a common manifestation of poisoning with an incidence rate greater than 70% [1,2]. This study investigated the predictive factors for progression of seizures to status epilepticus (SE) and refractory SE (RSE) in patients with endosulfan poisoning. This study also investigated delayed neurologic sequelae in patients with endosulfan poisoning who develop seizures.
Methods: This retrospective, observational case series of patients who developed at least one seizure after endosulfan ingestion. Data were collected regarding seizure characteristics (progression to SE or RSE) and management, the development of complications during hospitalization, the Glasgow Outcome Score (GOS) value upon discharge, and the neurologic sequelae after discharge. Patients were divided into two groups according to the progression of seizure to SE or RSE. The study design was

approved by the Institutional Review Board of Chonnam National University Hospital, South Korea.
Results: The study included 72 patients with endosulfan poisoning who had least one seizure. The progression from seizures to SE and RSE occurred in 77.8% and 53.6% patients, respectively. The SE and RSE fatality rates were 19.2% and 43.3%, respectively. No patients reported the development of post-discharge seizures or neurological deterioration at least 1 year post-discharge. The Glasgow coma scale (GCS) value was identified as an independent factor for the progression of seizures to SE (odds ratio (OR) 0.643, 95% confidence interval (CI) 0.501–0.826, $p = .001$) and RSE (OR 0.699, 95% CI 0.516–0.921, $p = .012$). The administration of lorazepam was independently associated with preventing the progression from SE to RSE (OR 0.049, 95% CI 0.008–0.297, $p = .001$).
Conclusion: Seizures in patients with endosulfan poisoning have higher progression rates to SE and RSE and higher fatality rates compared to patients with drug-induced seizures. However, delayed neurologic sequelae after discharge were not demonstrated. Due to the high progression rates to SE and RSE and the absence of an established management protocol for endosulfan-related SE, physicians should aggressively treat patients with endosulfan poisoning who experience a seizure and who present with decreased GCS. Lorazepam should be considered a first-line antiepileptic drug for controlling seizures in patients with endosulfan poisoning. Further studies are needed to assess the optimal management of SE and identify prognostic factors for RSE.

References

[1] Moses V, Peter JV. Acute intentional toxicity: endosulfan and other organochlorines. Clin Toxicol. 2010;48:539–544.
[2] Moon JM, Chun BJ. Acute endosulfan poisoning: a retrospective study. Hum Exp Toxicol. 2009;28:309–316.

75. Initial laboratory parameters and correlation to intermediate syndrome in patients with acute organophosphate poisoning

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Objective: The association of serial serum cholinesterase (SChE) activity and the occurrence of intermediate syndrome (IMS) in patients orally poisoned with organophosphate (OP) were investigated [1]. In addition, other clinical and laboratory factors were assessed for their ability to predict the subsequent development of IMS.
Methods: A total of 125 patients presented to our Emergency Department (ED) with acute OP ingestion between 2010 and 2015 were enrolled in this prospective study. Of these patients, 67 who needed mechanical ventilation (MV) for 5 or more days were in the IMS group. The 47 patients weaned from MV within four days after admission, or who did not receive the assistance of MV, were in the non-IMS group. The activity of SChE at admission, 48 hours, and 96 hours after admission and at discharge was measured. The APACHE (Acute Physiology, Age, Chronic Health Evaluation) II score, the quantity ingested, exposure route, gender, age, and the laboratory test results were collected. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 20.0).
Results: Overall 102 (89.5%) patients intentionally ingested the OP and the mean volume ingested was 102.5 ± 64.9 mL. The mean time from ingestion to when patients sought medical care was 5.4 ± 10.5 hours. Mean SChE activity at admission was 1586 ± 796 U/L and APACHE II score was 28.81 ± 19.7. The arterial pH, bicarbonate and PCO_2, and serum protein and albumin were significantly lower in the IMS group than the non-IMS group. In contrast, the serum amylase, lipase, and glucose were higher in the IMS group. The APACHE II score, serum albumin and amylase, arterial bicarbonate, and the SChE at 48 and 96 hours after ingestion were independent factors that predicted the occurrence of IMS in patients with OP poisoning. The rate of recovery was 86.6% in the IMS group and 100% in the non-IMS group.
Conclusion: Patients with a higher APACHE II score and concentrations of serum amylase, and lower concentrations of serum albumin and arterial bicarbonate, may be at risk of IMS. Furthermore, patients with SChE activity that did not increase after 48 hours and 96 hours, compared to the activity at admission, were more like to develop IMS.

Reference

[1] Abdollahi M, Karami-Mohajeri S. A comprehensive review on experimental and clinical findings in intermediate syndrome caused by organophosphate poisoning. Toxicol Appl Pharmacol. 2012;258:309–314.

76. An outbreak of bromadiolone poisoning after ingestion of treated rice

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Objective: Bromadiolone, a second-generation anticoagulant rodenticide, is used worldwide. In China, bromadiolone is usually a pink liquid to be mixed with some grains such as rice and corn, to prevent mistaking the treated grain for food. Repeated small dose exposures are also likely to produce cumulative toxicity. We described mass poisoning involving six people.
Case series: Six Taiwanese working in China presented to the emergency department with several days' history of gingival oozing, multiple sites of ecchymosis and hematuria. They had eaten some kind of pink rice three weeks ago when they were working in China. On physical examination, their vital signs were stable. Five patients had multiple sites of ecchymosis and three had prolong prothrombin time (PT) (>81 s). All of them were admitted to our toxicological ward and received vitamin K anticoagulant therapy. One patient had lower back pain radiated to the right leg. The nerve conduction velocity results showed bilateral S1 and left L5 intraspinal lesion. Magnetic resonance imaging showed extramedullary-intradural spinal hematoma at the L1-L2 level. He was treated conservatively. The serum concentrations of bromadiolone were 6.17–74.5 mg/L. All patients were discharged after intravenous vitamin K therapy with all bleeding tendency symptoms resolved. Two patients continued with oral vitamin K due to persistent prolongation of the PT.
Conclusion: In humans, the half-life of bromadiolone is 243–1656 hours, compared to 17–37 hours for warfarin [1,2]. Bromadiolone is commonly used in China. Ingestion of a small amount does not cause significant symptoms. In our cases, they ate the rice every day, so all developed variable degrees of coagulopathy. The clinical manifestations of bromadiolone toxicity can include vaginal bleeding, epistaxis, hematuria, bleeding from the gums, ecchymosis, gastrointestinal bleeding, spontaneous abortion, hemoptysis, abdominal pain, and intracranial haemorrhage [3]. Abdominal compartment syndrome, haemarthrosis and

intestinal obstruction are also reported. One of our patients had a rare manifestation of spinal hematoma after bromadiolone poisoning.

References

[1] Weitzel JN, Sadowski JA, Furie BC, et al. Surreptitious ingestion of a long-acting vitamin K antagonist/rodenticide, brodifacoum: clinical and metabolic studies of three cases. Blood. 1990;76:2555–2559.

[2] Stanton T, Sowray P, McWaters D, et al. Prolonged anticoagulation with long-acting coumadin derivatives: case report of a brodifacoum poisoning with pharmacokinetic data. Blood. 1988;72:310A.

[3] Wu YF, Chang CS, Chung CY, et al. Superwarfarin intoxication: hematuria is a major clinical manifestation. Int J Hematol. 2009;90:170–173.

77. The economic efficiency of the Belgian Poison Centre and its impact on national healthcare expenses

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Objective: In times of budgetary constraints, the Belgian Poison Centre sought to examine its potential impact in terms of public healthcare expenses. This study evaluates the value of the Poison Centre in the Belgian health system through a cost-benefit analysis in two cases: the presence or absence of the Poison Centre.
Methods: Different methods were used to gather all information needed to create a decision tree: a 7-day telephone survey (February/March 2016), a statistical analysis of all data of the period of the survey and of all data 2010–2015 from the Poison Centre. The costs of the Poison Centre in combination with a visit to a general practitioner and/or a hospital were compared. Through a cost-benefit analysis, including a decision tree, we calculated the cost–benefit ratios in the scenarios of presence or absence of the Poison Centre. The ratios were calculated for incoming calls coming from the public related to an unintentional intoxication and for incoming calls related to any type of poisoning both from public and medical professionals.
Results: The presence of a Poison Centre provides a positive cost–benefit ratio, compared with the absence of a Poison Centre. In the scenario of an unintentional intoxication the cost–benefit ratio is 4.37 (€43.68/€190.78). In the scenario taking into account all types of intoxication, the cost–benefit ratio is 1.6 (€117.25/€190.78). The average cost of a call to the Poison Centre is €25.87. In the case of an unintentional intoxication, the cost for the Poison Centre represents 59.2% of the total cost (€25.87/€43.68). The other 40.8% is allocated to the cost related to the general practitioner and/or the hospital. For all types of intoxications, the cost for the Poison Centre only represents 22.1% (€25.87/€117.25) versus 77.9% allocated to the cost of the doctor and/or the hospital.
Conclusion: It is recommended to encourage the public to first contact the Poison Centre in case of a supposed intoxication. The activities of a Poison Centre are cost-efficient as the efficient triage it provides saves money.

78. Calls to the Finnish Poison Information Centre concerning poisoning during pregnancy 2001–2015

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Objective: To explore calls to the Finnish Poison Information Centre (FPIC) concerning poisoning during pregnancy. FPIC can consult the Teratology Information Service (TIS) about calls concerning pregnant patients and poisoning during office hours. The TIS is affiliated to the FPIC, and both function side by side sharing the same premises.
Methods: Calls concerning pregnant patients during 2001–2015 were retrieved from the FPIC database and grouped according to exposure, e.g., detergents, medicine (intentional/accidental exposure), mushrooms, plants, petroleum products, poisonous gases, thermometers and viper bites.
Results: The FPIC receives approximately 35,000 calls/year from healthcare professionals and the public. The total number of calls concerning pregnant patients and poisonings during 2001–2015 was 662. The number of calls concerning pregnant patients and poisoning have increased over the years, being 23 (0.09%) out of 25,556 calls concerning acute poisonings in 2001 and 63 (0.22%) out of 28,562 in 2015. The number of calls concerning pregnant patients and poisoning peaked in 2012 with 74 (0.25%) out of 30,139. The biggest exposure groups were medicines (27.3%, $n = 181$), detergents (17.8%, $n = 118$) and poisonous gases (15.3%, $n = 101$). Other groups of exposure were plants (5.7%, $n = 38$), petroleum products (3.5%, $n = 23$), mushrooms (2.9%, $n = 19$), snake bites (2.1%, $n = 14$), thermometers (2.2%, $n = 15$) and others (23.2%, $n = 153$). Most common medicine exposures were: psychopharmaceuticals, 43 calls in total (35 intentional); paracetamol (repeated and acute overdose), 20 in total (12 intentional); levothyroxine, 20 in total (4 intentional); iron supplementation, 14 in total (4 intentional) and veterinary medicines, 14 in total (none intentional).
Conclusion: Poisoning in pregnancy is a challenging topic and requires safety assessment of both the mother and the child. In some exposures, for example carbon monoxide and snakebites, pregnant patients are treated more actively, but in most situations, treatment of the poisoned pregnant patient follows the same protocol as for a non-pregnant patient. The FPIC is in a unique position to collaborate with the Teratology Information Service.

79. Changes in smoking habits and the sales of nicotine replacement therapy seem to explain the variation in the number of calls to FPIC concerning nicotine exposure

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Objective: To explore the relationship between the use of nicotine products and nicotine replacement therapy (NRT) to the number of calls to the Finnish Poison Information Centre (FPIC) related to these substances.
Methods: Calls to FPIC from June 2000 to December 2014 concerning nicotine and tobacco products were extracted from the FPIC database. Finnish Tobacco Statistics data from the National Institute of Welfare and Heath, based on annual randomised postal research with standardised age groups, and Finnish Statistics on Sales of Medicines NRT products (in defined daily doses per 1000 inhabitants/day) from the National Agency for Medicines and the Social Insurance Institution were used for comparison. Spearman's rho (correlation coefficient r_S) was used to explore the relationship between the prevalence of tobacco use, the sales of NRT products, and the number of FPIC calls.
Results: From 12,066 calls retrieved, duplicates and irrelevant product subcategories (not containing nicotine) were excluded, leaving 11,364 calls to FPIC concerning nicotine products for analysis. Of them, 80% concerned combustible nicotine products (cigarettes, cigarette butts and cigars), medicinal nicotine 12%, snuff 8%, and e-cigarettes 1%. The majority (87%) of enquiries concerned children aged ≤2 years. During the 15-year study period, annual nicotine-related calls to FPIC decreased from over 800 to less than 700 calls/year, mainly due to the fall in the number of conventional cigarette and cigarette butt enquiries, paralleling a decrease in smoking prevalence (r_S=0.981, $p < .001$). The proportion of smokers in the Finnish population explained 95% of the yearly variation in the number of FPIC calls (r^2=0.953) concerning combustible nicotine products. Increase in the proportion of calls concerning snuff (from 5 to 16%) and NRT products (5 to 15%) was observed. The sales of NRT products increased by 3.6-fold and calls concerning these products by 2.5-fold, the former explaining 93% of the yearly variation in the latter. FPIC calls concerning NRT and the sales of NRT were in-line (r_S = 0.890, $p < .001$). During the years 2012–2014, the proportion of FPIC calls due to e-cigarettes rose from 0 to 8%.
Conclusion: New trends such as e-cigarettes appear quickly in FPIC calls concerning nicotine exposure. For the last 15 years, in general, these calls have followed closely both the population smoking prevalence and the wholesale sales of nicotine replacement products.

80. Exposure to fabric protector sprays: analysis of trends and clinical features reported to the UK National Poisons Information Service, 2008–2014

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Objective: Aerosolized fabric protectors typically consist of a waterproofing agent, usually a fluorinated carbon polymer, a solvent and a propellant, such as propane or butane. Cases of clinical features related to the use of fabric protector sprays have been reported in the literature. This study aimed to analyse the UK trend in enquiries to the National Poisons Information Service (NPIS) related to exposure to aerosolised fabric protectors.
Methods: Enquiries to the National Poisons Information Service and stored on the UK Poisons Information database (UKPID) concerning fabric protectors between April 2008 and April 2014 were analysed.
Results: A total of 69 telephone enquiries were received. The number of enquiries per year were 13 in 2008, 10 in 2009, 14 in 2010, 18 in 2011, six in 2012, six in 2013 and two in 2014. Fifty-eight exposures occurred in the home, nine in the workplace, one in a public place and one in an unknown venue. Sixty-four exposures were accidental, two were from recreational abuse, two were thought to be adverse reactions and one was unknown. Fifty enquiries related to inhalation, 11 to ingestion, three to skin contact and three to eye contact. One enquiry related to both ingestion and eye contact and one related to inhalation and skin contact. Of all calls received, 19% of patients were aged under 5 years, 2% were between 5 and 9 years, 2% were between 10 and 17 years, 20% were between 20 and 29 years, 21% between 30 and 39 years, 19% between 40 and 49 years, 7% between 50 and 59 years, 3% between 60 and 69 years and 7% were of unknown age. Thirteen patients (19%) were asymptomatic. Dyspnoea was the most common feature, reported in 17 patients (25%), followed by coughing and bronchospasm in 12 (17%), chest pains in seven (10%), headaches in six (9%), nausea in five (7%), hypoxia in three (4%), dizziness in three (4%) and general irritation in three (4%). Twenty patients were referred to their local Accident and Emergency Department for monitoring, supportive care, investigations and irrigation, where necessary.
Conclusion: The number of enquiries concerning fabric protectors has declined over the last two years. The majority of exposures were in the age range of 20–49 years and occur accidentally, by inhalation, in the home. The majority of patients suffered from mild respiratory symptoms, however, more severe symptomatology was reported in a minority of patients.

81. How tackling an increase in call volume resulted in a drop of complaints at a Poisons Information Center (PIC)

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Objective: In 2015, our PIC had a recurrent problem of telephone callers being placed in a queue during weekends. This was because only one member of staff was available to take calls in the late afternoon and early evening hours. This was experienced as very stressful by most Specialists in Poison Information (SPIs). In January 2016, the roster for all days of the week was altered so as to guarantee more than one person available at peak hours. In addition, an extra shift was implemented during the peak hours at weekends. Our aim was to investigate whether the new roster had a significant impact on the average waiting time before receiving an answer and the rate of complaints about this wait time for callers using the PIC.
Methods: Data concerning call volume and wait time were collected over time using a computerized system. Complaints were separately registered. Time was divided in two periods: before (January–August 2015) and after the implementation of the new work schedule (January–August 2016). For the statistical analyses, a mixed model was used to test the difference in the number of calls over the two years. Interrupted Time Series analyses were used to test significant changes in average wait time and rate of complaints.

Results: The PIC received significantly more calls in 2016 than in 2015 (mean monthly increase of 180 calls) ($p = .005$). The average waiting time before receiving an answer decreased from 87 seconds in 2015 to 73 seconds in 2016 ($p = .01$). The change in the weekends was even larger: from 108 seconds in 2015 to 82 seconds in 2016 ($p = .007$). Furthermore, the number of complaints decreased from 114 in 2015 to 40 in 2016 during the week, and from 44 in 2015 to 11 in 2016 during the weekends (significant decrease in complaint rate, $p = .04$).
Conclusion: Despite a larger call volume in 2016 compared to 2015, the new roster, without employing new SPIs, resulted in a significant decrease both in the wait time before receiving an answer, and in the rate of callers' complaints. Listening to SPIs complaints followed by an improved use of human resources at peak hours has increased the PICs efficiency, without additional financial costs.

82. Human tilmicosin exposures, clinical features and outcome: a review of enquiries received by the UK NPIS, 2008–2016

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Objective: Tilmicosin phosphate is a semi-synthetic macrolide antibiotic indicated to treat infections in ovine and bovine populations. It is available only on a veterinary prescription (300 mg/mL solution, 50 mL and 100 mL vials) [1] with excipients including propylene glycol and phosphoric acid. Given as a single injection it has little toxicity to livestock but has been associated with serious features and deaths in humans.
Methods: Enquiries to the National Poisons Information Service (NPIS), stored on the UK Poisons Information Database (UKPID), concerning human tilmicosin exposures (between September 2008 and August 2016) were retrospectively reviewed. Clinical features, outcomes and circumstance of exposure were analysed.
Results: Twenty-two enquiries involving human tilmicosin exposures were received by the UK NPIS over the study period. Of these, nine enquiries related to four patients. A total of sixteen patients were included in these data. A distinct seasonal pattern was observed with 63% ($n = 10$) of cases occurring between December and March. All cases were acute exposures, 13% ($n = 2$) occurring with suicidal intent. No clear distinction in gender was found (male 56%). All patients were adults and where known, were aged 17–56 years. Needle-stick injuries accounted for 25% of cases ($n = 4$), with ingestion and ingestion with concurrent skin contact each accounting for 19% ($n = 3$). Other exposure routes included intravenous injection ($n = 2$), subcutaneous injection ($n = 2$), eye ($n = 1$) and skin contact ($n = 1$). Both intravenous exposures resulted in death. Severe features of toxicity occurred in one patient after tilmicosin ingestion and skin contact (Poison Severity Score [PSS] 3/MAXPSS3). Other routes reported either nil or minor features (MAXPSS0 or MAXPSS1). Features of toxicity occurred within 45 minutes of exposure and in some cases, persisted for up to 3 days. Hypotension, acidosis, cardiac arrest, coma and death were reported following intravenous administration. Six patients remained asymptomatic following accidental exposure: needle-stick/subcutaneous injection ($n = 5$) and ingestion ($n = 1$).
Conclusion: Most cases of exposure to tilmicosin are accidental. Severity of clinical effects in humans depends on the route of administration. Intravenous injection is the most likely route causing severe clinical effects. To date IV injection is the only known route of administration to have caused death in the UK; however, there are reports of deaths following accidental needle-stick injections elsewhere.

Reference

[1] Micotil® 300. Summary of product characteristics [Internet]. Elanco Animal Health [cited 2016 Sep 20]. Available from: http://www.vmd.defra.gov.uk/productinformationdatabase/SPC_Documents/SPC_134985.DOC

83. Impact of Zika virus spread on a Florida Poison Information Center

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Objective: Florida has been the state hit hardest by the northward spread of the Zika virus to the US. On 3 February 2016, the Governor declared a state of emergency followed by the establishment of a state-specific information hotline on 12 February 2016 [1]. The Florida Poison Information Network consisting of three Poison Control Centers assumed the duties of answering all hotline calls within days of its creation [2]. Although the additional call volume has opened up supplemental funding opportunities, it has also added strain on the ability of the centers to manage its toxicological duties [3].
Methods: We evaluated the monthly call volume of one of the three Poison Centers for six months including the proportion of Zika and non-Zika calls following the hotline stand up. Modifications to operations including duty hours and funding streams were analyzed.
Results: A wide variation in Zika-related calls was noted from less than 10% to greater than 70% of total call volume. For more than half of August, Zika-related call volume exceeded a 25% call volume threshold. Delays in Zika funding at the federal and state level have placed budgetary restraints on monthly operations.
Conclusion: Zika has had and continues to impact the Florida Poison Information Network. Non-toxicological and finite but sustained preparedness place the greatest strain on the staff and operations of the Poison Centers.

References

[1] Florida Health. Department of Health Daily Zika Update [Internet] [cited 2016 Oct 17]. Available from: http://www.floridahealth.gov/newsroom/2016/10/101716-zika-update.html
[2] American Association of Poison Control Centers (AAPC) Press release [Internet]. Nation's Poison Centers Provide Assistance Combating Zika Virus Concerns [cited 2016 Oct 29]. Available from: http://www.aapcc.org/press/65/
[3] Darracq MA, Clark RF, Jacoby I, et al. Disaster preparedness of poison control centers in the USA: a 15-year follow-up study. J Med Toxicol. 2014;10:19–25.

84. Primary poisoning prevention and awareness: the Estonian experience

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Objective: With decreasing resources, it is important to consider what role toxicologists and poison centers (PC) play in poison prevention (PP). While PCs have demonstrated their expertise in the treatment of poisonings (secondary and tertiary prevention), it is equally important to act in primary prevention [1,2], reducing the occurrence of poisonings and raising awareness of the PC [3]. We describe the national multilevel effective prevention interventions and ensuring the messages reach all target groups of the population (1.3 million).
Results: In Estonia secondary prevention was delivered through the hotline (16662) and broader primary PP through interventions, simultaneously at the national, county and local community level. The PC had the opportunity to intervene in the shaping of legislation, poisoning prevention strategies and discussion in the county's supervisory boards of injury prevention to carry out projects of health education. In 2009–2014 hospital and ambulance medical staff was routinely educated (178 hours) and training on effective prevention strategies were provided to the general public (115 hours). As well as the website (16662.ee), articles provided continuous warnings about poisons through the media (newspapers, television, radio; 225 times). The PC also participated in developing a prevention-related educational toolkit, the floor game AgaMina/ButMe (http://agamina.ee/porandamang/), with a cartoon http://www.16662.ee/lastele.html and coloring books and playing cards for children. In 2009–2015 awareness of the PC's hotline was increasing (calls increased from 331 to 2461), and a nationwide survey showed awareness about the hotline increased from 16% (2011) to 18% (2014). There was a decrease in the number of accidental deaths from poisonings (309 in 2009 and 235 in 2014) and the number of emergency calls due to poisonings via the ambulance service decreased from 2538 calls (2009) to 1597 calls (2014).
Conclusion: Integration of primary PP activities of the national PC into a coherent model of public health services can be used as an effective toolkit for increasing awareness of PP and decreasing the number of poisonings. It therefore may have an impact in reducing healthcare costs through decreasing the number of poisoned patients and having a defensive role in ensuring the security of the population.

References

[1] Krenzelok E, Mrvos R, Mazo E. (2008) Combining primary and secondary poison prevention in one initiative. Clin Toxicol. 2008;46:101–104.
[2] Marcus SM. Poison prevention: engineering in primary prevention. Clin Toxicol. 2012;50:163–165.
[3] Põld K, Oder M. The effect of active poisoning information education on the call volume and structure. Clin Toxicol. 2011;49:241–241.

85. Publicity as a public relation strategy in poisons information centre survival

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Objective: Within the last few years two neighbouring Poisons Information Centres (PIC) have been abolished, among others, due to financial reasons. The study aims to show the correlation between media coverage and people's perception of the causes of accidental death compared to statistical data. This information might be used to increase recognition among the public and politicians of the importance of PICs.
Methods: The following search string (in Danish) "news death <insert cause of death >" was used in Google search engine. The number of hits for each death cause was compared with statistical data from the Danish Health Data Authority (2014, absolute figures). A Facebook poll among author's friends was used to gather data about perceived causes of accidental death. Annual budgets for the Danish PIC [2] and Ministry of Transport improvements in traffic safety [3] were used for comparison.
Results: With focus on poisoning and traffic accidents the results from the statistics show that fatal cases from traffic accidents and death by poisoning is almost the same (Table 1). The news coverage (Google) is much higher for traffic-related deaths. The results are supported by a Facebook poll where traffic death was voted as the most common cause for accidental death. Poisoning was far behind.
Conclusion: Substantial governmental investments in traffic safety have led to continuously declining death rates [1]. Those investments are many times the annual budget of the Danish PIC [2,3]. Politicians would typically invest most in the areas that are perceived important by public. Therefore we need to create publicity and use PR to increase awareness and achieve higher financing priority.

References

[1] Danish Health Data Authority Register of death causes p33. [cited 2017 Mar 29]. Available from: http://sundhedsdatastyrelsen.dk/-/media/sds/filer/find-tal-og-analyser/andre-analyser-og-rapporter/doedsaarsagsregisteret/doedsaarsagsregisteret_2014.pdf?la=da
[2] Annual Budget Ministry of Health p7. [cited 2017 Mar 29]. Available from: https://www.fm.dk/~/media/publikationer/imported/2015/afl15/16-ministeriet-for-sundhed-og-forebyggelse.ashx?la=da
[3] Annual Budget Ministry of Transport p24. [cited 2017 Mar 29]. Available from: https://www.fm.dk/~/media/publikationer/imported/2015/afl15/28-transportministeriet.ashx?la=da

Table 1. Comparison of data from the Danish Health Data Authority (2014), Google search, Facebook poll results and annual budgets for the Danish PIC and Ministry of Transport improvements in traffic safety.

Accidental death	Statistics		Google hits		Facebookpoll		Budget (million Euro)
Fall	50.5%	514	4.6%	27700	6.2%	5	
Poisoning	21.1%	215	6.8%	41100	19.8%	16	1.24
Traffic	20.7%	209	12.4%	75700	53.0%	43	9.84
Drowning	3.9%	40	18.9%	115000	Other causes		
Murder	3.8%	39	57.3%	349000	21.0%	17	

86. Risks from and concerns about methamphetamine exposures: a review of enquiries to the New Zealand Poisons Centre

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Objective: "Recreational" use of methamphetamine ("P") has been a significant issue in New Zealand for several years. Makeshift clandestine "laboratories" are important sources of exposure to this drug. The aim of this study was to utilise NZ Poisons Centre data to help assess current concerns regarding its manufacture and use.
Methods: All poisons call records concerning methamphetamine for a 3-year period from July 2013 to June 2016 were reviewed. The enquiries were classified according to whether they related to an exposure (actual or potential) or were requests for information only. Our recorded descriptions and assessments of the incidents were also reviewed.
Results: There were 217 individual situations giving rise to a total of 236 calls over this period. Of total calls, 128 concerned actual or potential exposures (121 human, 7 animal) and 108 involved requests for information only. Of the latter, there were 25 related to risks/contamination after manufacturing methamphetamine, 23 calls regarding testing of a person for exposure, 15 calls regarding potential secondary exposure arising from the smoking of methamphetamine by others, 12 concerning clean-up of premises, 9 regarding testing of property or possessions, 5 related to potential risks during pregnancy or breastfeeding, and 19 calls were other miscellaneous enquiries. In some cases irritant symptoms or detection of odours on entering a residence precipitated enquiries as to whether it could have previously been the site of a methamphetamine laboratory. Concern extended to the potential risk (especially to young exploring children) from contamination of homes where residents smoked or previously smoked methamphetamine. Anxiety also arose when surface concentrations of methamphetamine modestly exceeded the Ministry of Health Guidelines adopted remediation standard for clandestine laboratory sites of 0.5 µg/100 cm^2 (0.005 µg/cm^2) [1].
Conclusion: There exists a relatively high level of concern in New Zealand regarding chronic unsuspected residential exposure to methamphetamine, which could arise either due to unrecognised contamination or inadequate remediation of affected houses. The concern involves not only former P Labs but also increasingly houses where methamphetamine has or might have been smoked. There is limited knowledge of the basis for the Ministry of Health Guidelines adopted remediation standard for surface concentrations of methamphetamine. While this is generally in the range of other international standards, it is conservative and its slight exceedance likely does not imply immediate tangible health risk.

Reference

[1] Ministry of Health. Guidelines for the remediation of clandestine methamphetamine laboratory sites. New Zealand: NZ Ministry of Health; 2010.

87. The CLP Unique Formula Identifier (UFI) for hazardous mixtures will help poisons centres (PC) give the best advice and will increase the value of PC case records for regulatory risk assessment under REACH

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Objective: Soon the European Commission (EC) will fix a harmonised European format for product data to be submitted to poisons centres (PC). This will include the "Unique Formula Identifier" (UFI) which will be printed on many labels in the future. The meaning of UFI for PC daily work and for regulatory activities needs investigation.
Methods: EC Regulations directed to chemical safety, i.e., the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC No 1907/2006) and the latest draft of Classification, Labelling and Packaging (CLP) Regulation (EC No 1272/2008) amendment (including the new Annex VIII) were analysed with respect to the role of UFI in PC daily service and the scientific value of PC case documentation.
Results: Each UFI, a 16-character alphanumeric code, is linked to one specific product formula. Access to UFIs will facilitate identification of a formula in the PC database, even if the product name is unclear. In most cases transmission of only a few UFI characters will allow reliable product identification. The harmonised European format will allow product data notification using a reference to another notification, called "mixture in mixture" notification (e.g., Mixture A contains 100% Mixture B). In these cases, the UFI will secure processing and evaluation of the real formula. Furthermore, the UFI might be included in PC case documentation in the future. Case documents including UFI could be used for regulatory toxicology evaluations, i.e., as a valuable source for "REACH Monitoring"; REACH is "aiming to achieve that chemicals are produced and used in ways that lead to the minimisation of significant adverse effects on human health (and the environment)". This goal would mainly be achieved by reducing the exposure of workers and consumers to chemical substances of high toxicological concern. PC case documentation could be used as a probe for exposures to substances under investigation if case datasets would contain comprehensive information, not only on products patients were exposed to but also on product formulations. This goal could easily be achieved by including the UFI in case documentation for an unambiguous link between the product name given on the telephone and formula information in the database.
Conclusion: By 2020, UFI will support PCs in identification of hazardous products. Including UFI registration in PC case data recordings would provide a valuable source for exposure assessment related to chemical substances of the European population that might be used to assess a general goal of REACH, the reduction of hazardous exposures to chemicals.

88. The role of the Serbian National Poison Control Center in the management of poisoning in children

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Objective: Data on pediatric poisoning in Serbia are scarce. The Serbian National Poison Control Centre (NPCC) provides services for the population of about 7 million people, which consist of telephone information, treatment of poisoning, and determination of xenobiotics in biological material. The treatment applies only to the patients over 14 years of age, while younger patients are treated in pediatric hospitals. Based on telephone calls, we assessed the frequency and causes of poisoning in children.
Methods: Analysis of calls to the Centre during a 3-year period (2013–2015) revealed that children represent a significant proportion of enquiries (28–37%) to the centre from doctors or citizens requesting help from the information service in order to recognize and treat possible poisoning.
Results: The NPCC receives a relatively small number of telephone calls in comparison with the number of treated patients (about 800 calls versus more than 4000 patients per year in recent years). The calls are mainly received from medical doctors, pediatricians (81%), or children's parents (18%) and rarely from children's organizations (those with children in their care and telephone support services) (1%). The most frequently suspected toxic exposures include accidental ingestion of drugs belonging to family members, or prescribed to the child, but given by parents in doses higher than recommended (31%), miscellaneous household products and cosmetics (24%), pesticides (8%), plants and mushrooms (5%), some small items like silica gel balls, parts of toys or button batteries (5%), solvents (3%) and alcohol (2%). The rest are suspected harmful effects of gases or questions about the possibility of poisoning as the differential diagnosis of vague disorders in children. More than 90% of enquiries relate to children of 6 years or younger. There were no cases with lethal outcome.
Conclusion: NPCC data on current trends in pediatric exposure to toxic agents in Serbia can help more efficient management of poisoning in children. The main goals should include education of pediatricians to recognize toxic and non-toxic exposures and efforts on prevention of exposure to harmful chemicals, especially medications.

89. Therapeutic errors: the experience of the Florence Poison Center

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Objective: A medication error is an unintended failure in prescribing, dispensing, storing, preparing or administering a medication that leads to or has the potential for patient harm [1]. Therapeutic errors are widely described in the hospital setting, while little information is available for those occurring in outpatient settings. We analysed cases of medication error reported to the Poison Center of Florence Careggi University Hospital.
Methods: Case data for the period January 2011 to December 2015 were searched for cases relating to medication errors.
Results: Over the study period the Poison Center received 20,840 calls, of which 1143 (5.5%) were related to therapeutic errors. Requests were received from private citizens ($n = 469$; 41.0%), hospitals ($n = 372$; 32.5%), on-call doctors ($n = 206$; 18.0%), and family doctors ($n = 48$; 4.2%). Most therapeutic errors occurred at home or at work ($n = 1076$; 94.2%), while 5.8% occurred in healthcare facilities. Of the total sample, adults represented 50.5% ($n = 577$). Children under 5 years of age represented 33.7% ($n = 378$), while children aged between 6 and 18 years represented 13.4% ($n = 153$). The most frequent medications involved were psychotropic drugs (22.5%), antibiotics (10.8%), non-steroidal anti-inflammatory drugs (NSAIDs) (9.9%), cardiovascular medications (9.6%), anti-asthmatic medications (9.2%), opioids (4.9%), hormones and vitamins (2.6%), while the remaining 26.9% included other drugs. More than 75% of all patients that required a toxicology consultation were asymptomatic ($n = 866$). A medical examination was recommended for only 15% of patients. Most patients were kept at home without any medical treatment (69.3%). Symptomatic treatment was sufficient in 20.2% of the sample, while decontamination was necessary for 8.4%. Less than 2% of patients needed antidotal treatment.
Conclusion: Although the hospitalization rate is low and toxicology consultation is effective in reducing inappropriate hospital admissions, therapeutic errors are still an important cause of calls to poison centers. The activities of poison centers, pharmacovigilance centers, physicians, and the pharmaceutical industry should be improved in order to promote safe and appropriate drug use, risk reduction, and error prevention.

Reference

[1] Koren G. Trends of medication errors in hospitalized children. J Clin Pharmacol. 2002;42:707–710.

90. Trends in enquiries to the UK National Poisons Information Service (NPIS) involving "preschool" (0–4 years) children in 2015. Might knowledge of circumstances help plan prevention strategies?

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Objective: To investigate trends in the ingestions of the "preschool" population to see if knowledge of circumstances of exposures might help in planning prevention strategies to prevent suspected poisonings. The UK National Poisons Information Service (NPIS) receives around 47,000 telephone calls annually and around 30% concern children less than five years old.
Methods: Telephone enquiries to the NPIS, recorded on the UK Poisons Information Database (UKPID), were analysed retrospectively from 1 January to 31 December 2015 inclusive.

Results: There were 13,690 enquiries to the NPIS regarding children aged 0–4 years. Most had a feature code of "asymptomatic" ($n = 11,748$, 86%), and 11,763 (86%) had a corresponding poisons severity score of 0 [1]. Most were classed as accidental (93%) and occurred in the home (92%). The majority of exposures were in children between 1 and 2 years of age (37%). Older children had a slightly higher likelihood of symptoms occurring after exposures; 15% developing minor and 2% moderate features in the 4-year-olds compared to a 12% and 1% average. Therapeutic errors only accounted for 773 enquiries (6%), but were far more common in children under 1 year (45%), mostly occurring in the home, although some enquiries were regarding therapeutic errors from general practitioners (GPs) and hospitals (14%). The time of exposure is bimodal with a peak between 17:00 and 20:00 and another shallower peak between 10:00 and 14:00. This pattern is more pronounced in children between 1 and 2 years (27% calls between 17:00–20:00 and 20% between 10:00 and 14:00) but is present within most age groups, apart from the 4-year-olds which shows a fairly flat distribution throughout the day, with a small increase hourly, up until 21:00. In children less than 1 year old, the earlier peak is absent but still shows that most exposures occur between 17:00 and 20:00 (25%). There is no noticeable correlation between severity of symptoms and time, apart from the times most exposures occur.
Conclusion: It is reassuring that exposures within this demographic are mostly asymptomatic. Whilst the vast majority of cases are accidental they seem to coincide with particular times of day, e.g., mealtimes or possible times for medicine administration. These results suggest that it could be worth exploring in more detail the circumstances of exposure to inform the targeting of prevention programmes; for example, are parents distracted at mealtimes?

Reference

[1] Persson HE, Sjöberg JK, Haines JA et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.

91. Venlafaxine overdoses reported to the UK National Poisons Information Service over a 5-year period

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Objective: Venlafaxine is a selective serotonin and noradrenaline reuptake inhibitor licensed in the UK. Death is frequently attributed to cardiac toxicity (early) or the complications of serotonin syndrome (late). We reviewed enquiries to the UK National Poisons Information Service (NPIS). We also reviewed the literature to determine the relationship between reported dose and death where venlafaxine was taken alone and analytical confirmation was present.
Methods: Records of telephone enquiries received by the NPIS, between 1 April 2011 and 31 March 2016, stored on the UK Poisons Information Database (UKPID) were reviewed. A literature search of PUBMED and MEDLINE was conducted to identify reports of analytically confirmed fatalities associated with ingestion of venlafaxine alone.
Results: A total of 656 enquiries regarding venlafaxine overdoses were received by the NPIS during this period. Of these 430 involved overdoses in females, 216 in males, 10 were unrecorded ($p < .01$). The ages ranged from less than one year to 95 years old. Overall 346 cases (53%) were reported as asymptomatic, 44 (6%) experienced cardiovascular features, 28 (4%) neurological disorders including convulsions, tremors, confusion, rigors and nervousness and 23 (3.5%) had gastrointestinal effects. Seventeen patients (2%) had a Poisoning Severity Score of severe (PSS3), 43 (7%) were moderate (PSS2), 184 (28%) were minor (PSS1) and 376 (57%) were given a score of zero (PSS0). For enquiries reported to the NPIS the mean dose with a Poisoning Severity Score of zero was 1.2 g with PSS1 was 1.9 g, with PSS2 was 4.1 g and with PSS3 was 6.4 g. The literature search identified six papers, describing a total of nine cases where venlafaxine was measured. Five patients died and four recovered. The majority of deaths occurred within 30 hours of exposure despite receiving supportive care. The reported doses taken ranged from 37.5 mg to 18 g (median dose 750 mg). The average reported dose taken by those who died was 11.3 g (±5.8 g) and the average dose of those who survived was 6.8 g (±2.3 g) ($p = .178$).
Conclusion: There is a positive link between the dose of venlafaxine and the Poisoning Severity Score. The lowest reported ingested dose with analytical confirmation associated with death was 4.2 g and the highest dose survived was 15 g of a modified release preparation.

92. Vietnamese centipede: a new trend in dangerous pets?

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Objective: To analyse enquiries made to the UK National Poisons Information Service (NPIS) concerning Vietnamese centipede (*Scolopendra subspinipes*) bites. The Vietnamese centipede is a large species of arthropod native to America, Asia, Australia, and Africa. The adults usually grow up to 20 cm in length. They can be found in zoos and have recently started being sold as household pets in the UK. Toxins found within the venom of the Vietnamese centipede include serotonin, polypeptides, enzymes, histamines, and cardiotoxic proteins, cytolysin, proteinases and lipoproteins [1]. Features of envenoming include vomiting, oedema, erythema, chest pain, palpitations, and necrosis. Lymphangitis and lymphadenopathy have rarely been reported. Allergic reactions to the venom, including anaphylactic reactions, have been described. Single cases of rhabdomyolysis and renal failure, and acute coronary syndrome have been reported [2].
Methods: Telephone enquiries to the NPIS recorded on the UK Poisons Information Database (UKPID) between 1 January 2008 and 31 August 2016 relating to exposures concerning Vietnamese centipede bites were examined to determine incidence and clinical features.
Results: During this period, the NPIS received 19 enquiries relating to centipede exposures, of which four were related to Vietnamese centipede bites. All cases were reported in 2015, three included single bites from a household pet in a domestic setting and one was a workplace exposure in a pet store involving a total of three bites over two limbs. The cases involved two males aged 18 and 20 years and two females aged 51 and 55 years. The patients were assessed in hospital between one and 12 hours post-exposure and had all developed mild features

including oedema, paraesthesia and erythema. This corresponded to a maximum Poisoning Severity Score (MAXPSS) of 1.
Conclusion: As the Vietnamese centipede increases in popularity as a household pet in the UK, the incidence of bites sustained by patients is likely to become more frequent. Although serious outcomes were not encountered in this small case series, patients should be observed closely, treated supportively and clinicians should be aware of the rare but serious features that can develop.

References

[1] Logan JL, Ogden DA. Rhabdomyolysis and acute renal failure following the bite of the giant desert centipede *Scolopendra heros*. West J Med. 1985;142:549–550.
[2] Fung HT, Lam SK, Wong OF. Centipede bite victims: a review of patients presenting to two emergency departments in Hong Kong. Hong Kong Med J. 2011;17:381–385.

93. The impact of repackaging from bottle to blister on paediatric intoxications with the levothyroxine brand Thyrax®

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Objective: In December 2013, the packaging of levothyroxine with the brand name Thyrax® was changed by the manufacturer from a bottle to a blister pack in order to improve protection against various environmental factors such as light, air, and humidity. We hypothesized that this change also increased child safety, and analysed the telephone inquiries to our Poisons Information Center (PIC) to investigate the influence of this repackaging on intoxications in young children.
Methods: Cases of exposure and acute overdose with Thyrax® in children under 7 years were included from January 2010 to December 2015. A bottle of Thyrax® contained 90 tablets, so it is likely that between January and March 2014 patients were still using the remaining tablets from their bottle. Cases from January to March 2014 were therefore considered not representative for evaluating the effect of repackaging. Trends in the number of cases per month before and after repackaging were compared using Interrupted Time Series analyses. An unknown dose or an ingested dose of more than 0.05 mg/kg of levothyroxine was defined as a toxic dose. The proportional decreases in the number of cases exposed to a toxic versus a non-toxic dose, before and after repackaging were compared, using a *z*-test.
Results: After repackaging, the number of enquiries per month concerning exposures to Thyrax® decreased from a mean of 12.1/month in 2010–2013 to 5.8/month in 2014–2015 ($p = .03$). Furthermore, the decrease in the number of children exposed to a toxic dose of Thyrax® was proportionally larger (−65%) compared to children exposed to a non-toxic dose (−38%; $p = .002$). Remarkably, even two years after repackaging, part of the Thyrax® tablets were still packed in a bottle. It is unclear whether the tablets were still delivered in a bottle. In five cases the parents indicated that they transferred the tablets from a blister to a bottle themselves. In 2015, 50% of the cases with a toxic dose of levothyroxine still came from bottled tablets.
Conclusion: Changing the packaging of Thyrax® from bottle to blister has led to a significant decline in the total number of accidental exposures to Thyrax®. The proportion of decrease was even larger for the number of toxic doses. Clearly, blister packaging of tablets is more child safe than bottle packaging. Users, especially those with small children in their household, should be instructed not to repackage tablets from blisters to bottles.

94. Alphachloralose poisoning in dogs: a case series

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Objective: Alphachloralose is a rodenticide used to kill mice. It is clearly stated in the directive that the products are for indoor use only and that the bait must be placed in tamper-resistant bait boxes. However, pets may still get poisoned, e.g., from chewing the package or the baits exposed incorrectly without boxes. In mice, alphachloralose serves as an anaesthetic that also reduces the metabolic rate. The unconscious animals will die from hypothermia within minutes of ingestion. Larger animals, with slower metabolism, will not be as severely affected, but may still experience central nervous system depression as well as hypothermia, seizures, coma and even death. The present report describes three recent cases of alphachloralose poisonings in dogs.
Case series: Case 1: A dog of mixed breed ingested a package of rodenticide bait corresponding to 290–363 mg alphachloralose/kg. On arrival at the animal hospital, the dog was unconscious, hypothermic, and hypoxic. The dog received treatment with whole body warming and supportive oxygen. It remained unconscious for 2 days and recovered without sequela. Case 2: A dachshund ingested 34 mg alphachloralose/kg and was brought to the animal hospital with reduced consciousness and seizures. It received treatment with anticonvulsants, supportive oxygen, and whole body warming. After 4 hours, the dog was stable and awake. It was fully recovered the following day. Case 3: A Labrador ingested a package of rodenticide corresponding to 93 mg alphachloralose/kg. On arrival at the animal hospital, the dog had severe seizures, was unconscious, hypothermic, and hypoxic. The dog received treatment with anticonvulsants, supportive oxygen, and whole body warming. After 14 hours, the unconscious dog vomited, aspirated stomach contents, and became severely hypoxic. Due to this, it was euthanized.
Conclusion: Treatment of alphachloralose-poisoning in pets should be focused on symptomatic and supportive care with emphasis on administration of oxygen, whole body warming, and anticonvulsant therapy. If a large amount of rodenticide has been ingested, emptying the stomach with a gastric tube should be considered, provided that the airway of the animal is protected. This may prevent voluminous vomiting and aspiration during treatment (see Case 3). Poisoned animals may remain unconscious for several days but still have a favourable outcome, provided supportive treatment is maintained.

95. Fatal mushroom poisoning in a dog

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Objective: To report a fatal case of mushroom poisoning. Mushrooms of the genus *Inocybe* contain muscarine, a potent parasympathomimetic compound structurally similar to

acetylcholine which competes for some acetylcholine receptor sites. Dogs are particularly susceptible to muscarine with rapid onset of effects. Atropine typically results in rapid improvement in signs.

Case report: A 22-month-old, 8.1 kg pug developed vomiting and diarrhoea soon after returning from the garden. During the journey to the veterinary surgery he became unresponsive with shallow breathing. On arrival 30 minutes later he was weak and unresponsive, with pale mucous membranes, collapse, tachycardia and haemorrhagic diarrhoea. He was given IV fluids, dexamethasone and oxygen. On returning home the owner found pieces of 3 mushrooms in the vomitus. Approximately 30 minutes after arrival he became hypothermic and was placed on a heat pad. He was drooling and given maropitant and ranitidine. Activated charcoal was not given as he continued vomiting despite the antiemetic. Images of the mushroom were sent for identification. At around 3 hours he developed bradycardia (20–40 bpm) and was given atropine with rapid improvement (pulse 120 bpm). He vomited copious watery brown liquid but was more responsive and pulses improved in strength. The mushrooms were identified within 35 minutes as *Inocybe* species, probably *I. rimosa* and less toxic species of *Galerina, Panaeolus* and *Mycena* species. He was stable and responsive when referred to an overnight service but drooling with watery, bloody diarrhoea, very lethargic, respiration 28/minute, weak pulse (140 bpm) and temperature 37.6 °C. He was constantly passing bloody fluid and continued to deteriorate with collapse, laboured breathing and hypothermia (34.7 °C). Despite supportive care, he died approximately 13 hours post-ingestion.

Conclusion: Similar signs are reported in other canine cases of *Inocybe* poisoning. One dog recovered without atropine [1], another improved rapidly after atropine [2] and a 1 kg Pomeranian died 2 hours after ingestion before atropine could be given [3]. In our case although cardiovascular signs resolved with atropine, gastrointestinal signs continued and the dog developed hypoperfusion and organ failure. Poisoning from muscarine-containing mushrooms can be fatal in dogs.

References

[1] Yam P, Helfer S, Watling R. Mushroom poisoning in a dog. Vet Rec 1993;133:24.
[2] Lee S, Nam SJ, Choi R, et al. Mushroom poisoning by *Inocybe fastigiata* in a Maltese dog. J Anim Vet Adv 2009;8:708–710.
[3] Tosterud M, Bjørnstad M, Eliassen FØ. Lethal mushroom (*Inocybe*) poisoning in a puppy. Clin Toxicol 2011;49:234.

96. Gabapentin ingestion in dogs and cats

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Objective: Gabapentin is an anticonvulsant and analgesic used in both human and, increasingly, veterinary medicine as adjunctive therapy for seizures or in the treatment of neuropathic pain. Exposure in pets is not expected to cause more than mild neurological and gastrointestinal signs. The recommended dose in cats is up to 90 mg/kg/day and in dogs up to 180 mg/kg/day. The clinical signs, treatment and outcomes in dogs and cats exposed to gabapentin in cases reported to the Veterinary Poisons Information Service (VPIS) were reviewed.

Methods: A retrospective analysis of canine and feline cases of exposure to gabapentin reported to the VPIS. All cases with exposure to gabapentin as a single agent and known outcome with returned veterinary practice follow up (via postal questionnaire) were included.

Results: There were 26 cases of gabapentin exposure as a single agent in dogs reported to the VPIS. Of these, 16 dogs (62%) remained asymptomatic with a mean reported dose of 79 mg/kg (range of 10 mg/kg up to 273 mg/kg). Ten dogs developed clinical signs, with the mean reported dose of 53.7 mg/kg (ranging from 3 mg/kg to 120 mg/kg). Drowsiness was the most commonly reported sign ($n = 7$, 64%). Three dogs (12%) developed vomiting. Of these 10 symptomatic cases, only two dogs were given an emetic; five dogs (50%) received no treatment and made a full recovery. All symptomatic cases made a full recovery and where known, the time to recovery ranged from 3 to 24 hours ($n = 3$). There was only one case with follow up in a cat. The cat of unknown weight ingested 300 mg of gabapentin and developed mild drowsiness within 10 minutes of ingestion. It was given activated charcoal and made a full recovery. No fatalities as a result of gabapentin exposure in cats and dogs have been reported to the VPIS.

Conclusion: Gabapentin is well tolerated in dogs and most animals remain asymptomatic. In symptomatic animals, common signs are lethargy, drowsiness and, occasionally, vomiting. There does not appear to be any correlation between the dose of gabapentin ingested and likelihood of clinical signs. As serious cases have not been reported, emesis is unlikely to be required and administration of activated charcoal should be sufficient for gut decontamination. Signs resolve rapidly after gabapentin overdose.

97. Lamotrigine is cardiotoxic to dogs

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Objective: The anticonvulsant lamotrigine is not used in veterinary medicine. In humans it is metabolized predominantly by glucuronic acid conjugation and the major metabolite is an inactive 2-N-glucuronide conjugate. In dogs, however, lamotrigine is extensively metabolised to a 2-N-methyl metabolite and this causes dose-dependent prolongation of the PR interval, widening of the QRS complex and at higher doses AV block. We reviewed canine cases of lamotrigine ingestion to evaluate clinical signs and outcome.

Methods: A retrospective study of cases of lamotrigine ingestion in dogs reported to the VPIS between 1996 and September 2016. All cases with exposure to lamotrigine as a single agent and known outcome with returned veterinary surgeon follow up (via postal questionnaire) were included.

Results: There were 35 cases of lamotrigine ingestion in dogs with follow up. Of these 22 dogs remained asymptomatic. Where known the mean dose ingested in asymptomatic dogs was 11 mg/kg ($n = 17$). Treatments given in asymptomatic dogs were emesis ($n = 10$), adsorbants ($n = 9$), IV fluids ($n = 2$), gastroprotectants ($n = 2$) or none ($n = 9$). Thirteen dogs developed signs and the mean dose where known in these cases was 77 mg/kg ($n = 11$). Signs reported in symptomatic dogs ($n = 13$) were vomiting ($n = 5$), drowsiness ($n = 3$), diarrhoea ($n = 3$), tachycardia ($n = 2$), bradycardia ($n = 2$), lethargy/depression ($n = 2$), arrhythmias ($n = 2$) and collapse ($n = 2$). Treatments given in symptomatic dogs were emesis ($n = 4$), adsorbants ($n = 5$), IV fluids ($n = 3$), lipid infusion ($n = 1$) or none ($n = 3$). Eleven dogs recovered but two dogs died. In both fatal cases the dogs developed bradycardia and arrhythmias (AV block in one dog). The dose of lamotrigine ingested in the two fatal cases was 40.1 and 360.5 mg/kg. Death occurred between 8 and 15.5 hours in the dog that ingested 40.1 mg/kg and 12 hours after ingestion following 360.5 mg/kg.

Conclusion: Lamotrigine is potentially lethal in dogs (case fatality rate in VPIS cases is 5.7%). Doses of lamotrigine up to 11 mg/kg are well tolerated but doses above this are potentially toxic,

although the dose at which there is risk of cardiotoxicity is not known. Bradycardia and arrhythmias after lamotrigine ingestion in dogs have a poor prognosis.

98. Metaldehyde ingestion in 18 domestic equines

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Objective: To examine the typical clinical signs and outcome of metaldehyde exposure in equines. Metaldehyde ingestion typically results in neurological signs with twitching and convulsions.
Methods: A retrospective study of 18 cases of metaldehyde ingestion in domestic equines reported to the Veterinary Poisons Information Service (VPIS) between December 1986 and June 2013.
Results: There were seven incidents at different establishments involving 18 domestic equines. Where known, the body weight ranged from 200 to 600 kg. In this case series, the onset of clinical signs was unknown, although in two cases effects were reported from 2.5 hours and within 15 hours post-exposure. Also, following the ingestion of an unknown strength and quantity of metaldehyde a 400 kg animal presented with bradycardia 24 hours after exposure and developed diarrhoea 48 hours post-exposure, but made a full recovery, whilst another equine at the property was found dead. Of the animals that presented with clinical signs, ataxia was the predominant sign; 66.7% ($n = 12$) of animals presented with ataxia. Convulsions occurred in 55.6% ($n = 10$) cases, and excitability (44.4%), hyperaesthesia (27.8%), and muscle fasciculation/spasms/twitching (16.7%) were other frequently reported signs. Overall, two animals (11.1%) were found dead, two (11.1%) died and three (16.7%) were euthanized. Only one animal remained asymptomatic. This was a 400 kg equine that had ingested a "handful" of 1.5% metaldehyde. Another equine, approximately 220 kg in weight, became ill after it was estimated to have eaten up to 500 g (maximum of 2.27 g bait/kg) from a packet of 3% metaldehyde that the animal had knocked over. Clinical signs included muscle spasms, twitching and hyperaesthesia, but the animal made a full recovery with supportive measures. However, three donkeys (approximately 200 kg in weight) that ate an unknown quantity of 6% metaldehyde all died. In the symptomatic animals that survived ($n = 10$, 55.6%), the treatment protocols were largely supportive, principally involving the use of intravenous fluid therapy, anticonvulsants and sedation.
Conclusion: Metaldehyde is the active agent commonly found in a number of molluscicide products widely used across the world and incidents of poisoning have occurred in a number of wild and domestic species. In this case series, only one animal remained well following metaldehyde exposure. In the symptomatic cases clinical effects were predominantly ataxia and convulsions. The overall fatality rate was 38.9%, resulting in the death of seven equines.

99. Neonicotinoid insecticide exposure in cats and dogs

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Objective: Neonicotinoid insecticides including acetamiprid, imidacloprid, nitenpyram, and thiaclopridare are widely used insecticides. Imidacloprid is available in dermal veterinary products and nitenpyram is used orally for the control of fleas. The remainder are available in domestic products. We determined the clinical signs and outcome in cats and dogs exposed to neonicotinoid insecticides.
Methods: Retrospective analysis of cases of neonicotinoid pesticide exposure in cats and dogs reported to the VPIS between 2001 and September 2016.
Results: Data were available for 42 feline cases; 7.1% ($n = 3$) involved thiacloprid, 21.4% ($n = 9$) nitenpyram and 73.8% ($n = 30$) imidacloprid. Overall 69% ($n = 29$) involved ingestion, 23.8% ($n = 10$) skin exposure and 3 (7.1%) cats were exposed via multiple routes. Eight (19.0%) cats remained asymptomatic and 34 cats developed signs. Hypersalivation was the most common clinical sign occurring in 9 cats (21.4%). Hyperthermia, diarrhoea and anorexia occurred in 5 cats (11.9%) each. Most cats (80.6%, 25/31) exposed to imidacloprid had clinical signs with hypersalivation ($n = 7$, 22.5%), and ataxia ($n = 5$, 16.1%). For nitenpyram 8 out of 9 cats (88.8%) had clinical signs with diarrhoea and panting observed in a third of cases. Three deaths were reported, all involving imidacloprid (two oral, one dermal exposure). In all cases the animals were euthanized and clinical signs included twitching, convulsions, muscle fasciculation, ataxia and hypersalivation. There were 34 canine cases involving acetamiprid (3.0%, $n = 1$), imidacloprid (67.6%, $n = 23$), thiacloprid (14.7%, $n = 5$), nitenpyram (11.7%, $n = 4$) and imidacloprid + nitenpyram (3.0%, $n = 1$). Ingestion was the most common route of exposure (79.4%, $n = 27$), followed by dermal (8.8%, $n = 3$), and buccal (3.0%, $n = 1$); multi-route exposure occurred in 3 dogs (8.8%). Fifteen dogs remained asymptomatic. Vomiting (20.5%, $n = 7$) and diarrhoea (14.7%, $n = 5$) were the most common signs. Of the 18 symptomatic dogs, 13 (75.0%) had gastrointestinal, 2 (11.1%) respiratory, 1 (5.5%) dermal and 11 (61.1%) neurological signs. Most dogs (92.5%, $n = 16$) recovered. One dog presented with pulmonary haemorrhage, pyrexia and seizures after dermal exposure to imidacloprid and died 21 hours after presentation.
Conclusion: Exposure to neonicotinoid pesticides can result in gastrointestinal, dermal, neurological and respiratory signs in cats and dogs. Imidacloprid is the most common neonicotinoid involved in veterinary cases. Overall, 7% of feline cases resulted in death as the animals were euthanized. The reasons for euthanasia are not always clear but may involve clinical or financial reasons. In at least one of these cases, there was no improvement after 48 hours of treatment. In the canine cases one dog (3%) died. Exposure to neonicotinoid pesticides appears to be generally well tolerated in cats and dogs but severe poisoning occurs in a small percentage of cases with neurological signs such as convulsions.

100. Phenoxyacetic acid derivative herbicide exposure in 101 dogs

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Objective: To examine typical clinical signs and outcome of phenoxyacetic acid derivative herbicide exposure in dogs. These herbicides are selective to broad leaf plants and are often used as lawn weed killers. They are present in many products both alone and with fertilisers (lawn feed and weed). There are few reports of confirmed myotonia in dogs following phenoxyacetic acid exposure [1,2].
Methods: A retrospective study of cases of phenoxyacetic acid exposure in dogs reported to the Veterinary Poisons Information Service (VPIS) between August 1985 and June 2015. All cases with exposure to phenoxyacetic acids as a single agent and known outcome with returned veterinary surgeon follow up (via postal questionnaire) were included.
Results: There were 101 cases of phenoxyacetic acid exposure in dogs with follow up. The majority involved ingestion (92.1%) with the remainder dermal (7.9%), ocular (1%), buccal (1%) or

unknown routes. In total 23 dogs were asymptomatic (22.8%). The most common signs in symptomatic animals were vomiting (41.6%), diarrhoea (17.8%), lethargy (15.8%), depression (10.9%), hypersalivation (10.9%) and ataxia (8.9%). Treatment in symptomatic dogs ($n = 78$) was supportive; 41 dogs received antibiotics and 32 rehydration (29 were given IV fluids and 3 received oral fluids). Most symptomatic dogs (91%) recovered but there were 6 fatalities (5 died, 1 euthanized), although limited information is available on the circumstances of exposure and the cause of death in these cases. Time to death was only known in 2 cases and was 2 and 5 days. There was no laboratory confirmation of exposure in any of the cases. Signs suggestive of myotonia were reported in two cases but not confirmed with electromyography. One dog developed bradycardia, hyperthermia, pale mucous membranes, tremor and weakness 4 days after ingestion of grass treated with 2,4-D and mecoprop. The other had hind-limb ataxia, pyrexia, inappetence, respiratory depression, vomiting and weakness after ingestion of 2,4-D and MCPA. Both dogs made a full recovery (time to recovery unknown).

Conclusion: Phenoxyacetic acid exposure generally causes mild gastrointestinal upset in dogs. While there were cases of possible myotonia in this case series, this was unconfirmed; however incidence appears to be low (<2% in VPIS cases). The case fatality rate in our series was 6.9%.

References

[1] Harrington ML, Moore MP, Talcott PA, et al. Suspected herbicide toxicosis in a dog. J Am Vet Med Assoc. 1996;209:2085–2087.

[2] Chen AV, Bagley RS, Talcott PA. Confirmed 2,4-dichlorophenoxyacetic acid toxicosis in a dog. J Am Anim Hosp Assoc. 2010;46:43–47.

101. Pregabalin ingestion in dogs and cats

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Objective: To review the clinical signs and outcome following pregabalin ingestion in dogs and cats. Pregabalin is used in human and veterinary medicine as an anticonvulsant and for neuropathic pain. The recommended dose in dogs and cats is 3–4 mg/kg three times daily.

Methods: A retrospective study of canine and feline cases of pregabalin ingestion reported to the Veterinary Poisons Information Service (VPIS) between January 2006 and July 2016. All cases with exposure to pregabalin as a single agent and with known outcome from follow up questionnaires (sent to the veterinary practices involved) were included.

Results: There were 48 pregabalin cases with follow up (31 in cats and 17 in dogs). Cats were more severely affected with 6.5% ($n = 2$) remaining asymptomatic, at a reported dose of <10 mg/kg in one case, compared to 52.9% of dogs ($n = 9$) with a mean reported dose of 14.1 mg/kg (range 3.4–26.3 mg/kg). The mean reported dose in symptomatic cats was 70.8 mg/kg (range 13.9–600 mg/kg) and in dogs 37.7 mg/kg (range 6.25–76.7 mg/kg). The most common signs in both cats and dogs were ataxia (23.5% dogs, 58% cats) and lethargy (29% dogs, 26% cats). Dogs also had vomiting (11.7%), excitability (5.8%) and vocalisation (5.8%). Cats displayed varied signs including dilated pupils (22.5%), tremor/twitching (12%), weakness (12.9%), depression (9.6%), vomiting (9.6%), diarrhoea, tachycardia and collapse (all 6.4%). Onset of signs ranged from 10 minutes to 12 hours in cats and 0.5–8 hours in dogs and was not dose related. Time to recovery was 3–48 hours in cats and 2–12 hours in dogs. Nine symptomatic cats (29%) and 3 symptomatic dogs (37.5%) received no treatment and recovered. Treatment was given to 21 cats (68%) (including one asymptomatic case) comprising fluid therapy (42%), activated charcoal (19%), blood tests (16%), emesis (6.4%), supportive (6.4%) and diazepam (3%); 11 dogs (65%) received treatment (including 6 asymptomatic cases) with emesis and activated charcoal ($n = 8$) and IV fluids ($n = 1$). There were no fatalities.

Conclusion: Pregabalin is fairly well tolerated in dogs resulting in only mild effects even, in one case, at over 6 times the daily dose. One dog remained asymptomatic after ingesting over twice the daily dose. Cats are more sensitive to pregabalin and only 2 out of 31 cats reported to the VPIS remained well. They suffer more pronounced, particularly neurological, signs. All the animals fully recovered within 48 hours, many without treatment.

102. Suspected synthetic cannabinoid ingestion in dogs: a case series

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Objective: Synthetic cannabinoids (SCs) are a group of novel psychoactive substances that are of public health concern due to their increased prevalence, unpredictable toxicity and abuse potential. Reports of exposure to SCs in companion animals are limited. We reviewed cases of suspected SC ingestion in dogs reported to the Veterinary Poisons Information Service (VPIS) to determine clinical signs and outcomes.

Methods: All canine cases of suspected SC exposure were retrieved from the VPIS case database. All cases with known outcome with returned veterinary practitioner follow up questionnaire were included.

Results: There were 10 cases involving suspected SC ingestion with follow up reported to VPIS. The cases occurred between May 2015 and June 2016 and all the dogs developed clinical signs and required treatment. One dog had possible co-ingestion of lamotrigine and levetiracetam after ingestion of the vomitus of an epileptic, SC-using human family member, but signs were consistent with SC exposure. The mean onset of clinical signs in all the dogs was rapid (mean of 3.3 hours, range 2–6 hours). The most common signs reported were convulsions ($n = 4$), bradycardia ($n = 4$), dilated pupils ($n = 4$), ataxia ($n = 3$), twitching ($n = 3$), mild hypothermia ($n = 3$), hyperthermia ($n = 2$), coma ($n = 2$), collapse ($n = 2$) tachycardia ($n = 2$), hyperaesthesia ($n = 2$) and aggressive behaviour ($n = 2$). The most common treatments were intravenous fluids ($n = 8$), activated charcoal ($n = 3$) and benzodiazepines ($n = 3$) for sedation and seizure control. Intravenous lipid emulsion was used in two dogs with severe neurological signs; the follow-up did not include information on effectiveness. There were no fatalities and all the dogs recovered fully within 24–48 hours. There was no laboratory confirmation of exposure in these cases.

Conclusion: SC toxicity varies considerably, but may produce long-lasting cardiovascular and neurological clinical effects in dogs [1] and humans [2]. Benzodiazepines for sedation, and IV fluid therapy were the mainstay of treatment following ingestion of these agents in dogs. In severe cases, lipid infusion was given to dogs that did not respond to conventional treatment, as synthetic cannabinoids are lipophilic drugs but it is not clear if this was effective in these cases. Prognosis is good in dogs after ingestion of synthetic cannabinoids.

References

[1] Williams K, Wells RJ, McLean MK. Suspected synthetic cannabinoid toxicosis in a dog. J Vet Emerg Crit Care. 2015;25:739–744.

[2] Hoyte CO, Jacob J, Monte AA, et al. Characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. Ann Emerg Med. 2012;60:435–438.

103. Accidental poisoning in dogs from intraruminal monensin devices expelled by cows

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Objective: Monensin is an antibiotic produced by *Streptomyces cinnamonensis*, used in lactating dairy cattle for control of ketosis as an intraruminal capsule releasing 32.4 g monensin. Since 2014 we have received 5 enquiries related to accidental poisoning in dogs following ingestion of capsules regurgitated by treated cattle.
Case series: Case 1: A 32 kg dog ingested 1/10th of the content of a regurgitated Kexxtone® capsule corresponding to 3 g of monensin. The veterinarian was consulted one week after ingestion. Examination revealed a very ill, tachypnoeic dog with signs of major rhabdomyolysis (creatine kinase 318.305 IU/L, myoglobinuria). The dog was euthanised. Case 2: While playing with a regurgitated Kexxtone® capsule, a 20 kg dog ingested some content. After 45 minutes, the dog appeared sleepy with stiff hindquarters. Induction of emesis was unsuccessful and activated charcoal was given with forced diuresis. The dog was discharged a day later but according to the owner he deteriorated after 5 days and died 3 days later in respiratory distress. Case 3: A 35 kg dog played with a regurgitated Kexxtone® capsule and a day later appeared severely ill. The veterinarian noticed signs of somnolence, hypersalivation, diarrhoea, tachycardia and paresis and the dog was euthanised. Case 4: A dog ingested an unknown quantity from a Kexxtone® device. A few hours later, it vomited and developed hindquarter paresis but recovered after symptomatic treatment. Case 5: A 11 kg Border Collie swallowed a small amount of the contents of a Kexxtone® capsule. Three days later, the dog presented with tachycardia, marked dyspnoea, hyperthermia (39.5 °C) and myoglobinuria. Despite forced diuresis, he deteriorated and died a few hours later.
Conclusion: Toxic myopathy has been reported in dogs after monensin exposure [1,2]. Kexxtone® capsules retched by treated cows put dogs at risk for severe monensin poisoning. Ingestion of a small amount can lead to rhabdomyolysis and myoglobinuria. Dogs should be kept away from treated animals. A warning was issued by the competent authorities following reports of poisoning in dogs [3].

References

[1] Condon FP, McKenzie RA. Fatal monensin toxicity in a dog after chewing a bovine intra-ruminal slow-release device. Aust Vet Pract. 2002;32:179–180.
[2] Wilson JS. Toxic myopathy in a dog associated with the presence of monensin in dry food. Can Vet J. 1980;21:30–31.
[3] Belgian Centre for Pharmacotherapeutic Information (CBIP). Intoxicatiegevaar na accidentele opname van Kexxtone® bolus bij honden [Warning intoxication risk after accidental poisoning of Kexxtone® bolus in dogs] [Internet]. [cited 2017 Mar 29]. Available from: http://www.cbip-vet.be/nlgow.php

104. Comparison of the Poisoning Severity Score and National Poison Data System schemes for severity assessment of dog poisonings

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Objective: The objective of this study was to assess agreement between the Poisoning Severity Score (PSS) [1] (adapted for dogs) and the National Poison Data System (NPDS) medical outcome scheme [2] for the severity assessment of dog exposures reported to the Rocky Mountain Poison and Drug Centre (RMPDC) in Denver, Colorado, USA.
Methods: The first 196 dog exposures reported to RMPDC between 1 January to 31 August 2016 and classified with a medical outcome of "minor", "moderate" or "major" effect were selected. Exposures were randomly allocated into two even groups; both of which were scored by two independent raters and assigned so that each rater scored one group with the NPDS scheme and the other with the PSS. Case notes were only accessed when clinical effect reported was "other". Using the Power3Cats function in R, a minimum sample size of 193 was estimated to detect agreement between the schemes with the weighted kappa (K) statistic (squared weights) [3] in a test of H0: Kappa = 0.4 versus H1: Kappa =0.6 at a power of 80% and two-sided significance level (α) of 0.05. The K estimate was interpreted as follows: ≤0 = poor, 0.00–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, and 0.81–1 = almost perfect [4].
Results: We found low moderate agreement (K 0.42; 95% CI 0.34–0.58) between the PSS and NPDS medical outcome. For the PSS, 83.7% ($n = 164$) of cases were scored as minor, 15.3% ($n = 30$) as moderate, and 0.5% ($n = 1$) as severe. For the NPDS, 83.2% ($n = 163$) of exposures were scored as minor, 14.8% ($n = 29$) as moderate, and 1.5% ($n = 3$) as severe.
Conclusion: This study shows a low moderate agreement between the NPDS and PSS schemes for canine exposures severity assessment. However, the influence of intra- and interrater variation as well as the predominance of minor cases on the study findings should be taken into account. Further evaluation of these schemes is warranted and could help inform their future use for poisoning severity assessment in animals.

References

[1] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.
[2] Mowry J, Spyker D, Brooks D, et al. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. Clin Toxicol. 2015;53:962–1146.
[3] Cohen J. Weighted kappa: Nominal scale agreement provision for scaled disagreement or partial credit. Psychol Bull. 1968;70:213–220.
[4] Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159–174.

105. Life-threatening 3,4-methylenedioxy-methamphetamine (MDMA) poisoning: clinical features and prognostic value of MDMA and its major metabolite concentrations on admission

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Objective: 3,4-Methylenedioxymethamphetamine (MDMA) is a widely consumed recreational amphetamine derivative. The objectives of our study were to describe the features of life-threatening MDMA poisonings admitted to the intensive care unit (ICU) and to investigate the prognosticators on admission including plasma concentrations of MDMA and its main active metabolite, 3,4-methylenedioxyamphetamine (MDA).
Methods: We conducted a retrospective single centre observational study including all MDMA-poisoned patients admitted to the ICU from 2007 to 2016. Plasma MDMA and MDA concentrations were determined using high-performance liquid chromatography coupled to mass spectrometry. Comparisons were performed using chi-squared and Mann–Whitney tests. Pharmacokinetics were modeled using PKsolver® software and the usual parameters calculated.
Results: Twenty patients (16M/4F; age 25 years [21; 36] (median [25; 75 percentiles]; poly-intoxications 80%) were included. On admission, patients presented marked consciousness impairment (Glasgow Coma Scale 3 [3; 14]), hyperthermia (45%; 37.6 °C [37.3; 39.4]), serotonin syndrome (35%) and seizures (25%). Three patients (15%) experienced prehospital cardiac arrest. Management mainly consisted of the administration of adequate supportive care with massive fluid repletion (60%), mechanical ventilation (55%; duration 1 day [1; 4]), sedation (50%), external cooling (40%), catecholamines (35%), defibrillation (20%), massive transfusions (20%) and arterio-venous extracorporeal membrane oxygenation (ECMO) (20%). Cyproheptadine, the antidote for serotonin syndrome, was administered to 20% of patients. During the ICU stay, the following complications were observed, aspiration pneumonia (40%), cardiovascular failure (30%), disseminated intravascular coagulation (30%), acute renal failure (30%), liver failure (30%), rhabdomyolysis (25%), hemorrhage (20%), ventilator-acquired pneumonia (20%) and nerve/vessel compressions (10%). Five patients (25%) died in the ICU and among the survivors, one patient developed significant neurological sequelae. Based on a univariate analysis, prehospital cardiac arrest onset ($p = .009$), massive hyperlactatemia ($p = .01$) and marked coagulation disturbances ($p = .004$) on ICU admission were associated with death. Plasma MDMA (638 ng/mL [167; 989]) and MDA concentrations (25 ng/mL [17; 39]) on admission did not significantly differ according to the final outcome. The pharmacokinetic analysis showed that all patients were in the elimination phase when admitted to the ICU, with prolonged MDMA and MDA half-lives in relation to liver and renal failure and possibly to the elevated ingested doses of MDMA too.
Conclusion: MDMA poisoning may be life-threatening and even fatal despite optimal ICU management. Strengthening the information among drug users about the dangers of MDMA still remains a public health necessity.

106. Cathinones, and in particular mephedrone, remain the biggest novel psychoactive substance (NPS) associated with acute harm and Emergency Department presentations in Europe

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Objective: There is increasing use and availability of novel psychoactive substances (NPS) across Europe, with 1–2 new compounds per week detected and reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). This study aimed to determine whether there have been changes in the pattern of NPS use associated with acute harm across Europe.
Methods: The Euro-DEN Plus project collects longitudinal data from 16 sentinel centres in 10 European countries on Emergency Department (ED) presentations with acute recreational drug toxicity. The Euro-DEN database was searched for presentations involving the use of one or more NPS, and data extracted on these cases as to the reported NPS involved.
Results: Overall there were 109 different NPS reported in presentations to the Euro-DEN Plus project, with a total of 1167 (10.7%) presentations involving an NPS. There was great variability between the proportion of presentations in each Euro-DEN Plus centre (0–52.2%) that involved an NPS. Four centres had more than 20% of presentations involving an NPS: Gdansk, Poland (52.2% of Euro-DEN Plus cases); York, UK (30.4%), Munich (26.3%) and London STH, UK (22.7%). There were three centres with no NPS presentations (Tallinn and Pärnu, Estonia and Drogheda, Ireland). The cathinones were the biggest group of NPS (757 reported, 63.2% of all NPS reported). Within the cathinone group, mephedrone was most commonly reported (554 presentations); 70% of mephedrone presentations were reported from the UK (London 2 centres, York 1 centre) and 23% in Ireland (Drogheda and Dublin). There was an increase in mephedrone-related presentations between Year 1 (Oct 2013–Sept 2014 254 presentations) to Year 2 (Oct 2014–Sept 2015 309 presentations). The second most common cathinone reported was methedrone (115 presentations); this was only seen in the two London centres (London STH and London KCH). The majority of methedrone presentations were in Year 1 ($n = 92$), with fewer presentations in Year 2 ($n = 23$); in Year 2, all methedrone presentations were to the London STH centre. Other reported cathinones included methylenedioxypyrovalerone (MDPV) ($n = 40$); 3-methylmethcathinone ($n = 17$); "cathinone not known" (9); α-pyrrolidinovalerophenone ($n = 6$); ethylcathinone ($n = 3$); pentedrone ($n = 3$); 4-methylethcathinone ($n = 2$); butylone ($n = 2$); methylone ($n = 2$); 4-chloromethcathinone ($n = 1$); buphedrone ($n = 1$); "eth-cat" ($n = 1$); and methylcathinone ($n = 1$).
Conclusion: Despite the increasing availability and detection of other NPS in Europe, ED presentations with acute NPS toxicity remain predominately related to the use of cathinones, and in particular mephedrone.

107. Emergence of fentanyls on the Swedish novel psychoactive substance market: analytically confirmed intoxications from the STRIDA project

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Objective: The increasing sale of fentanyl analogs on the Internet market for new psychoactive substances (NPS) is worrying. Already, many severe intoxications and fatalities attributed to NPS fentanyls have appeared in Sweden, primarily among known drug abusers but also in subjects seeking self-medication for pain relief. New fentanyl analogs have been continuously introduced over the last few years, mainly in response to legislation. The danger inherent to fentanyls is their high potency and the induction of respiratory depression, with potentially fatal consequence unless the antidote naloxone is rapidly administered. Opioid overdose kits are, however, not available among drug addicts in Sweden. This work summarizes analytically confirmed intoxications involving NPS fentanyls in the STRIDA project, from the first consultation to the Swedish Poisons Information Centre (PIC) in May 2014 to October 2016.
Methods: In the STRIDA project, blood and urine samples are collected from intoxicated patients with suspected exposure to NPS admitted to Swedish hospitals. Analysis of fentanyls was performed using a multi-component liquid chromatography–high-resolution mass spectrometry method. Information on basic demographic and clinical data was retrieved from PIC, ambulance, and hospital medical records.
Results: A total of 33 patients tested positive for NPS fentanyls. The substances detected, in time order, were butyrfentanyl ($n = 6$), 4-fluorobutyrfentanyl ($n = 6$), acetylfentanyl ($n = 9$), 4-methoxybutyrfentanyl ($n = 4$), furanylfentanyl (=2), acrylfentanyl ($n = 9$), 4-chloroisobutyrylfentanyl ($n = 1$), 4-fluoroisobutyrylfentanyl ($n = 1$), and tetrahydrofuranfentanyl ($n = 1$). Five patients tested positive for a combination of NPS fentanyls. The age of patients was 19–51 (mean 28) years, and 88% were men. In 21 cases, the drug formulation was known, being nasal sprays ($n = 12$), tablets ($n = 5$) and powders ($n = 4$). The triad of opioid symptoms, central nervous system depression ($n = 24$), miosis ($n = 16$), and respiratory depression ($n = 22$) were the most common clinical signs, and 29 patients were brought to hospital by ambulance. Naloxone was given in 21 cases (total injected dose 0.1–1.2 mg) and 4 needed repeated administrations. Eight patients required intubation and 17 were admitted to the intensive care unit, two of whom died.
Conclusion: This series of intoxications involving NPS fentanyls from the STRIDA project confirms their presence and involvement in severe adverse events. In addition, the number of confirmed deaths related to these substances exceeded the number of confirmed non-fatal intoxications in Sweden. Without specific drug testing covering NPS fentanyls, which is rarely performed in patients with opioid symptoms, the type of substance(s) responsible for overdoses will remain unknown.

108. Synthetic cannabinoid receptors agonists (SCRA) toxicity associated with reduced level of consciousness: an analytically confirmed case series

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Objective: SCRAs are a group of new psychoactive substances (NPS) that have been reported to be associated with severe clinical effects [1]. We describe the clinical features in a case series of analytically confirmed use of SCRAs.
Case series: Seven men, all homeless, were brought by ambulance from a similar geographical area to a central London Emergency Department (ED) in one 18 hour period in September 2016; 4 presented within an hour. All reported smoking "Spice" products. Their demographics, clinical features and observations on arrival in the ED are shown in Table 1; of particular note, 6 had a reduced level of consciousness prior to or on arrival in the ED. Only one patient had an abnormal creatinine (138 µmol/L,

Table 1. Clinical features of seven males exposed to SCRAs presenting to a hospital within one 18 hour period.

No.	Age	Symptoms	Baseline observations on admission to hospital	Analytical confirmation of SCRA	Additional substances detected
1	36	Seizure, vomiting	GCS 11; HR 120 bpm; BP 140/60 mmHg	5F ADB, MDMB-CHMICA, AB-FUBINACA, 5F AKB-48	None
2	39	Vomiting	GCS 15; HR 102 bpm; BP 139/87 mmHg	5F ADB, AB-FUBINACA, 5F AKB-48	Metronidazole
3	34	Reduced level of consciousness	GCS 13; HR 64 bpm; BP 123/73 mmHg	5F ADB, MDMB-CHMICA, AB-FUBINACA, 5F AKB-48, AMB-CHMICA	Carboxy-tetrahydrocannnabinol
4	38	Reduced level of consciousness	GCS 8; HR 55 bpm; BP 85/40 mmHg	5F ADB, MDMB-CHMICA, AB-FUBINACA, 5F AKB-48, AMB-CHMICA, AB-CHMINACA	Cyclizine, diazepam, codeine, methadone, EDDP, mirtazapine, oxazepam, nordazepam, paracetamol, pregabalin, temazepam, oxycodone, oxymorphone
5	27	Reduced level of consciousness	GCS 6; HR 102 bpm; BP 112/67 mmHg	5F ADB, MDMB-CHMICA	None
6	21	Seizure, vomiting	GCS 9; HR 78 bpm; BP 90/47 mmHg	5F ADB, MDMB-CHMICA, 5F AKB-48, AMB-CHMICA	None
7	27	Reduced level of consciousness	GCS 12; HR 80 bpm; BP 95/67 mmHg	5F ADB, MDMB-CHMICA, AB-FUBINACA, 5F AKB-48, AMB-CHMICA	None

1.6 mg/dL). All patients were discharged from hospital within 24 hours with no immediate sequelae. Analysis of serum samples collected at the time of admission identified at least one SCRA in each patient (Table 1); additional substances detected are also shown in Table 1. Of note ethanol was not screened for but was only self-reported by patients 1 and 5.

Conclusion: We report a case series of seven homeless males presenting within a short time period with acute SCRA-related toxicity. The frequent detection of reduced level of consciousness is in keeping with that reported previously following the use of third generation SCRAs as detected here. This cluster of use amongst homeless individuals presents a public health challenge in ensuring that health prevention messaging around the use of SCRAs also reaches this population of high-risk vulnerable patients not typically associated with using NPS in the UK.

Reference

[1] Tait RJ, Caldicott D, Mountain D, et al. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol. 2016;54:1–13.

109. Trends in the surveillance of mephedrone, MDMA and cocaine detected in anonymous pooled street urine samples: is mephedrone use decreasing in the UK?

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Objective: Over the last 10 years there has been a global increase in the use of synthetic cathinones, with mephedrone being the most commonly used cathinone in the UK. The 2015–16 Crime Survey for England and Wales (CSEW) reported that 0.3% of those aged 16–59 years had used mephedrone in the last year; slightly lower than in the 2014–15 survey (0.5%). This information is based on self-reported use, and there is now increasing interest in waste-water and urine analysis to provide analytically confirmed data on drug use. This study aimed to investigate trends of detection of mephedrone compared to cocaine and 3,4-methylenedioxymethamphetamine (MDMA) over a 3-year period through analysis of pooled urine samples from street urinals in London, UK.

Methods: Anonymised pooled urine samples were collected from street urinals in central London, UK on the first Saturday night each month from July 2013 to June 2016. Samples were analysed using full-scan accurate mass high-resolution liquid chromatography tandem mass-spectrometry against databases containing more than 1700 drugs and metabolites. Data are presented as percentage urinals positive per month for each drug.

Results: Cocaine and MDMA were consistently detected in the majority of urinals over the 3-year period. However, there was greater variation in the detection of mephedrone with a downward trend in detection in the final year of the study (Table 1).

Conclusion: There is a suggestion in this longitudinal study on the detection of mephedrone, MDMA and cocaine that despite relatively consistent detection of both MDMA and cocaine over the three years, that there was a decrease in mephedrone detection in the last 12 months. This is in keeping with data from population surveys, however further work is needed to determine whether the mephedrone is being replaced by other NPS and/or whether this trend continues with ongoing surveillance and data from other complimentary datasets.

Table 1. Surveillance of mephedrone, MDMA and cocaine detected in anonymous pooled street urine samples, 2013–2016.

	Percentage urinals positive per month for each drug		
Time period	Cocaine	MDMA	Mephedrone
July 2013–Dec 2013	83–100%	73–91.7%	17–73%
Jan 2014–Jun 2014	100%	58–100%	17–75%
July 2014–Dec 2014	92–100%	83–100%	42–100%
Jan 2015–June 2015	100%	60–100%	17–100%
July 2015–Dec 2015	80–100%	67–100%	0–50%
Jan 2015–June 2016	100%	83–100%	0–8.3%

110. Marijuana and synthetic cannabinoid patterns in a US state with legalized marijuana: a 5-year NPDS review

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Objective: US poison center trends of marijuana and synthetic cannabinoid exposure indicate rising popularity. While 25 states and the District of Columbia have adopted provisions for legalizing medical marijuana, only 4 states and the District of Columbia have legalized recreational marijuana. We sought to evaluate patterns of marijuana and synthetic cannabinoid exposure in a medical-marijuana state where recreational marijuana was also legalized in 2012.

Methods: We queried National Poison Data System (NPDS) for aggregate poison center data in a state with legalized medical and recreational marijuana involving closed, human exposures to marijuana and synthetic cannabinoids (SCs) from 2011 to 2015 using American Association of Poison Control Centers (AAPC) generic codes 0083000 and 0200617, respectively. Cases were not limited to single-substance exposures. Parameters evaluated: age, clinical effects, gender, management site, and medical outcome. Descriptive statistics were used.

Results: We identified a consistent rise in marijuana exposures from 2011 ($n = 86$) to 2015 ($n = 231$) with a 5-year total of 777 exposures; 426 (54%) were male. The age group with the most number of marijuana exposures was 0–14 years ($n = 220$, 29%) followed by age 15 to 21 years ($n = 204$, 26%). Median [min, max] age was 29 years [3 days, 85 years]. A majority ($n = 428$, 55%) were already in or en route to a healthcare facility when the poison center was called; 17% ($n = 135$) were managed on site. The 5 most frequently reported clinical effects were drowsiness, tachycardia, agitation, vomiting, and confusion. Overall 62% ($n = 484$) reported minor or no effects, 22% ($n = 169$) had moderate effects, and 2% ($n = 17$) had major effects. There was 1 death reported. Regarding SC exposures, there were 243 exposures from 2011 to 2015. The year with the most exposures was 2013 ($n = 100$) and dropped to the least ($n = 17$) in 2014 which was the year recreational marijuana dispensaries opened. A majority ($n = 185$, 76%) were male. The age group that accounted for 43% of exposures was 15–21 years. Median [min, max] age was 32 years [1 day, 61 years]. Most (81%, $n = 197$) were already en route or in a healthcare facility when the poison center was called. The top 5 clinical effects mimicked marijuana. Overall 43%

($n = 105$) reported minor or no effects, 40% ($n = 96$) had moderate effects, 6% ($n = 14$) had major effects, and 1 death was reported.
Conclusion: Our findings show that in a state that has legalized marijuana; synthetic cannabinoid use has gone down. As there were more serious outcomes in the SC group, the impact of this pattern may have public health significance.

111. Modified-release paracetamol overdose: a prospective observational study

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Objective: There is little data on modified-release (MR) paracetamol ingestion, and whether patients have a higher rate of liver injury or are more likely to require prolonged treatment. Our aim was to describe the clinical characteristics and outcomes of MR paracetamol acute overdoses.
Methods: The Australian Paracetamol Project is a prospective observational study, recruiting patients from January 2013 to July 2016, from 5 clinical toxicology units and calls to the Poisons Information Centre in New South Wales and Queensland. Included were patients >14 years who ingested ≥10 g or 200 mg/kg (whichever is less) of MR paracetamol over ≤8 hours or developed acute liver injury following a MR paracetamol ingestion.
Results: In total 54 patients were recruited over the study period (Table 1). The median dose ingested was 31.9 g; 39 patients had an initial paracetamol concentration above the nomogram line (150 mg/L at 4 hours). A further 7 (13%) crossed the nomogram after repeat paracetamol concentration measurements, of which 3 crossed after 2 non-toxic concentrations 4 hours apart. Six patients had a double paracetamol peak (in 3 occurring >24 hours post-ingestion). Thirty patients required prolonged treatment with acetylcysteine, in 18 (33%) this was due to a paracetamol concentration >10 mg/L at completion of 21 hours of intravenous acetylcysteine (range 13–272 mg/L). Eighteen developed an ALT >50 U/L, of which ten developed hepatotoxicity (ALT >1000). Three patients with hepatotoxicity were treated within 8 hours of ingestion and all had a paracetamol concentration >150 mg/L at 24 hours post-ingestion. A further patient developed hepatotoxicity despite ingesting <10 g and having non-toxic paracetamol concentrations (4 and 8 hours).
Conclusion: Following acute overdose of MR paracetamol patients may have persistently high paracetamol concentrations for >24 hours. Paracetamol concentrations can be erratic with double or delayed paracetamol peaks. Later doses of acetylcysteine may need to be increased in patients with persistently high paracetamol concentrations.

112. Analysis of an abbreviated acetylcysteine infusion protocol for repeated supratherapeutic ingestion (RSTI) of paracetamol

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Objective: In Australia, the treatment guideline for patients with RSTI of paracetamol recommends an abbreviated acetylcysteine regimen if the paracetamol concentration is <20 mg/L and alanine aminotransferase (ALT) is normal or static after 8 hours of infusion. There are currently no studies reporting outcomes of this recommendation. In a previous study of RSTI treated with 12 hours of acetylcysteine, hepatotoxicity only developed when AST was >50 IU/L on presentation [1]. We report a series of patients treated using the Australian guideline.
Methods: A prospective database of paracetamol overdose presentations was reviewed, from October 2009 to August 2016 at two toxicology networks (Monash Health, Victoria and Western Sydney Toxicology Service, NSW, Australia). All cases of RSTI, treated with acetylcysteine according to current the Australasian guideline were extracted. Data included demographics, number and duration of abbreviated acetylcysteine infusions, paracetamol dose and concentration, ALT, presence of hepatotoxicity, duration of acetylcysteine, and number of representations.
Results: Of 1995 paracetamol overdose presentations, 91 cases of RSTI were treated with acetylcysteine. Fifty-six (62%) were female with median age of 43 years (IQR 29–54). Median reported paracetamol ingested dose was 12 g (IQR 8–17) taken over a median time of 24 hours (IQR 24–48). Median time to initial blood tests was 6 hours post-last paracetamol dose (IQR 4–6). Sixty-three (69%) presentations had an initial detectable paracetamol concentration; median 195 µmol/L (IQR 118–400). Median ALT on presentation was 48 IU/L (IQR 18–109). After 8 hours of acetylcysteine the median ALT was 34 IU/L (IQR 16–71) in those receiving abbreviated treatment, and 74 IU/L (IQR 40–231) in those continuing acetylcysteine. Thirty-nine presentations (43%) had an abbreviated regimen. Nine (10%) patients had an initial ALT >50 IU/L and subsequently developed hepatotoxicity (ALT >1000 IU/L). The median duration of acetylcysteine for those with hepatotoxicity was 36 hours (IQR 29–60) versus 10.4 hours (IQR 4.8–12.0) who received an abbreviated regimen. The decreased duration of infusion correlated with a decreased length of stay. There were no re-presentations with liver failure.
Conclusion: In this study, no RSTI presentations with an initial ALT <50 IU/L developed hepatotoxicity during admission. Results support the observations of the previous study with a 12-hour regimen [1]. This suggests that an abbreviated 8 hour acetylcysteine infusion regimen for treatment of paracetamol RSTI may be safe and probably reduces length of stay for patients at low risk of hepatotoxicity.

Table 1. Demographic data, treatments and outcome in patients with modified release paracetamol ingestion.

Demographic data, treatments and outcome	All patients ($n = 54$)
% Females	40 (74%)
Median age (years) (IQR)	28 y (17–46)
Median dose ingested (grams) (IQR)	31.9 g (21.6–52.7)
Median dose ingested (g/kg) (IQR)	0.47 g/kg (0.29–0.7)
Median time to presentation (hours) (IQR)	2.5 h (1.1–7.3 h)
Received activated charcoal: median time to activated charcoal (hours) (IQR)	15 (27%): 1.5 h (1–3.5)
Commenced on acetylcysteine	54 (100%)
Median time to acetylcysteine (hours) (IQR)	4.3 h (2.7–8.5 h)
Prolonged acetylcysteine required beyond standard 21 h intravenous infusion	30 (56%)
Hepatotoxicity (ALT ≥1000 U/L)	10 (19%)

Reference

[1] Daly FFS, O'Malley GF, Heard K, et al. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med. 2004;44:393–398.

113. Review of the availability of paracetamol sold as over-the-counter drugs in European pharmacies; a descriptive cross sectional study

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Objective: Paracetamol is a very frequently used drug for overdose [1,2] and enquiries to poison information centres (PIC) concerning paracetamol-related poisonings are common. Availability of paracetamol varies in European countries; some have no pack size restriction in pharmacies, while others do [3]. The aim of the study was to describe availability of paracetamol sold over-the counter (OTC) in European pharmacies, secondly to investigate the association between availability and the frequencies of enquiries to PICs concerning poisoning with paracetamol.
Methods: A cross-sectional survey using a questionnaire describing the European status of paracetamol sold OTC in pharmacies and non-pharmacy outlets.
Results: In total, 21 European countries participated. In 67% ($n = 14$) pack size restriction in pharmacies were implemented. In 57% ($n = 12$), mild analgesics were not available in non-pharmacy-outlets. No significant difference ($p = .362$, median difference 0.7) was found when comparing median frequencies of enquiries concerning paracetamol poisonings in countries with pack size restriction to countries without. However, a significant difference was found between the median frequencies of paracetamol-related enquiries in countries with no non-pharmacy outlet sales to those with non-pharmacy outlet sales ($p = .020$, median difference 2.2). All PICs provided telephone hotline services. Routine risk assessment of paracetamol enquiries was performed in 77% of PICs of which 36% applied the Poisoning Severity Score (PSS).
Conclusion: Two-third of European countries had implemented restriction on mild analgesics in pharmacies. Fewer contacts to PICs concerning paracetamol poisonings were recorded in countries where pack size restrictions of mild analgesics sold as OTC in pharmacies were not implemented, and where sales in non-pharmacy outlets were prohibited. The small difference in median frequencies of enquiries between no pack size restriction and pack size restriction when no non-pharmacy outlet sale in the country demonstrates a probable safer profile of paracetamol use and with fewer poisonings when implementing pack size restriction and prohibiting sales in non-pharmacy-outlets.

References

[1] Craig DGN, Bates CM, Davidson JS, et al. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharmacol. 2011;71:273–282.

[2] Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav. 2000;30:313–326.

[3] Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. BMJ. 2013;346:f403.

114. Evaluation of a US Food and Drug Administration mandate to limit acetaminophen in prescription combination products

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Objective: In January 2014, the US Food and Drug Administration (FDA) limited the production of prescription acetaminophen-opioid combination products to 325 mg of acetaminophen per dose unit [1] in an effort to decrease the likelihood of unintentional acetaminophen overdose. The goal of our study was to determine if this FDA regulation has succeeded in its goal of reducing unintentional acetaminophen-induced hepatotoxicity.
Methods: Using data from the National Poison Data System (NPDS), we analyzed all calls to US Poison Control Centers in the years 2013 and 2015 for ingestions of acetaminophen-opioid combination products. The year 2014 was defined as a washout period, in which higher concentration products already manufactured could still be sold. Cases classified as intentional (suicidal intent, deliberate drug abuse, etc.) non-human exposures and patients aged 12 years and younger were excluded. We used a primary endpoint of N-acetylcysteine (NAC) administration; secondary endpoints included evidence of hepatotoxicity defined as aspartate aminotransferase (AST) elevation, opioid antagonist administration and severity of overall medical outcome. Two proportion *z*-test and Wilcoxon rank sum test were used to determine statistical significance.
Results: A total of 18,259 calls met inclusion criteria. Of those 5.2% and 5.0% of calls resulted in NAC administration in 2013 and 2015, respectively. In total 3.63% and 4.02% received naloxone in 2013 and 2015, respectively, and 0.9% in each year developed hepatotoxicity. Rates of NAC administration, naloxone administration, and hepatotoxicity did not differ significantly between 2013 and 2015. When compared to 2013, the severity of medical outcome was significantly worse in 2015 ($p = .007$: Wilcoxon Rank Sum) with more cases being categorized as having a "major" clinical effect (1.8% versus 1.4%, respectively) or a "minor" effect (18.3% versus 16.9%) and fewer cases being categorized as "no effect" (64.5% versus 65.7%). Overall mortality rates were identical in the two groups at 0.3%.
Conclusion: The FDA limitation on acetaminophen content per dose unit in combination products did not reduce the risk of acetaminophen-induced hepatotoxicity from unintentional exposures. Despite the lack of statistical significance, there was an overall decrease in NAC administration and an increase in naloxone administration.

Reference

[1] Food and Drug Administration. FDA Drug Safety Communication: Prescription acetaminophen products to be limited to 325 mg per dosage unit; Boxed warning will highlight potential for severe liver failure (13 January, 2011) [cited 2016 Sep 30]. Available from: www.fda.gov/drugs/drugsafety/ucm239821.htm

115. A characterization of levetiracetam abuse and misuse reported to US Poison Centers through the National Poison Data System (NPDS)

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Objective: Levetiracetam is an antiepileptic medication commonly prescribed for partial and generalized seizures. It is used frequently as seizure prophylaxis for patients with brain tumors and intra-cerebral hemorrhage. Reports of abuse and misuse of levetiracetam have been increasing, yet a clinical pattern of abuse and misuse is unknown. Therefore, the purpose of this study was to characterize calls reported to the National Poison Data System (NPDS) of levetiracetam abuse and misuse.
Methods: All cases of levetiracetam abuse and misuse reported to the NPDS between 1 January 2012 and 31 December 2015 were extracted with NPDS generic codes and product codes for levetiracetam. Only cases involving single-agent abuse and misuse of levetiracetam as the major category were analyzed. Descriptive statistics were generated for demographic data, symptoms, disposition, clinical effects, route of administration, treatments, and severity of clinical effects.
Results: During the 48-month study period, there were 109 single agent reports of abuse or misuse of levetiracetam. The mean age was 26.1 years and the range was 13–61 years. Cases were nearly evenly distributed between men and women (women $n = 56$; 51.4%). Most cases involved ingestion ($n = 106$; 97.2%) and the most common clinical effects were drowsiness/lethargy ($n = 22$; 20.2%), agitation/irritability ($n = 8$, 7.3%), nausea ($n = 8$; 7.3%), and seizures ($n = 8$; 7.3%). Of the medical outcomes, 22 were minor (20.2%), 8 were moderate (7.3%) and none were major. Most patients were treated and released ($n = 43$; 39.4%) and 14 (12.8%) were admitted. No treatment was administered in 83 patients (76.1%). The most common therapeutic intervention was intravenous fluids ($n = 13$; 11.9%). There were no deaths.
Conclusion: Most exposures resulted in non-life-threatening effects not requiring treatment, although a minority of exposures resulted in more clinically significant effects, including seizures. Cases of levetiracetam abuse and misuse are rising, and healthcare providers should be aware of the clinical patterns associated with this drug.

116. Acute lamotrigine overdoses treated at the Department of Emergency and Clinical Toxicology during a 3-year period clinical overview

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Objective: The aim of the present study was to analyze the clinical features of acute lamotrigine overdose [1].
Methods: Data were collected from medical records of patients treated under the diagnosis of lamotrigine overdose at the Department of Emergency and Clinical Toxicology during a 36-month period. Case records were reviewed for age, gender, ingested dose, lamotrigine serum concentrations, type of concomitants, symptoms, hemodynamic parameters, complications and overdose severity according to Poisoning Severity Score (PSS).
Results: There were 27 patients with an average age of 40 ± 13 years; most (78%) were female. All analyzed cases involved intentional ingestion. The average ingested dose was 2222.2 mg, while the mean lamotrigine serum concentration was 16.3 ± 7.5 mg/L. There was a statistically significant positive linear correlation between ingested doses and lamotrigine concentrations ($r = 0.692$; $p < .001$). The average time interval between the lamotrigine intake and admission was 6.4 ± 3.4 hours. Lamotrigine was the only ingested drug in 30% of patients. Benzodiazepines were the most commonly used concomitants, reported in 15 cases, followed by antipsychotics and antidepressants in 5 and 2 patients, respectively. Clinical effects at admission were dysarthria (48.2%), somnolence (22.2%) and ataxia (22.2%). Drowsiness was reported by 33.3% of patients, while 7.4% of patients experienced nausea. Stupor and coma were presented in 18 cases. Tachycardia was noted in 52% of patients, QTc prolongation in 22% while 30% of patients were hypotensive. One or more complications developed in 12 patients: bicytopenia ($n = 1$), rhabdomyolysis ($n = 12$), bronchopneumonia ($n = 8$), respiratory failure ($n = 4$) and adult respiratory distress syndrome (ARDS) ($n = 3$). The PSS was 1 in 33% patients, 2 in 26% and 3 in 37% of patients. There was one lethal outcome. Patients with severe poisoning had significantly lower blood pressure at admission compared to patients with mild clinical features ($p < .01$). Correlation between PSS and lamotrigine concentration, dose ingested as well as concomitants was not found. The maximal detected lamotrigine concentration (34.7 mg/L) occurred with moderate clinical features with no concomitants detected. Fatal outcome of a female patient with lamotrigine concentration of 17.2 mg/L and coingested benzodiazepines was due to ARDS.
Conclusion: Although lamotrigine toxicity mainly produces mild to moderate effects, clinical manifestations can be severe and life-threatening.

Reference

[1] Moore PW, Donovan JW, Burkhart KK, et al. A case series of patients with lamotrigine toxicity at one center from 2003 to 2012. Clin Toxicol. 2013;51:545–549.

117. Clinical features of acute carbamazepine poisoning in children: a 5-year retrospective study

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Objective: To assess the clinical picture and evolution of poisoning in children with acute carbamazepine overdose.
Methods: We performed a 5-year retrospective study using the medical records of children with acute carbamazepine poisoning admitted in our hospital. The following criteria were taken into consideration: age, gender, symptoms and evolution.
Results: Overall 101 children with acute carbamazepine poisoning were registered between 2011 and 2015. Of these, 28 cases involved carbamazepine and other drugs: antiepileptics ($n = 8$), antipsychotics ($n = 7$), nonsteroidal anti-inflammatory drugs and

benzodiazepines ($n = 6$ each) and tricyclic antidepressants ($n = 1$). There were 72 girls (7.1%) and 29 boys (2.8%). Regarding the age we noted the peak of incidence between 12 and 18 years old ($n = 55$, 54.5%), followed by 1–5 years old age ($n = 31$, 30.7%). Neurological symptoms were the most frequently noted with ataxia ($n = 93$, 92%), lethargy ($n = 91$, 90.1%), coma ($n = 62$, 61.4%) and seizures ($n = 9$, 8.9%). Over 54 patients (53.4%) had vomiting which in 7 children lead to acute dehydration. Metabolic acidosis was observed in 37 children (36.6%). Cardiovascular disorders were noted in 44 patients (43.5%) with sinus tachycardia ($n = 30$, 29.7%), bradycardia ($n = 4$, 3.9%), hypertension ($n = 6$, 5.9%) and hypotension ($n = 4$, 3.9%). Of 101 patients, 32 (31.7%) were admitted to the intensive care unit and the median length of stay was 18.7 hours. The average length of hospitalization in our study was 2.95 days. There were no deaths in the study group.

Conclusion: Neurological events such as ataxia and varying degrees of consciousness alteration are the main symptoms in acute carbamazepine poisoning in children as well as in adults [1]. In our study these are followed by gastrointestinal and cardiovascular disorders that had lower incidence and severity compared to adults [1]. Although acute carbamazepine poisoning in children is severe, the evolution is favorable, with no deaths being noted [2].

References

[1] Dyon S. Anticonvulsants. In: Nelson LS, Levin NA, Howland MA, et al., eds. Goldfrank's Toxicologic Emergencies. 9th ed. New York (USA): McGraw Hill Medical; 2011; p. 699–702.

[2] Barrueto F, Nelson LS. Antiepileptics in: Erickson TB, Baum CR, Ling LJ, editors. Pediatric Toxicology: Diagnosis and Management of the Poisoned Child. New York (PA): The McGraw-Hill Companies; 2005. p. 287–288.

118. Severe toxicity following lamotrigine overdose: a review of calls to Australia's largest Poisons Information Centre

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Objective: Lamotrigine is an antiepileptic which has recently been used in bipolar disorder. Previous case series have reported that severe toxicity is rare after lamotrigine overdose. We report increasing lamotrigine use with several fatal overdoses in psychiatric patients.

Methods: A retrospective study of calls to New South Wales Poisons Information Centre (NSWPIC). Intentional exposures to lamotrigine 2004–2016 were included.

Results: Intentional lamotrigine overdoses have steeply increased, with 32 cases per year, 2004–06, increasing to 81 cases per year, 2013–15. This increase was not reflected in government subsidised scripts for epilepsy, and may instead signal increasing use for non-subsidised psychiatric conditions. Although many overdoses followed a benign course, fatalities have been reported in NSWPIC cases, including two deaths in 2016 despite maximal resuscitation including bypass attempts. Case 1: A 54-year-old female ingested 5 g of lamotrigine, 3 g of modified release quetiapine, and 75 mg of zopiclone. Three hours post-ingestion she became hypotensive and developed electrocardiogram (ECG) abnormalities (QT prolongation, QRS widening, horizontal ST depression) and hyperdynamic bedside echocardiogram indicating distributive shock. This progressed to cardiac arrest with pulseless electrical activity. The patient died despite aggressive resuscitation including bicarbonate, methylene blue, vasopressin, high-dose insulin euglycaemic therapy (HIET), lipid emulsion and bypass. Case 2: A 43-year-old female ingested 11 g lamotrigine, 500 mg temazepam, and an unknown amount of fluoxetine. She required intubation and 24 hours post-ingestion developed hyperthermia, clonus, seizures, and had a cardiac arrest. Treatment included HIET, phenobarbital, bicarbonate, adrenaline, noradrenaline and extra-corporeal membrane oxygenation (ECMO), however she progressed to multi-organ failure.

Conclusion: Here, we describe two cases of fatal lamotrigine toxicity in the context of an increase in exposures over the past decade. It appears that lamotrigine is being increasingly used in psychiatry, in an at-risk population for self-poisoning, and thus these cases are likely to continue to occur. Bicarbonate failed to be effective in these fatalities. *In vitro* evidence suggests that bicarbonate may have a neutral or detrimental effect on sodium channel blockade caused by some drugs, notably lamotrigine and carbamazepine [1]. Furthermore, lamotrigine may inhibit monoamine oxidase, which is particularly relevant for Case 2 who co-ingested fluoxetine. There does not appear to be a clear dose-related toxicity and outcomes may depend on co-ingestants or individual patient factors.

Reference

[1] Lazar A, Lenkey N, Pesti K, et al. Different pH-sensitivity patterns of 30 sodium channel inhibitors suggest chemically different pools along the access pathway. Front Pharmacol. 2015;6:210.

119. Severe valproic acid poisoning associated with atrial fibrillation and extremely high serum concentrations

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Objective: Massive overdose of valproic acid (VPA) may result in deep coma, organ dysfunction and death; it can also mimic brain death. We present a case of a patient who developed hypernatraemia, shock, repetitive atrial fibrillation, cerebral oedema, long-lasting toxic encephalopathy and bone marrow depression with an extreme serum valproate concentration exceeding 3000 mg/L.

Case report: A 27-year-old male was found unresponsive at home. He was last witnessed to be awake about 8 hours earlier. Endotracheal intubation mechanical ventilation was commenced by the emergency medical service. On admission to our department his vital signs and parameters were: blood pressure 76/44 mmHg, heart rate 67 bpm, pH 7.28, potassium 5.60 mmol/L and sodium 160 mmol/L. Taking the hypernatraemia and deep coma into consideration severe valproate overdose was suspected. The patient's serum valproate concentration was 2346 mg/L. He was treated with gastric lavage followed by repeated whole bowel irrigation along with multiple dose activated charcoal. After starting pressor amine therapy extracorporeal elimination with haemoperfusion was initiated 4 hours after admission followed by haemodialysis. The VPA concentration was 3188 mg/L at the start of haemoperfusion and dropped to 690 mg/L after the

termination of haemodialysis. In the first 3 days he developed several episodes of atrial fibrillation requiring DC shock and initiation of amiodarone. Echocardiography revealed left ventricular dysfunction (ejection fraction of 40%) without regional wall motion abnormality. During this period clinical examination revealed absence of all brain stem reflexes including absent pupillary responses to light along with mild hyperammonaemia and elevated S-100 protein concentrations. The patient's cerebral oedema was checked by computerised tomography (CT) scan and repeated optic nerve measurements. He developed severe thrombocytopenia, leucopenia and sepsis. After treatment with antibiotics, filgrastim and repeated transfusions his parameters gradually stabilized and the patient was discharged from intensive care 15 days after admission. A repeat echocardiography showed an ejection fraction of 50%.
Conclusion: To our best knowledge, this is the first case when a patient survived an ingestion of valproate of 135 g with a serum concentration over 3000 mg/L. In such severe cases repeated gastric and intestinal decontamination and repeated elimination could be effective even several hours after ingestion. Bedside ultrasonography is useful to monitor cardiac function and to assess the severity of cerebral oedema in patients with life-threatening valproate poisoning.

120. Lamotrigine enquiries to the Austrian Poisons Information Centre: a retrospective 14-year study

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Objective: Lamotrigine is an antiepileptic drug which is also used in the treatment of bipolar disorders. The aim of this study was to analyse circumstances and symptoms after overdose with lamotrigine.
Methods: A retrospective and descriptive review of enquiries to the Austrian Poisons Information Centre (PIC) concerning lamotrigine from 2002 to 2015 was conducted.
Results: In total 514 cases were extracted from the database. In 124 patients mono-intoxications occurred, the amount of intake was known, the route was oral, and in patients under the age of 15 years the weight also was known. The majority of patients were ≥15 years old (81 cases; 65%). No symptoms occurred in 12 cases after accidental exposure (25 mg to 1.2 g). One patient developed symptoms (dystonia, dysarthria, fatigue) after 100 mg due to a therapeutic error. Intentional overdose occurred in 68 patients (200 mg to 16 g). At the time of PIC consultation 19 out of this group had no symptoms (200 mg to 10 g). In 37 cases the symptoms were mild (500 mg to 8 g) with drowsiness, nausea, vomiting, vertigo, headache, tremor, nystagmus, diplopia, tachycardia, hypotension, and hypertension. Moderate symptoms occurred in 10 patients (1.5–16 g) with agitation, muscle fasciculation, convulsion, dyskinesia, choreoathetosis, and repolarisation disorder. Two patients developed deep coma (4 and 6 g). No fatalities were documented. In the paediatric group there were 43 (35%) cases; with an age ranging from 9 months to 14 years; the ingested amount was 0.7–53.8 mg/kg. Most intakes ($n = 40$) were accidental overdoses and 3 cases were intentional. At the time of PIC consultation the majority ($n = 35$) had no signs of intoxication. Seven children (15.4–53.9 mg/kg) had the following symptoms: nausea, vomiting, ataxia, muscle fasciculation, tachycardia, and drowsiness. A 2-year-old child developed symptoms after 6.5 mg/kg with vomiting, ataxia, muscle fasciculation, convulsion, and agitation. The serum lamotrigine concentration was 25.25 µg/mL.
Conclusion: In our series, adults developed mild symptoms after exposure of ≥500 mg lamotrigine. One paediatric patient suffered moderate symptoms after intake of 6.5 mg/kg lamotrigine. Since infants seem to have a higher susceptibility, ingestion of lamotrigine in children should be evaluated very carefully.

121. Exposures to valproic acid: a 14-year descriptive study of Austrian Poisons Information Centre data

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Objective: Valproic acid is often used in the treatment of seizures, bipolar affective disorders and migraine. The aim of this study was to evaluate calls concerning valproic acid made to our poisons centre.
Methods: In a retrospective and descriptive study enquiries to the Austrian Poisons Information Centre (PIC) regarding exposures to valproic acid from 2002 to 2015 were analysed.
Results: A total of 746 cases of valproic acid ingestion were identified in our database, including 274 patients exposed to only valproic acid. Of these, the dose intake was known in 219 cases, the route was oral and in patients under the age of 15 the weight was also known. The majority of cases involved patients over the age of 15 years ($n = 159$; 72.6%). No symptoms occurred in 15 cases after accidental exposure (250 mg to 3 g), in 14 patients due to a therapeutic error (150 mg to 2.5 g) and in 5 cases with unclear reasons of exposure (500 mg to 7.5 g). Intentional overdose occurred in 125 patients (1.5–60 g). At the time of PIC consultation 57 patients in this group had no symptoms. In 55 cases the symptoms were mild with miosis, hypotension, nausea, vomiting, headache, vertigo, drowsiness, and somnolence (4.5–45 g). Moderate symptoms occurred in 13 patients (5–60 g) including sinus tachycardia, agitation, confusion, unconsciousness with response to pain ($n = 2$, 25 g, 60 g) and hyperammonaemia (intake of more than 7.8 g). In the paediatric group there were 60 cases (27.4%); the age range was 4 months to 14 years, weight: 5.5–95 kg and dose ingested 3.3–142.9 mg/kg. The exposures were accidental in 48 patients (80% of pediatric group), therapeutic error in 8 cases (13.4%), intentional in 2 cases (3.3%) and unknown in 2 cases (3.3%). At the time of PIC consultation 3 children had minor symptoms (50–83.3 mg/kg) with nausea, vomiting and fatigue. A 3-year-old child developed mild sinus bradycardia (136.5 mg/kg) and a 2-year-old child developed convulsions and somnolence (107.1 mg/kg). No fatalities were documented.
Conclusion: Intoxications with valproic acid are generally reported to be low [1], however, severe intoxications have been described in single cases [2]. Our data confirm the assumption that overdose with valproic acid does not cause severe symptoms in the majority of cases.

References

[1] Isbister GK, Balit CR, Whyte IM, et al. Valproate overdose: a comparative cohort study of self poisonings. Br J Clin Pharmacol. 2003;55:398–404.
[2] Andersen GO, Ritland S. Life threatening intoxication with sodium valproate. Clin Toxicol. 1995;33:79–284.

122. Comparative extractive efficiency of continuous veno-venous hemodiafiltration (CVVHDF) and molecular adsorbent recirculating system (MARS) in simulated verapamil poisoning: an *ex vivo* study

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Objective: No analytical studies have quantified the extractive efficiency of the different compartments of continuous veno-venous hemodiafiltration (CVVHF) and molecular adsorbent recirculating system (MARS). The objective of this study was to quantify and compare these methods in an *ex vivo* model providing the most favorable conditions for both methods to assess their maximum extractive capability.
Methods: *Ex vivo* studies simulated verapamil poisoning with an initial plasma concentration of 1, 2.5 and 5 mg/L injected into a 5-liter central compartment. Sampling was carried out at various points of the circuits. The EC extraction coefficient (EC = (in concentration – out concentration)/in concentration) was calculated for each compartment of the CVVHDF and MARS and the cumulative amount eliminated in the effluents. Three manipulations were performed for each concentration. In both systems the flows were maintained constant at 210 mL/min with a net zero hemofiltration. The solute was lactated Ringers without protein in the central compartment. The MARS system was primed with human albumin (500 mL at 20%).
Results: Mean CVVHDF ECs were always concentration-dependent becoming negative after 14 hours, suggesting late release from the cartridge. At the end of the sessions the mean amounts remaining in the central compartment were 6, 3 and 4% of the injected dose, respectively. The mean cumulative amounts found in the effluent were 16, 20 and 28% of the injected dose, respectively. The amounts "not found" accounted for 78, 79 and 69% of the injected dose, respectively. Ultrasonic desorption of the membranes revealed that verapamil was fixed by the membrane of the CVVHDF. In contrast, the different compartments of the MARS resulted in undetectable output concentration at the end of the session and even earlier. The mean concentrations of verapamil in the central compartment were undetectable at the end of the sessions. The mean ECs were concentration-dependent of about 20% of the injected dose. The mean amounts withdrawn by the activated charcoal compartment were 92, 82 and 89% of the injected dose. The mean charcoal ECs of the MARS cartridge was stable and in the order of 70% throughout the manipulations, independent of the concentration.
Conclusion: With CVVHDF the process for verapamil elimination is far more complex than previously reported resulting from a combination of limited HDF and extent of adsorption. The dose-dependency elimination of verapamil precludes modelling using first-order kinetics. MARS elimination works faster and was more extensive owing to the dose-independent adsorption of verapamil on activated charcoal.

123. Leukotriene-mediated neuroinflammation and toxic brain damage in methanol poisoning

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Objective: The role of endogenous leukotriene-mediated neuroinflammatory mechanisms in the pathophysiology of toxic methanol-induced brain damage has not been studied. We studied acute concentrations and the dynamics of leukotrienes (LTs) in peripheral blood serum in hospitalized patients with acute methanol poisoning and in survivors two years after discharge.
Methods: A series of acute cysteinyl-LT (LTC4, LTD4, LTE4) and LTB4 concentration measurements were performed in 28 of 101 patients hospitalized with confirmed methanol poisoning (mean observation time 88 ± 20 hours, mean number of samples/patient 12 ± 2). LTs were measured by liquid chromatography-electrospray ionization-tandem mass spectrometry. In 36 survivors of poisoning included in the follow-up clinical examination program, control LT measurements were performed two years after discharge. Optical coherence tomography with retinal nerve fiber layer thickness evaluation (RNFL), visual evoked potentials (VEP), magnetic resonance imaging (MRI) of the brain, complete ocular and neurological examination and biochemical tests were performed within the follow-up examination.
Results: The acute maximum (C_{max}) LT concentrations were higher than the follow-up LT concentrations in survivors two years after discharge: C_{max} for LTC4 was 80.7 ± 5.6 versus 47.9 ± 4.5 pg/mL; for LTD4, 51.0 ± 6.6 versus 23.1 ± 2.1 pg/mL; for LTE4, 64.2 ± 6.0 versus 26.2 ± 3.9 pg/mL; for LTB4, 59.8 ± 6.2 versus 27.2 ± 1.4 pg/mL (all $p < .001$). The patients who survived had higher LT concentrations than those who died (all $p < .01$). Among survivors, those with central nervous system (CNS) sequelae had lower LTE4 and LTB4 than those without sequelae (both $p < .05$). The LT concentrations increased at a rate of 0.4–0.5 pg/mL/h and peaked 4–5 days after admission. The patients with better outcomes had higher acute cys-LTs (all $p < .01$) and LTB4 ($p < .05$). More severely poisoned patients had lower acute LT concentrations than those with minor poisoning. The follow-up LT concentrations in survivors with and without CNS sequelae did not differ (all $p > .05$). The mean decrease in LT concentration was 30.9 ± 9.0 pg/mL for LTC4, 26.3 ± 8.6 pg/mL for LTD4, 37.3 ± 6.4 pg/mL for LTE4, and 32.0 ± 8.8 pg/mL for LTB4. The follow-up LT concentrations did not correlate with age, gender, acute laboratory parameters or outcome of poisoning. No correlation of control LT concentrations was found with any follow-up laboratory parameter and the results of VEP, RNFL, and MRI of the brain.
Conclusion: Leukotriene-mediated neuroinflammation plays an important neuroprotective role in the mechanisms of methanol-induced brain damage in humans. Acute elevation of LT concentrations was moderate, transitory, and not followed by chronic neuroinflammation in survivors two years after discharge.
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124. Transient receptor potential (TRP) channels as therapeutic targets in toxic lung injury

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Objective: Exposure to highly toxic inhalation hazards can cause severe acute and chronic health effects. Harmful compounds can be released during occupational accidents, combustion processes or in terrorist attacks as demonstrated by the recent use of the alkylating agent sulfur mustard (SM) in Syria and Iraq. The underlying molecular toxicology of lung injury evoked by these agents has long been described as rather unspecific. As a consequence, an antidote is not available yet and therapy is limited to symptomatic measures. However, ion channels of the transient receptor potential (TRP) family have been identified to act as specific sensor molecules for highly reactive substances, thereby regulating pulmonary blood flow, the integrity of the epithelial lining, and the mucociliary clearance of the bronchial system.
Methods: TRPA1 expressing in lung epithelial cells and tissue was investigated using Western Blot, polymerase chain reaction (PCR), immunocytochemistry and functional calcium-measurements. TRPA1-overexpressing HEK cells and A549 cells, endogenously expressing TRPA1, were challenged with different alkylating agents. Influence on intracellular calcium concentrations ($[Ca^{2+}]_i$) was assessed using aequorin-based probes. Impact on cytotoxicity was analyzed using cell viability assays.
Results: Expression of TRP-chemosensors (i.e., TRPA1) was found in pulmonary neuronal but also non-neuronal cells like the pulmonary epithelium. Activation of respiratory TRPA1 chemosensors by highly toxic alkylating agents *in vitro* resulted in immediate elevation of intracellular calcium concentrations. In addition, TRPA1-overexpressing was associated with increased cytotoxicity after SM exposure. Remarkably, specific TRPA1-channel inhibitors (e.g., AP18) prevented channel activation and significantly reduced cytotoxicity. Moreover, exposure with alkylating compounds resulted in the initiation of complex signaling networks directly or indirectly mediated through TRPA1 channels [1,2].
Conclusion: Chemosensing TRP channels have to be recognized as a novel, initial target in the pathophysiology of toxic inhalation hazards suggesting that acute health effects are likely to be mediated by these channels. Thus, medical countermeasures, addressing these chemosensing TRP channels may represent a specific, early approach counteracting acute health effects of toxic lung injury.

References

[1] Stenger B, Popp T, John H, et al. N-acetylcysteine inhibits sulfur mustard-induced and TRPA1-dependent calcium influx. Arch Toxicol. 2016. [Epub ahead of print].
[2] Stenger B, Zehfuss F, Mückter H, et al. Activation of the chemosensing transient receptor potential channel A1 (TRPA1) by alkylating agents. Arch Toxicol. 2015;89:1631–1643.

125. Pharmacogenetics of 3,4-methylenedioxymethamphetamine (MDMA): cytochrome P450 polymorphisms moderate pharmacokinetics and pharmacodynamic effects of MDMA in healthy subjects

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Objective: *In vivo* and *in vitro* studies respectively showed that cytochrome P450 (CYP) 2D6, CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") [1,2]. However, the role of genetic polymorphisms in CYP2D6, CYP2C19, CYP2B6, and CYP1A2 in the metabolism of MDMA in humans is unknown. Therefore, we characterized the effects of genetic variants in these CYP enzymes on the pharmacokinetics and pharmacodynamic effects of MDMA.
Methods: The genetic variants in these CYP enzymes were characterized in 139 healthy subjects (69 male, 70 female, aged between 18–45 years) in a prospectively designed pooled analysis of eight double-blind, placebo-controlled, crossover studies. MDMA was administered orally in a single dose of 75 or 125 mg (0.8–2.7 mg/kg; mean 1.7 mg/kg). Blood samples and pharmacodynamic measures were taken repeatedly up to 6 hours after dosing. Subjective effects were assessed using Visual Analogue Scales (VAS) including: "any drug effect" and "drug liking". Genomic DNA was extracted from whole blood. Genotyping was performed using TaqMan SNP genotyping assays.
Results: CYP2D6 poor metabolizers (PMs) exhibited increased peak plasma concentrations of MDMA (+15%) and its active metabolite, 3,4-methylenedioxyamphetamine (MDA, +50%), compared to extensive metabolizers (EMs), and decreased concentrations of the inactive metabolite 4-hydroxy-3-methoxymethamphetamine (HMMA, −50%). Blood pressure and subjective drug effects increased more rapidly after MDMA administration in CYP2D6 PMs than in EMs. MDMA-MDA conversion was positively associated with genotypes known to convey higher CYP2C19 or CYP2B6 activities. Additionally, CYP2C19 PMs showed greater cardiovascular responses to MDMA compared with other CYP2C19 genotypes. Furthermore, the maximum concentration of MDA was higher in tobacco smokers that harbored the inducible CYP1A2 rs762551 A/A genotype compared with the non-inducible C-allele carriers.
Conclusion: The findings indicate that genetic polymorphisms in CYP2D6, CYP2C19, CYP2B6, and CYP1A2 contribute to the metabolism of MDMA in humans. Additionally, genetic polymorphisms in CYP2D6 and CYP2C19 may moderate the pharmacodynamics effects of MDMA.

References

[1] Kreth K, Kovar K, Schwab M, et al. Identification of the human cytochromes P450 involved in the oxidative metabolism of "Ecstasy"-related designer drugs. Biochem Pharmacol. 2000;59:1563–1571.
[2] Meyer MR, Peters FT, Maurer HH. The role of human hepatic cytochrome P450 isozymes in the metabolism of racemic 3,4-methylenedioxy-methamphetamine and its enantiomers. Drug Metab Dispos. 2008;36:2345–2354.

126. Age of misuse exposures reported by the Global Toxicosurveillance Network (GTNet)

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Objective: To determine the age of misuse exposures with the top drugs of misuse reported by GTNet poison centres (PCs) in Italy, the UK, Germany, and France.
Methods: Data collected on prescription opioids, stimulants, sedatives, benzodiazepines, cannabinoids, and anticonvulsants from participating PCs in GTNet were obtained for 2013–2015. The five drugs with the highest misuse, defined as an exposure resulting from the intentional improper or incorrect use of a substance, were determined for Italy (Milan), the UK (Birmingham, Cardiff, Edinburgh, Newcastle), Germany (Göttingen), and France (Paris). The median age in years and interquartile range were calculated for each country's top five drugs excluding exposures reported with missing ages. A Kruskal–Wallis test was used to test for differences between the distribution of ages within the top 5 drugs of each country. The UK provides medical management advice to healthcare providers only, while the other PCs also offer services to the public.
Results: Italy reported median ages in the 30s and 40s. Within the top five reported drugs in the UK, four different drug classes (benzodiazepines, stimulants, opioids, and anticonvulsants) were represented. Benzodiazepines appear to be most commonly misused across all countries except France. The distribution in age was significantly different between the drugs for all countries except the UK, keeping in mind the UK only receives calls from healthcare providers.
Conclusion: Each country identified different top five prescription drugs of misuse as well as the associated age. While poison centre methods vary across countries, these data are indicative of diverse regional trends in prescription drug misuse and allow for better understanding of age groups at highest risk.

127. Using Swedish Poisons Information Centre data to identify chemical accident hazards at the workplace

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Objective: Official occupational accident statistics are often incomplete which reduces their value as a decision basis for risk management measures [1]. The present study aims to investigate whether calls made to the Swedish Poisons Information Centre (PIC) concerning occupational exposures can improve the knowledge about occupational accidents involving hazardous substances in Sweden.
Methods: A retrospective review of calls made to the PIC during the five year period 2010–2014 identified 8236 occupational incidents. Cross tabulations and descriptive statistics were employed to describe the occupational incidents found in the material. The findings were compared to accident statistics from the Swedish Work Environment Authority (SWEA). Ethical vetting was applied for and granted by the ethical review board in Stockholm, Sweden.
Results: A majority of the 8236 occupational incidents were considered as posing no to minor or moderate risk to the exposed individuals (76%). One third of the calls were made by healthcare staff and two thirds by the general public. For the latter group, more than half (62%) received advice on how to manage on site. The three most commonly reported chemical groups were alkali ($n = 1518$, excluding ammonia), hydrocarbons ($n = 1125$, including halogenated hydrocarbons) and acids ($n = 969$). Eye exposure was the most common exposure route recorded ($n = 3048$), followed by inhalation ($n = 2638$) and skin ($n = 1425$). Reviewing the SWEA database of occupational accidents during the study period we were able to identify 1234 accidents involving injuries caused by chemical exposures. However, these data are less detailed with regards to chemical identity, for instance only the source of the spill (e.g., "bucket"/"hose"), not the content of the specific product, was entered in 44% of the cases.
Conclusion: Although the Swedish PIC records are not collected for the purpose of occupational surveillance, they may complement official statistics on occupational accidents with chemicals. For instance PIC data are more precise regarding product and chemical identity and may thus help identify problematic occupational uses. Importantly, the PIC records also cover incidents leading to minor or no injuries. Such incidents are generally not reported to the SWEA as employers' reporting obligations mainly cover severe injuries.

Table 1. Top 5 prescription drugs of misuse per country with associated median age in years and interquartile range.

Italy ($n = 716$)			UK ($n = 574$)			Germany ($n = 648$)			France ($n = 98$)		
Top 5 Drugs	Median Age (IQR)	Wilcoxon *p*-value	Top 5 Drugs	Median Age (IQR)	Wilcoxon *p*-value	Top 5 Drugs	Median Age (IQR)	Wilcoxon *p*-value	Top 5 Drugs	Median Age (IQR)	Wilcoxon *p*-value
Lorazepam	43.5 (33.5–55.0)	<.0001	Diazepam	27.0 (21.0–36.0)	.0738	Amphetamine	27.0 (22.0–32.0)	<.0001	Codeine	27.5 (20.0–36.5)	.0105
Alprazolam	37.0 (24.0–46.0)		Amphetamine	27.0 (20.0–36.5)		Diazepam	36.5 (30.0–47.0)		Zolpidem	35.0 (26.0–61.0)	
Methadone	33.5 (27.5–41.5)		Codeine	33.0 (23.5–38.5)		Methadone	36.0 (31.0–44.0)		Tramadol	30.5 (24.0–32.0)	
Diazepam	40.0 (28.0–47.0)		Pregabalin	32.0 (24.0–38.0)		Lorazepam	38.0 (31.0–49.0)		Diazepam	30.0 (22.5–36.0)	
Zolpidem	46.0 (35.0–66.0)		Methadone	30.0 (25.0–39.0)		Buprenorphine	33.0 (30.0–42.0)		Methadone	46.5 (38.5–51.0)	

Reference

[1] Leigh JP, Marcin JP, Miller TR. An estimate of the U.S. government's undercount of nonfatal occupational injuries. J Occup Environ Med. 2004;46:10–18.

128. Utilisation of desferrioxamine in iron poisoning: experience of the UK National Poisons Information Service (NPIS) 2014–2016

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Objective: Despite significant reductions in severe iron (Fe) poisoning following pack and utilisation changes, and lower mortality (England approximately 1/year), clinicians remain uncertain about when to use desferrioxamine (DFO). Current UK indications include large oral dose (elemental Fe >150 mg/kg), high serum concentration (>90 µmol/L) and/or lower dose (>75 mg/kg) and plasma iron concentration (>55 µmol/L) with symptoms suggestive of severe poisoning. This study compares use of DFO in the UK against these criteria.
Methods: We prospectively collected NPIS data on medicinal iron overdose from 1 February to 4 September 2016. We compared all enquiries for single Fe ingestion, or mixed ingestions including Fe, and assessed indications used for DFO.
Results: There were 172 calls regarding iron ingestion in children (<15 years) and 498 regarding adults. DFO was administered in 10 children (1 mixed overdose) and 52 adults (25 mixed overdoses). In 6 children (60%) DFO was commenced before NPIS advice, but in all these cases treatment was probably unnecessary (2 no indication, 2 asymptomatic with concentrations 79 and 82 µmol/L, 2 drowsy with low ingested dose). NPIS advised DFO in 4 children (1 concentration only [92 µmol/L]; 1 haematemesis, coma, dose 148 mg/kg; 1 vomiting, acidosis, dose 88 mg/kg; 1 vomiting, haematemesis, concentration 70 µmol/L). In 36 adults (67%), DFO was commenced before NPIS advice. Indications for treatment included: concentration and/or features ($n = 15$), features only ($n = 5$), ingested dose (114 mg/kg) or concentration (75, 83, 89, 90, 104 µmol/L) in the absence of features ($n = 6$). Features of toxicity occurred in 20 patients: gastrointestinal $n = 13$; acidosis $n = 13$; hypotension $n = 2$; reduced consciousness $n = 2$. In 10 cases there was no clear indication for DFO. NPIS advised DFO in 16 adults (9 single, 7 mixed ingestions). Of the single ingestions, 8 were treated for features and concentration (57, 61.5, 64, 73, 73, 82, 98 µmol/L) while 1 was treated on ingested dose only (100 mg/kg). DFO was advised for the mixed ingestions based on dose ingested and features. There were 2 deaths, neither attributable to Fe.
Conclusion: Significantly more children (60%) than adults (20%) treated with DFO were treated without definitive indication prior to contacting NPIS (chi-squared 7.28, $p < .01$). Most DFO use in adults was in cases with intermediate iron dose or concentration and features suggestive of poisoning. Overall, only 4 patients (1 child), had concentrations >90 µmol/L. Life-threatening iron toxicity is rare. Concerns over the risks may lead to unnecessary use of DFO. A better understanding of the relationship between iron toxicity, ingested dose, serum concentration and features is required.

129. Please "like" us: Facebook as an outreach tool for a poisons information centre

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Objective: In April 2012, the National Poisons Information Centre (NPIC) launched a Facebook page with the aims of increasing awareness of the NPIC telephone information service to the general public and sharing poison prevention messages. The initial target audience for the page was carers of young children and parents in the 25–34-year-old age group. It is an information only page and is not used to answer poisoning enquiries. Two administrators manage the page posting poisons information every 2 weeks, sharing relevant news items and supporting annual safety campaigns such as Carbon Monoxide Awareness week. Page visitors are invited to "Like" and "Share" the page. We describe the experience of introducing and maintaining a Facebook page, monitoring page activity and subsequent trends in members of the public (MOP) enquiries to the NPIC.
Methods: The review period was from 1 January 2010 to 1 April 2016 inclusive. Facebook defines "Likes" as the number of people who follow the page and "Reach" as the number of people the posts were served to. We reviewed the data generated by Facebook and assessed the impact on MOP enquiries to the NPIC.
Results: During the first 3 months of Facebook activity, the number of "Likes" was 130 and the average weekly "Reach" was 736. Numbers remained consistent until the end of 2014, when the administrators increased the number of posts and monitoring activity, specifically targeting parenting groups, childminders and paramedics with requests to "Like" and "Share" the page. From this time onwards "Likes" increased substantially. During the last 3 months of Facebook activity, "Likes" had increased to >18,200 and the average weekly "Reach" was >21,000. The demographics of NPIC followers are females (88%) with 27% aged 25–34 years old and 43% aged 35–44 years old. Reviews of our Facebook page average 4.9/5 stars. Over the review period telephone enquiries to the NPIC from members of the public increased by 73%; the number of enquiries had remained static in 2010 and 2011 but then rose year on year from 2012.
Conclusion: From our experience, maintaining a Facebook page is time consuming and requires considerable staff input. However, the growing popularity of the NPIC Facebook page has contributed to increased awareness of the poisons centre service and provided an alternative means of communication for us. MOP telephone enquiries to the poisons centre have increased by 73% since the introduction of the NPIC Facebook page.

130. Linguistic differences between Spanish and English tweets that mention opioids

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Objective: Social media provides invaluable data for analyzing the non-medical use of prescription opioids (NMUPO). Drug abuse research to date using social media has focused on English

Table 1. Comparing Spanish and English tweets with regard to lexical diversity, reading ease, and Jaccard similarity relating to non-medical use of prescription opioids.

	Non-medical use of prescription opioids (NMUPO)			General		
	Spanish	English	*p*-Value	Spanish	English	*p*-Value
Lexical diversity	0.258	0.251	.773	0.468	0.930	<.0001
Reading ease	94.68	63.02	<.0001	93.18	64.71	<.0001
Jaccard similarity	0.026		.88	0.022		.86

language communications despite the growing importance of Spanish language communications. We investigated whether English and Spanish tweets discuss different aspects of the non-medical use of prescription opioids.
Methods: A prospective study of publicly available tweets. We included tweets geocoded from the US that contained >1 Spanish/English keyword related to NMUPO, using English keywords, or their Spanish translation, from previous work. We compared these tweets with tweets that contained >1 word in English or Spanish, not restricted to NMUPO key words. We used Twitter and Google language identification algorithms to determine if the tweet was in English or Spanish. We compared Spanish and English tweets on lexical diversity, Flesh-Kincaid grade level, Jaccard similarity, and most common words.
Results: We acquired 64,909 tweets, of which 6410 were Spanish. The top 6 words were for Spanish NMUPO tweets were "gato, tiger, tigre, carga, dedico, caballo," recognized slang words for illicit opioids. The top 5 English words were "heroin, today, hope, world, and amazing". Table 1 compares Spanish and English tweets with regard to lexical diversity, reading ease, and Jaccard similarity.
Conclusion: Spanish and English NMUPO tweets use different vocabularies; English tweets use more unique words when discussing NMUPO than other topics and Spanish NMUPO tweets. Spanish NMUPO tweets use fewer words with shorter syllables than English NMUPO tweets.

131. YouTube™ is a feasible tool to disseminate educational toxicology videoconferences: The Global Educational Toxicology Uniting Project (GETUP)

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Objective: GETUP has filled an important void in global poisoning education by linking countries with and without toxicology services through videoconferencing and educating primary healthcare doctors and other health professionals [1]. However, time-zone incompatibilities among geographically remote sites may mean some parties are unable to attend all videoconferences. Recorded video is one potential solution for asynchronous learning using GETUP case materials, but its utilization has not been adequately defined. We aimed to assess the feasibility of YouTube to disseminate recorded toxicology videoconferences and analyse usage.
Methods: We performed a review of 9 videoconferences recorded on Google Hangouts™ and stored on YouTube™ from March 2014 to August 2015. YouTube Analytics™ data were used to measure web traffic and viewer trends. Information recorded for each recording included: number of views, viewer demographics, viewer geography, and playback devices used.
Results: There were 204 views of the nine videoconferences during the study period. The main groups involved in making the recorded conferences included the Austin Toxicology Service, Victoria, Australia; Fresno Toxicology Service, California, USA and the Emergency Department, Suva, Fiji. The majority of views (59%) were by viewers in the 25 to 34 age bracket. Viewers were located in 20 countries over six continents. Thirty-three percent (67 views) were from 18 states in the US. Devices used to playback these conferences included computer (93%), mobile phone (5.3%), tablet (1%) and unknown (0.7%).
Conclusion: Recorded video available over the Internet is a feasible method to disseminate toxicology based educational videoconferences around the world and gather important information about how medical professionals tend to consume case-based toxicology educational contents.

Reference

[1] Wong A, Vohra R, Koutsogiannis Z, et al. The Global Educational Toxicology Uniting Project (GETUP): The first year of a novel educational toxicology project. J Med Toxicol. 2015;11:295–300.

132. Analytically confirmed post-injection delirium/sedation syndrome (PDSS) after olanzapine long-acting injection

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Objective: Olanzapine long-acting injection (O-LAI) is a pamoate salt with slow release properties (approximately 1 month) when administered by deep intramuscular (depot) injection. However, after a single injection, some patients (2% or more) [1] experience symptoms suggestive of overdose. This adverse effect is known as post-injection delirium/sedation syndrome (PDSS) and may be due to an unintended intravascular injection or blood vessel injury [2], even during correct administration. We describe a case of PDSS with olanzapine concentrations measured by high-performance liquid chromatography (HPLC).
Case report: A 52-year-old woman received 405 mg of O-LAI by IM injection in a mental health center. Immediately after, she developed profound drowsiness, and was admitted to the emergency department. At admission, miosis, coma with decerebrate response to painful stimuli and moderate sinus tachycardia (118 beats/min) were present. One hour later, she began to improve, and flexion response to painful stimuli appeared. About 12 hours after admission, she was conscious, with heart rate of 100 beats/min. She never developed arrhythmias and 24 hours after administration was transferred to the psychiatric ward. Serum samples at 2, 9, 19 and 23 hours after administration showed olanzapine concentrations of 1026, 1192, 758 and 616 µg/L, respectively (therapeutic range after oral administration 20–80 µg/L and peak concentration 115 ± 26.7 µg/L).

Conclusion: PDSS is an adverse event that appears with a relative high frequency compared to other LAI medications. The greater solubility of pamoate salt in blood than in muscle may explain the observed high olanzapine concentrations. Clinical manifestations seen in this patient are consistent with elevated blood concentrations, confirming a post-injection overdose [3]. Nevertheless, a clear correlation between concentrations and signs is unproven in previous reported cases, even if not perfectly comparable (e.g., different method, sampling time) [4]. Reporting olanzapine PDSS cases will contribute to increasing knowledge of this syndrome.

References

[1] Bushe CJ, Falk D, Anand E, et al. Olanzapine long-acting injection: a review of first experiences of post-injection delirium/sedation syndrome in routine clinical practice. BMC Psychiatry. 2015;15:65.

[2] McDonnell DP, Detke HC, Bergstrom RF, et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. BMC Psychiatry. 2010;10:45.

[3] Łukasik-Głębocka M, Sommerfeld K, Tężyk A, et al. Post-injection delirium/sedation syndrome after olanzapine long-acting intramuscular injection – who is at risk? Basic Clin Pharmacol Toxicol. 2015;117:213–214.

[4] Theisen FM, Grabarkiewicz J, Fegbeutel C, et al. Olanzapine overdose in children and adolescents: two case reports and a review of the literature. J Child Adolesc Psychopharmacol. 2005;15:986–95.

133. Incidence and risk factors for hyperlactatemia in patients with metformin overdose

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Objective: Metformin causes hyperlactatemia by inhibiting hepatic lactate uptake and the conversion of lactate to glucose [1]. Known risk factors include renal impairment, heart failure, sepsis, liver disease, advanced age, alcohol abuse, and use of radiologic contrast material [2]. The goals of this study were to (1) describe clinical characteristics of patients with acute metformin overdose, (2) derive risk factors for metformin-associated hyperlactatemia in metformin overdose, and (3) correlate serum bicarbonate with lactate in these patients.
Methods: This was a prospective observational cohort of adult emergency department patients presenting with acute drug overdose at two urban tertiary care hospitals over 5 years. Chronic, pediatric, and non-drug overdoses were excluded as were those with missing data. Data included demographics, exposure details, laboratory information, initial serum lactate, and extracorporeal indications (EXTRIP guidelines) and performance. Patients with missing lactate data had this value interpolated based on the derived correlation. The primary outcome was initial hyperlactatemia (defined as lactate ≥2 mmol/L). The secondary outcome was initial metformin-associated lactic acidosis (MALA, defined as lactate ≥5 mmol/L and pH <7.35). Assuming 20% prevalence of our primary outcome, we needed to enrol 50 patients to show a 2-fold increased risk of hyperlactatemia with 80% power and 5% alpha. Univariate statistics were calculated with SPSS v20.
Results: We screened 3739 acute overdoses; 2872 met eligibility, and 56 involved self-reported metformin overdose (57% female, mean age 55.7 years). No patients had end-stage renal disease. Serum bicarbonate and lactate were highly correlated ($r^2 = 0.63$, $p < .01$). There was a high incidence of hyperlactatemia (51.8%); MALA was less frequent (25%) and there were no deaths. EXTRIP guidelines recommended hemodialysis for 3, of whom 100% received multiple rounds of dialysis. Clinical risk factors for hyperlactatemia included venous PCO_2 and oxygen saturation (both $p < .05$). Risk factors for MALA were serum bicarbonate ($p < .001$), PCO_2 ($p < .01$), and acetaminophen co-exposure (OR 11.0, 95CI 1.1–108, $p < .05$).
Conclusion: In contrast to prior literature, these data suggest relatively good prognosis for acute metformin overdose; while initial hyperlactatemia was common, MALA was unusual, indications for hemodialysis were rare, and there were no deaths. Acetaminophen co-exposure may predispose for MALA.

References

[1] Lalau J. Lactic acidosis induced by metformin: incidence, management and prevention. Drug Saf. 2010;33:727–740.

[2] Adam WR, O'Brien RC. A justification for less restrictive guidelines on the use of metformin in stable chronic renal failure. Diabetic Med. 2014;31:1032–1038.

134. Paracetamol-protein adducts following modified release paracetamol overdose

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Objective: Paracetamol-protein adducts (APAP-CYS) are a specific biomarker of paracetamol toxicity but there are limited data from patients ingesting modified-release (MR) paracetamol. This study was to characterise APAP-CYS concentrations in MR paracetamol overdoses.
Methods: The Australian Paracetamol Project is a prospective observational study, recruiting from 3 clinical toxicology units and calls to the Poisons Information Centre in New South Wales. Included were consenting patients >14 years who ingested ≥10 g or 200 mg/kg (whichever is less) of MR paracetamol over ≤8 hours from September 2013 to October 2015. It was planned to take at least 3 serum samples in the first 24 hours post-presentation. These were then analysed for APAP-CYS. Peak APAP-CYS concentrations (C_{max}) and time to peak concentrations (Tmax) were calculated (the latter only in patients with more than 3 samples).
Results: In total, 28 patients provided 138 samples. Median age was 25 years (IQR 17–50) with 22 (79%) female and a median ingested dose of 34.4 g (IQR23.2–45.6 g). Most patients ($n = 22$, 79%) had an initial paracetamol concentration above the nomogram line (150 mg/L at 4 hours). A further 4 (14%) crossed the nomogram after repeat paracetamol concentration measurement. All patients received acetylcysteine at a median time of 3.5 hours (IQR 1.9–8.5 hours). Three, all treated >12 hours post-ingestion, developed hepatotoxicity (ALT >1000 U/L). In those without hepatotoxicity, median APAP-CYS concentration taken with their initial paracetamol concentration was 0.25 nmol/L (IQR 0.15–0.35 nmol/L, range 0.02–0.97 nmol/L, $n = 22$) collected at a median time of 4 hours (IQR 4–6.6 hours) post-ingestion. The C_{max} in this

group was 0.65 nmol/L (IQR 0.37–0.80 nmol/L, range 0.07–2.2 nmol/L) at a Tmax of 10.5 hours (IQR 8.3–24 hours, range 3–27 hours, $n = 25$). Three patients developed hepatotoxicity and had APAP-CYS concentrations on arrival of 1.2, 1.8 and 4.9 nmol/L. Peak APAP-CYS values were higher (1.2, 11 and 13 nmol/L) and generally later (30, 60 and 67 hours post-ingestion).
Conclusion: In this study, patients with an acute ingestion of MR paracetamol but no hepatotoxicity, all but one had initial and maximum APAP-CYS concentrations lower than 1.1 nmol/L, the suggested threshold for determining those with hepatotoxicity [1]. Further, APAP-CYS concentrations were similar to those reported following acute immediate release paracetamol ingestions of >40 g and no liver injury [2].

References

[1] James LP, Capparelli EV, Simpson PM, et al. Acetaminophen-associated hepatic injury: evaluation acetaminophen-protein adducts in children and adolescents with acetaminophen overdose. Clin Pharmacol Ther. 2008;84:684–690.
[2] Chiew AL, James LP. Paracetamol-protein adducts following acute paracetamol overdose. Clin Toxicol. 2016;54:344–359.

135. Survival after varenicline and phentermine overdose with documented serum blood concentrations

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Objective: Varenicline is a partial agonist of alpha-4 beta-2 nicotinic receptors used to treat nicotine withdrawal. It is renally eliminated, with an elimination half-life of 24-hours (range 10–54). In overdose, vomiting, hypertension, tachycardia and tachypnoea are seen. Phentermine is a sympathomimetic amine anorectic agent. Phentermine overdose results in central and peripheral adrenergic stimulation with cardiovascular and central nervous system toxicity. To date, there are no published cases reporting serum drug concentrations in patients surviving varenicline overdose. We report a case of varenicline and phentermine overdose confirmed by high performance liquid chromatography-mass spectrometry (HPLC-MS) blood analysis.
Case report: A 13-year-old female presented to the emergency department 13 hours after ingesting her mother's varenicline (15 × 1 mg) and phentermine (15 × 30 mg). She began vomiting within 30 minutes of ingestion and this continued every 15–30 minutes throughout the night. On arrival, she complained of light-headedness, palpitations, anxiety and bilateral leg weakness. Initial observations were: pulse 125 bpm, sinus tachycardia, BP 123/72 mmHg, respiratory rate 24/min, saturation 97% (room air), temperature 36.7 °C. On examination, pupils were 4 mm, equal and reactive, and she had sweaty palms. There was no clonus or tremor. She was able to stand unaided but complained of subjective left-sided weakness. There was no focal weakness on objective neurological testing. Serum electrolytes, acid-base and renal function were normal. Symptoms resolved rapidly. She was observed for 22 hours and discharged well the next day. Serum concentrations of phentermine and varenicline were assayed by HPLC-MS at 13, 17 and 22 hours post-ingestion. Phentermine concentrations were 0.16 mg/L, 0.23 mg/L and 0.16 mg/L (therapeutic range 0.18–0.51). Varenicline concentrations were 4.2 ng/mL at 13-hours and 3.5 ng/mL 22-hours post-ingestion with calculated elimination half-life of 3-hours. Therapeutic concentration associated with reduced nicotine craving is reported to be approximately 8 ng/mL.
Conclusion: Our patient described rapid onset of recurrent vomiting and palpitations at home, 30-minutes post-overdose which are consistent with early features of varenicline intoxication. Other than sinus tachycardia, she did not exhibit signs of significant adrenergic toxicity in hospital and, most likely, presented after peak toxicity occurred. We theorise that early vomiting, induced by varenicline, reduced drug absorption and mitigated toxicity of both agents and resulted in lower than expected serum drug concentrations post-overdose. Treatment for intoxication with either agent is symptomatic and supportive.

136. Toxicity associated with the use of α-PVP (α-pyrrolidinovalerophenone): a case series of 417 patients presenting to a regional poisons treatment centre

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Objective: α-PVP (α-pyrrolidinovalerophenone) is a pyrrolidine cathinone novel psychoactive substance (NPS) which was controlled in Europe in 2016. The aim of this study is to describe the pattern of toxicity and outcome in series of analytically confirmed acute α-PVP exposure.
Methods: Demographic, clinical and outcome data were collected on all acute recreational drug/NPS toxicity presentations to the Sverdlovsk Regional Poisoning Treatment Centre, Yekaterinburg, Russia between January 2015 and March 2016. A comprehensive screen for illicit/recreational drugs, NPS and ethanol was carried out using gas-chromatography mass-spectrometry (GC-MS) and gas chromatography with flame-ionisation detection (GC-FID) in all cases. Lone α-PVP cases were compared with α-PVP/ethanol, α-PVP with other drugs but no ethanol, and cases in whom α-PVP/ethanol were not detected. Data were analysed using Excel® and SPSS v16; Kruskal–Wallis was used to study differences between groups.
Results: There were 917 presentations: 812 (88.5%) male, median (IQR) age 26 (18–33) years. α-PVP was detected in 417 (45.5%) cases; α-PVP was the only drug detected in 162 (38.6%), in 87 (20.9%) only ethanol was detected with α-PVP and additional drug(s) were detected with α-PVP in 168 (40.3%); in 30 (17.9%) of these ethanol was also detected. Clinical features/outcomes are shown for these groups in Table 1. The median length of hospital stay was 80 hours 20 minutes (IQR 64 h 25 m to 100 h 52 m). As shown in Table 1 there were no differences in length of stay between the different groups. Five (1.2%) of the 417 patients in whom α-PVP was detected died. Other drugs and/or ethanol were detected in four of these in addition to α-PVP.

Table 1. Clinical features and outcome in α-PVP presentations compared to those in whom α-PVP was not detected.

	Reference group: cases not involving α-PVP		Lone α-PVP		α-PVP with ethanol		α-PVP with other drugs but no ethanol	
Clinical signs	*n*	%	*n*	%	*n*	%	*n*	%
Total	300	100	162	100	87	100	138	100
Anxiety	21	7.0	15	9.3	10	11.5	18	13
Hallucinations	37	12.3	43	26.5*	16	18.4*	32	23.2*
Agitation or aggression	102	34.0	79	48.8*	39	44.8*	72	52.2*
Psychosis	107	35.7	104	64.2*	57	65.5*	89	64.5*
Seizures	50	16.7	23	14.2	14	16	22	15.9
Consciousness								
GCS 15	27	9.0	11	6.8	11	12.6	11	7.9
GCS 13–14	158	52.7	78	48.1	47	54	66	47.8
GCS 8–12	91	30.3	60	37.0	23	26.4	50	36.2
GCS <8	24	8	13	8.0	6	7	11	7.9
Vomiting	29	9.7	6	3.7*	5	5.7*	3	2.2*
Hyperthermia (≥39 °C)	0	0	1	0.6	2	2.3	2	1.4
Hypertension (BPsys ≥180 mmHg)	4	1.3	3	1.9	2	2.3	4	2.9
Hypotension (BPsys ≤90 mmHg)	20	6.7	13	8	11	12.6	11	8.0
Arrhythmia	3	1.0	0	0	1	1.1	1	0.7
Bradycardia (HR <60)	52	17.3	4	1.3*	0	–	4	2.9*
Tachycardia (HR >120)	28	9.3	36	22.2*	26	29.8*	36	26.1*
Palpitations	2	0.7	4	2.4	2	3.2	2	1.4
Chest pain	2	0.7	–		2	3.2	2	1.4
Length of hospital stay								
<24 hours	12	4	0	0	2	2.3	3	2.2
24–48 hours	30	10	5	3.1	2	2.3	5	3.6
48–72 hours	111	37	55	34.2	29	33.3	43	31.2
72–120 hours	115	38.3	79	49	39	44.8	60	43.8
>120 hours	31	10.3	21	13	15	17.2	26	18.8

*Significant difference ($p<.05$) according to the Kruskal–Wallis test from reference group.

Conclusion: We have shown in this series of 417 patients with analytically confirmed α-PVP toxicity, that α-PVP is associated with stimulant toxicity, both in lone and mixed α-PVP toxicity. In addition, impaired consciousness is common in analytically confirmed α-PVP toxicity.

137. Severe cardiovascular toxicity, cerebral hemorrhage and mortality after 4-fluoroamphetamine (4-FA)

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Objective: Recently, the novel psychoactive substance 4-fluoroamphetamine (4-FA) has gained popularity in the Netherlands. The annual number of 4-FA intoxications reported to the Dutch Poisons Information Center (DPIC) increased from two in 2011 to 44 in 2015, making it the 6th most common drug of abuse the DPIC receives information requests on. Users appreciate its effects as intermediate between amphetamine and 3,4-methylenedioxymethamphetamine (MDMA). While initially reported adverse effects of 4-FA were amphetamine-like, recently more severe toxicity has been reported to the DPIC.

Case series: From January-September 2016, the DPIC was consulted about thirty-six 4-FA exposures. Follow-up by a standardized questionnaire was performed in 22 cases with either the physician and/or the patient. As expected with amphetamine derivatives, observed symptoms included restlessness (77%), headache (68%), anxiety (59%), tachycardia (59%), hypertension (50%), confusion, tachypnea, chest pain (all 41%), seizures and coma (both 14%). More pronounced cardiovascular toxicity was observed in 11 cases (2 analytically confirmed). These included conduction abnormalities (prolonged QTc or QRS interval, right bundle branch block), acute heart failure and arrhythmias (including bigeminy). One of these patients developed an inverted Takotsubo cardiomyopathy following the intake of two 4-FA capsules with a 30-minute interval (plus 5 units of alcohol, exposures not analytically confirmed). It is noteworthy that this rare specific cardiomyopathy has been described once before following 4-FA use [1]. In 4 cases, 4-FA exposure was analytically confirmed in blood/urine samples. Three of these patients ingested one 4-FA capsule (plus cannabis in 1 patient) and subsequently developed severe headache and cerebral hemorrhage. One of these patients died. The fourth patient died due to extensive bowel ischemia following chronic 4-FA use. In this patient and in one of the patients with cerebral hemorrhage, pronounced cardiovascular toxicity was also observed.

Conclusion: The number of reports of severe health effects following 4-FA use is increasing. In 4 out of 22 patients presented here, analytical confirmation of 4-FA in blood/urine was possible: one fatality with extensive bowel ischemia after chronic use of 4-FA and 3 cases with cerebral hemorrhage, including 1 fatality. Based on the relatively high frequency of case reports with severe toxicity, the toxicity profile of 4-FA seems to be more severe than that of amphetamine or MDMA.

Reference

[1] Al-Abri S, Meier KH, Colby JM, et al. Cardiogenic shock after-use of fluoroamphetamine confirmed with serum and urine levels. Clin Toxicol. 2014;52:1292–1295.

138. Rhabdomyolysis induced by psychoactive substances: an analysis of Euro-DEN data

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Objective: To study the relationship between rhabdomyolysis (quantified by creatine kinase [CK] activity) and potential kidney injury (quantified by serum creatinine concentration) and associated factors in patients presenting to the Emergency Department with acute recreational drug toxicity.
Methods: Data were collected by the 16 sentinel Euro-DEN centres in 10 European countries on all acute recreational drug toxicity presentations for 12 months (October 2013 to September 2014) using the Euro-DEN methodology. Presentations that had both a CK activity and creatinine concentration recorded were divided into 3 cohorts depending on peak CK activity based on the Poison Severity Scale: 1 minor rhabdomyolysis (CK 251–1500 IU/L), 2 moderate rhabdomyolysis (CK 1500–10,000 IU/L), 3 severe rhabdomyolysis (CK above 10000 IU/L). Patients with documented normal CK activity were the control group.
Results: From the 5529 Euro-DEN Plus presentations, 1015 (18.36%) had both a CK and creatinine recorded. The 5 most common agents amongst patients presenting with rhabdomyolysis were: cocaine ($n = 106$ presentations), cannabis ($n = 74$), gammahydroxybutyrate/gammabutyrolactone (GBH/GBL) ($n = 72$), amphetamine ($n = 71$) and heroin (65). In the group without rhabdomyolysis the most common agents were: cocaine ($n = 118$ presentations), cannabis ($n = 114$), GHB/GBL ($n = 81$), heroin ($n = 69$) and amphetamine ($n = 64$). There were 375 (37.0%) patients with minor rhabdomyolysis, 69 (6.80%) with moderate rhabdomyolysis, 24 (2.4%) with severe rhabdomyolysis and 547 (53.89%) in the control group. There was a positive correlation between CK activity and creatinine concentration ($R = 0.728$, $p < .0001$). There was also a positive correlation between CK activity and a temperature at presentation ≥39 °C ($R = 0.72$, $p < .001$), but not below that temperature threshold. There was no association between CK activity and the presence of seizures ($p = .33$) or agitation/aggression ($p = .45$). There was a positive correlation between CK activity and length of hospital stay ($R = 0.31$, $p < .001$).
Conclusion: In our study, rhabdomyolysis in recreational drug toxicity was associated with hyperthermia (≥39 °C) on admission. Cocaine, cannabis and GHB/GBL were represented with similar frequencies amongst the patients with rhabdomyolysis compared to those without. Elevated CK was associated with kidney failure assessed by creatinine concentration, and rhabdomyolysis was associated with prolonged length of hospitalisation but not with seizures or agitation/aggression reported in the clinical course.

139. A hard drug error: naloxegol-induced opioid withdrawal

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Objective: With the increased use of opioids for chronic pain and palliative care, opioid-induced constipation (OIC) is a major concern. Naloxegol, a PEGylated derivative of naloxone, is a peripheral opioid receptor antagonist taken orally for the management of OIC. In therapeutic doses it is well tolerated because of negligible central nervous system penetration. In clinical trials mild signs of opioid withdrawal (OW) were reported more often than with placebo [1]. A previous abstract reported one patient with mild OW weeks after starting naloxegol, but no reports of patients with more severe OW are reported [2]. We present a patient with moderate signs of precipitated OW following an inadvertent 4-fold overdose of his own naloxegol.
Case report: A 66-year-old male with hepatitis C, pancreatic cancer, and liver transplant presented to the emergency department (ED) complaining of opioid withdrawal. His home medications included methadone 20 mg QID, hydrocodone 30 mg QID, naloxegol 25 mg OD, aripiprazole OD, lamotrigine OD, rivastigmine OD, tizanidine OD, escitalopram OD, warfarin OD and tadalafil prn. Prior to arrival the patient inadvertently took four of his naloxegol (100 mg total), mistaking them for tadalafil. Two hours later, he noted uncontrollable leg shaking and the inability to control his body movements, but no nausea, vomiting, diarrhea or shortness of breath. His initial ED vital signs were: heart rate 63/min, blood pressure 194/77 mmHg, respiratory rate 26/min, oxygen saturation 100% and blood glucose 4.9 mmol/L. Physical examination was notable for agitation and marked diaphoresis. Standard laboratory analyses and chest radiograph were unremarkable. Using the Clinical Opioid Withdrawal Score (COWS) [3], he was in moderate OW. He was given methadone 20 mg and hydrocodone 30 mg and his symptoms resolved within 20–30 minutes. He became drowsy afterwards and was observed for 4 hours, after which he was alert and without symptoms or complaints of withdrawal.
Conclusion: Patients who are on chronic opioids should be counseled regarding appropriate dosing of naloxegol. Though precipitated OW may be uncommon in patients taking naloxegol, it appears to be short-lived and consistent with naloxegol pharmacokinetics.

References

[1] Naloxegol (NDA 204–760) Briefing Document for the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) 5/6/14 [cited 2016 October 14]. Available from: http://www.fda.gov/downloads/UCM400209.
[2] Sekhri N, Knox N. Delayed opioid withdrawal in a patient receiving naloxegol: a case report. J Pain. 2016;17:S88.
[3] Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35:253–259.

140. Antiepileptic drug-induced hypocalcemia as the main cause of uncontrolled seizures in long-term treatment of epilepsy

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Objective: Vitamin D deficiency-induced hypocalcemia is a life-threatening side effect of long-term treatment with antiepileptic drugs (AEDs) that can result in seizures. We report two such cases.
Case series: Case 1: A 33-year-old male with learning disabilities, was admitted to the Toxicology Centre with a 4-day history of loss of seizure control and status epilepticus. Epilepsy had been treated with AEDs for 15 years and he had been institutionalized since he was 12 years old. The serum total calcium was 1.29 mmol/L and phosphorus 2.17 mmol/L. A calcium gluconate infusion was started. Seizures stopped immediately when serum total calcium increased to 1.59 mmol/L. Vitamin D, 25-hydroxyvitamin D and parathormone were not measured. Case 2: A 30-year-old female, presented after a suicidal attempt with valproic acid (40–45 g). She has been receiving AEDs since epilepsy had been diagnosed 14 years previously. Despite AED therapy, seizures had continued at least twice per day for the last 3 months. The total serum calcium was 1.21 mmol/L on admission. Seizures stopped on the day 5 after vitamin D and calcium supplemental therapy and the patient was seizure-free for 3 months. Lamotrigine was added by her neurologist as soon as she returned to the outpatient department. Seizures did not occur for 18 months. She was admitted to the Toxicology Centre following a second suicide attempt with lamotrigine (~700 mg). The total serum calcium was reduced (1.94 mmol/L) and the phosphorus concentration was normal. The concentration of 25-hydroxyvitamin D was 36 nmol/L (normal range 75–250 nmol/L).
Conclusion: AEDs cause vitamin D deficiency through induction of hepatic microsomal enzymes that metabolize vitamin D [1]. Long-term AED treatment secondary hypoparathyroidism develops resulting in hypocalcemia. Serum calcium inhibits sodium leak channels, shifts the voltage dependency of voltage-gated sodium channels, stabilizes cyclic-nucleotide gated ion channels, and depresses the release of excitatory neurotransmitters [2]. Decreased calcium concentrations resulting in seizures can occur at therapeutic doses of AEDs [1,3]. AEDs can induce seizures by disturbing vitamin D metabolism and causing hypocalcemia.

References

[1] Ali FE, Al-Bustan MA, Al-Busairi WA, et al. Loss of seizure control due to anticonvulsant-induced hypocalcemia. Ann Pharmacother. 2004;38:1002–1005.
[2] Han P, Trinidad BJ, Shi J. Hypocalcaemia-induced seizure. Demystifying the calcium paradox ASN Neuron. 2015; 7:1–9.
[3] Hmami F, Chaouki S, Benmiloud S, et al. [Seizures revealing phosphocalcic metabolism abnormalities]. Rev Neurol (Paris). 2014;170:440–444. French.

141. Fatal outcome after ingestion of dimethyl sulfoxide as a miracle cure

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Objective: Dimethyl sulfoxide (DMSO) is a widely approved component in analgesic and anti-inflammatory ointments. However, on non-scientific websites, it is promoted as a miracle cure for a multitude of diseases including cancer, arthritis, mental disabilities or stroke and beside topical use oral, intravenous or ophthalmic applications are also recommended. DMSO appears to have very few toxic symptoms in humans. Typical acute effects involve irritation of the skin or mucosa, garlic odor, and nonspecific symptoms such as drowsiness or nausea. Single case reports in the literature show questionable evidence for hepatotoxic or nephrotoxic effects. However, the penetrance increasing properties of DMSO are known to increase the effectiveness of other substances such as medications, which can lead to serious adverse reactions. We describe a case of oral DMSO misuse with a fatal outcome.
Case report: A 77-year-old man with a history of alcohol-related liver damage and diabetic nephropathy (stage 2) ingested 750–900 mL of 99.9% DMSO over a period of 7–10 days in order to treat a chronic ulcer on his lower leg. Despite nephralgia and deterioration of his general condition, he continued intake until the point of hospitalization. During medical examination at the hospital, a strong smell of acetone or formalin was recorded. Several employees of the hospital reported headache, nausea and eye irritation after contact with the patient. The patient rejected intensive care treatment and dialysis to enhance poison elimination and during the following days, his condition worsened. He suffered from acute renal failure and liver dysfunction with coagulopathy. Tremor, somnolence and angina pectoris symptoms were also reported. The patient died on day 4 of hospitalization. Autopsy revealed a strong garlic/onion-like odor emanating from the tissue, yellow coloring of body fluids, pulmonary edema, liver fibrosis and acute tubular necrosis. Liver and kidney failure were ascertained as the cause of death. Toxicological investigations using gas chromatography-mass spectrometry (GC-MS) and gas chromatography with flame-ionisation detection (GC-FID) detected DMSO and 2 metabolites (dimethyl sulfide which causes the odor and dimethyl sulfone). Concentrations of DMSO and dimethyl sulfide in serum were 573 mg/L and 1.5 mg/L, respectively, on hospital admission.
Conclusion: DMSO is an approved active ingredient with low toxicity, frequently used in anti-inflammatory ointments. In contrast, the oral intake of DMSO, praised as a miracle cure in Internet forums, can lead to severe poisoning. In this case, pre-existing medical conditions along with a high oral dose of DMSO led to a rare fatal outcome.

142. Fatalities in low-weight children related to supratherapeutic doses of paracetamol in countries with unrestricted access to medication

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Objective: The main objective of the study was to identify the attributed causality and describe the toxidrome associated with the toxicity presented by children less than 5 years admitted to the Médecins Sans Frontières (MSF) paediatric hospital in Monrovia, Liberia.
Methods: In order to describe the toxidrome and identify the toxicant, the study was divided into two components: a case-series and a matched case-control. The case-series was based on a line-list of patients including all children presenting between July and December 2015 with two different organ-specific symptoms that could not be explained by any diagnosis. Blood plasma samples were collected from these patients for toxicology laboratory testing. The matched case-control study included patients admitted between September 2015 and January 2016. A sample size of 30 cases and 60 asymptomatic matched controls was needed to reach the desired power of 80% in the final sample. Two control groups were sampled for the 30 cases: hospital- and community-based cases comprising ideally 120 in total. Intoxication cases were included if they presented respiratory distress, normal oxygen saturation and either hepatomegaly, hypoglycaemia or absence of fever.
Results: The case series included 77 patients; 88% were 2 years old or less. The case-control included 30 cases matched with 53 asymptomatic hospital- and 48 community-based controls. Mortality among the cases in both components reached 46% and 30%, respectively. Clinical chemistry evidenced severe elevation in AST/ALT concentrations, mild increase in total bilirubin and alkaline phosphatase, hypoglycaemia, and increase in estimated anion gap associated with increased blood lactate concentrations. Blood coagulation tests were not available at the time due to the limited laboratory facilities in Liberia. The case-control study showed that children taking paracetamol supratherapeutic doses were significantly 5.5 (95% CI 2.0–15.9) times more likely to develop the condition. Toxicology laboratory tests also confirmed the presence of toxic paracetamol concentrations in blood plasma. No other drugs likely to have caused liver toxicity were found in biological samples. All cases tested negative for hepatitis B and C. One case was HIV positive.
Conclusion: The biological plausibility, statistical association, and toxicology laboratory tests confirm paracetamol as the primary suspected toxicant. This study highlights the risk of exposure of children aged 2 months to 2 years, with body weight less than 10 kg, to supratherapeutic doses of paracetamol in countries with unrestricted access to medications.

143. Generalised tonic-clonic seizures provoked after short term over-the-counter treatment with a combination of pseudoephedrine hydrochloride, paracetamol and dextromethorphan hydrobromide

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Objective: Pseudoephedrine, a stereoisomer of ephedrine, is an oral sympathomimetic, whose alpha-mimetic effects are greater than its beta-mimetic activity; due to its vasoconstrictor action, it has a decongestant effect on the nasal mucosa and is present in many over-the-counter (OTC) products for self-treatment of the common cold. We present a case report of a patient with generalised tonic-clonic seizures after short term OTC treatment with a combination of pseudoephedrine hydrochloride, paracetamol and dextromethorphan hydrobromide.
Case report: A 52-year-old generally healthy female was admitted to the Neurology ward after suffering two generalised epileptic attacks. She had been taking two tablets of combined OTC medicine every 12 hours for a day and a half (the maximum daily dose is 8 tablets). After the third dose she suffered from headache and 5 hours later, she suddenly lost consciousness. Her husband, who was present, explained that everything began with a scream, that she had foam around her mouth and that seizures lasted for 2 minutes. The ambulance arrived quickly and took her to emergency neurology clinic. After 2 hours observation in hospital she suffered another generalised tonic-clonic epileptic attack, which continued with tonic position of the whole body and clonic seizures. The episode lasted for approximately one minute and resolved spontaneously. Levetiracetam 1000 mg was given by intravenous infusion. Computed tomography and magnetic resonance imaging (MRI) of the head were normal. An electroencephalogram did not show any changes typical for epilepsy. Due to persistent pain in the thoracolumbar part of body, an MRI of the spine was performed and revealed fresh compression impression fractures of upper endplates of Th11, Th12 and L1, although she had only mild osteoporosis. Since seizures did not reoccur during 5 days of hospitalisation, antiepileptic treatment was not prescribed at discharge.
Conclusion: This patient did not take any other medication, all other possible causes for epileptic attacks were excluded and as these were her first and only epileptic attacks they were most likely related to self-medication with an OTC product containing pseudoephedrine. Awareness of the risks of pseudoephedrine in OTC products should be raised, since patients often consider OTC medications to be safe. In addition these nervous system disorders are not described under undesirable effects, or in the Summary of Product Characteristics, although several reports are found in the VigiAccess WHO database.

144. Hepatotoxicity of tyrosine kinase inhibitors

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Objective: Tyrosine kinase inhibitors (TKI) are a new generation of chemotherapeutic agents. The first approved TKI was imatinib, initially for treatment of chronic myeloid leukemia. Many other TKIs have since been approved for various indications. Although TKIs are generally less toxic than the classic chemotherapeutic agents, they still have a narrow therapeutic window. Hepatotoxicity, mostly hepatocellular necrosis, but also cholestasis and hepatic cirrhosis, has been reported for several TKIs, including erlotinib, imatinib, lapatinib and sunitinib. The mechanisms underlying these effects remain unclear. The aim of our study was to investigate the mechanisms of hepatotoxicity of erlotinib, imatinib, lapatinib and sunitinib *in vitro*.
Methods: We treated human hepatoma cells (HepG2) with different concentrations of the four TKIs (between 1 and 100 mM) for 6 to 48 hours.
Results: Imatinib, lapatinib and sunitinib showed a time- and concentration-dependent cytotoxicity as well as a drop in intracellular adenosine triphosphate (ATP) content in HepG2 cells. Reduced membrane potential in cells and isolated mitochondria, increased reactive oxygen species production, reduced glutathione (GSH) concentrations, reduced glycolytic flux, and induction of apoptosis was found for imatinib, lapatinib and sunitinib. Imatinib and sunitinib also showed a reduced maximal respiration with inhibition of complex III and I, respectively.

Conclusion: Our investigations showed that imatinib and sunitinib lead to mitochondrial dysfunction whereas lapatinib seems to be a weak inhibitor of mitochondria. Furthermore, erlotinib is non-toxic for HepG2 cells for the tested conditions. As next steps we aim to determine susceptibility factors according to the proposed mechanism of liver toxicity and test them *in vitro* and *in vivo*.

145. Hypersensitivity secondary to naltrexone depot injection

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Objective: Naltrexone is a mu-opioid antagonist approved for the use of relapse prevention in patients with a history of opioid or alcohol dependence following detoxification. We report a rare case of hypersensitivity following intramuscular (IM) depot injection of naltrexone.
Case report: A 35-year-old female with a history of chronic opioid addiction, enrolled in outpatient rehabilitation, presented to the emergency department (ED) with a diffuse pruritic rash 5 days after receiving an IM dose of naltrexone. She had a history of similar occurrences on two previous occasions, also within days of IM naltrexone injection. Each episode was more severe than the previous. The patient denied any other medications or illicit drug use. On physical examination, vital signs were normal; she had multiple blanching, erythematous, maculopapular, raised lesions on her neck, bilateral upper extremities, upper back, and anterior chest wall. She was treated with diphenhydramine and intravenous methylprednisolone. Her skin rash improved slightly over a 4-hour observation period and she was discharged home with oral diphenhydramine, famotidine and a three-week tapered dose of prednisone. One week later the patient reported complete resolution of her symptoms.
Conclusion: Naltrexone depot injections are typically administered on a monthly basis. The depot formulation uses biodegradable poly(D,L-lactide-coglycolide) microspheres to encapsulate the active ingredient, resulting in a gradual release from the injection site. Absorption is slow with biphasic peak plasma concentrations around 2 hours and 2–4 days post-injection. Plasma concentrations start to decline after 14 days post-injection [1]. A similar formulation is also used in the long-acting formulation of the antipsychotic risperidone. We theorize that our patient had a type IV hypersensitivity reaction to naltrexone as evident by the timing of the patient's symptoms. The worsening of her symptoms with each subsequent dosing is likely related to immune system priming from repeated exposures of naltrexone. A similar erythematous rash has been reported with the long-acting formulation of risperidone using poly(D,L-lactide-coglycolide) microspheres [2], which may also be a possible explanation of this reaction. It is unclear whether this formulation or the active ingredient contributed to this reaction. We report a potentially serious hypersensitivity reaction following IM naltrexone administration. Due to the extended half-life and inability to readily remove the drug, practitioners need to be aware of this potential reaction.

References

[1] Vivitrol package insert. Waltham MA: Alkermes, Inc.; 2015. [cited 2017 Mar 29]. Available from: https://www.vivitrol.com/Content/pdf/prescribing_info.pdf
[2] Sidhu K, Saggu H, Lachover L, et al. Rare case report of rash associated with risperidone long acting injection. Primary Psychiatry. 2010;17:38–40.

146. Monoclonal antibodies and other immunomodulating drugs: enquiries to a poisons information service

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Objective: To investigate enquiries to the UK National Poisons Information Service (NPIS) concerning monoclonal antibodies and other immunomodulating drugs.
Methods: We reviewed enquiries to the NPIS concerning such drugs from 1 January 2008 to 31 August 2016.
Results: Seventy-three enquiries were identified, of which 5 were for information only (3 concerning potential foetal effects resulting from paternal exposure). The remaining 68 enquiries involved 11 different drugs, the most common being adalimumab ($n = 27$)

Table 1. Features and Poisoning Severity Score (PSS) [1] in symptomatic cases (none 50; 2 unknown, 1 unspecified pain) following exposure to monoclonal antibodies and other immunomodulating drugs reported to a poisons information service.

PSS	Number	Age range/gender	Drugs	Features
Minor	11	11–71 years 4M, 6F	Adalimumab	Abdominal pain, oedema
			Adalimumab	Alopecia
			Adalimumab	Eye pain and irritation
			Adalimumab	Injection site reaction
			Adalimumab with methotrexate	Somnolence, postural hypotension
			Certolizumab	Arthralgia, fatigue
			Certolizumab with methotrexate	Chest pain, palpitations, dizziness
			Etanercept	Injection site bruising
			Golimumab	Swimming head
			Trastuzumab	Palpitations
			Rituximab	Eye pain and irritation
Moderate	2	44 years F	Tocilizumab	Increased muscle tone, convulsions
		13 years F	Tocilizumab (with cannabinoids, MDMA and opioids)	Hallucinations
Severe	2	29 years F	Infliximab	Sepsis
		10 years M	Rituximab	Fever, hypotension, dyspnoea and rash within 25 minutes

and etanercept ($n = 15$). Most enquiries involved a single agent (94%). Patients were aged 5 months to 89 years (plus 5 adults, 1 child, 1 unknown) with a mean age of 42 years (44 females, 23 males, 1 unknown). Route of administration most commonly involved injection or infusion with ingestion being reported rarely (two cases involving etanercept and solanezumab). Most exposures were accidental ($n = 62$; 91%) with reasons including: wrong interval between doses ($n = 24$), excess dosing ($n = 10$), needle-stick ($n = 8$), adverse reaction ($n = 7$), skin contact/eye contact ($n = 8$; patient/administering nurse; pain and blurred vision ($n = 1$) and pain/irritation in the eye ($n = 1$); others asymptomatic), other ($n = 5$). In the 2 deliberate overdoses 8–9 doses (40 mg) of adalimumab were injected with no features reported. There were also three children involved in enquiries about possible child protection issues (all asymptomatic) and one case of drug abuse in a patient on tocilizumab. Features in symptomatic cases are listed in Table 1.

Conclusion: The most common enquiries to a poisons information service concerning monoclonal antibodies involved errors in the interval between doses. Accidental exposures did not appear to result in serious consequences but in two cases serious adverse effects occurred after therapeutic doses.

Reference

[1] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–13.

147. Pediatric cardiac arrest after Cyclomydril(R) eye drops

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Objective: To describe the case of an 11-week-old premature infant who suffered a cardiac arrest after ophthalmic administration of Cyclomydril® (0.2% cyclopentolate hydrochloride and 1% phenylephrine hydrochloride) for evaluation of retinopathy of prematurity.

Case report: In this patient the course of pregnancy was complicated by maternal pre-eclampsia necessitating induction of labor at 31 weeks gestational age. The patient had mild cerebral intraventricular hemorrhage which did not require intervention. On the day of the visit to the ophthalmologist, the patient was in good health. Within 1 minute of receiving Cyclomydril®, the patient became flaccid and cyanotic. A pulse was absent and chest compressions were initiated by the ophthalmologist. The patient regained pulses after approximately 2 minutes of cardiopulmonary resuscitation. Paramedics found the patient bradycardic (84 bpm) and unresponsive, with a capillary glucose concentration of 160 mg/dL (8.8 mmol/L). The patient improved en route to the emergency department and arrived awake, crying, mydriatic, and with a heart rate of 178 bpm, respirations 34/min, temperature 35.9 °C (rectal), oxygen saturation 95% (room air). Initial laboratory analysis showed acidosis (pH 7.14, pCO_2 50 mmHg, bicarbonate 16.8 mmol/L) with hyperlactatemia (7.3 mmol/L) and hyperglycemia (205 mg/dL, 11.4 mmol/L), all of which normalized over 3 hours with a 20 mL/kg bolus of intravenous normal saline as the sole intervention. Subsequent workup including chest X-ray, electrocardiogram (EKG), echocardiogram, blood cultures, cranial ultrasound, and gas chromatography-mass spectrometry (GC/MS) toxicology and buprenorphine screen failed to demonstrate an alternative cause for the patient's cardiac arrest.

Conclusion: Only one prior infant cardiac arrest has been reported after Cyclomydril® administration in the literature, with striking similarities [1]. We hypothesize that absorption of phenylephrine through the nasal mucosa resulted in high intracerebral concentration of an alpha agonist with loss of receptor selectivity. Subsequent central alpha-2 agonism resulted in bradycardic arrest similar to clonidine toxicity. There was no evidence of sodium-channel blockade on EKG from cyclopentolate's bicyclic structure, and no seizure activity was observed. The incidence of this toxicity appears to be rare, and it is unclear which patients are at risk. Mechanical digital occlusion of the nasolacrimal duct during drug administration is non-invasive and will likely prevent significant systemic drug absorption.

Reference

[1] Lee JM, Kodsi SR, Gaffar MA, et al. Cardiopulmonary arrest following administration of Cyclomydril eyedrops for outpatient retinopathy of prematurity screening. JAAPOS. 2014;18:183–184.

148. Perampanel overdose causing a prolonged dissociated state

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Objective: We report a patient with a prolonged dissociated state following acute overdose of the novel antiepileptic agent perampanel (Fycompa®).

Case report: A 54-year-old man was admitted for altered mental status after overdosing on perampanel. He had a history of refractory seizures treated with multiple antiepileptic drugs including divalproex sodium, lamotrigine, levetiracetam and perampanel. His dose of perampanel had recently increased to 10 mg daily. He was found with altered mental status in his room with an empty bottle of perampanel. Approximately thirty tablets were missing. Initial vital signs and labs were remarkable for bradycardia (58 bpm) and hyponatremia (128 mEq/L). Physical exam found markedly decreased mental status with only slight grunting to painful stimulation. Pupils were 3 mm and reactive bilaterally with disconjugate gaze. Despite significantly depressed mentation, he continued to protect his airway without the need for intubation and was noted to occasionally reposition his limbs if moved. Electroencephalogram performed the day after admission demonstrated diffuse slowing and disorganization of the background consistent with generalized dysfunction. His levetiracetam and valproic acid concentrations were 4.4 µg/mL (reference range 10–40), and 33.6 µg/mL (reference range 50–100), respectively. Phenytoin and carbamazepine were not detected and a urine toxicology screen was negative. On the day after admission the sodium was 133 mEq/L. A computed tomography scan of the brain was negative, and lumbar puncture was unremarkable. The patient's clinical exam remained unchanged over several days. On hospital day 4, his mental status gradually improved. He was discharged on hospital day 12 to a skilled nursing facility at which time he was noted to have poor memory, expressive aphasia and significant ataxia requiring work with speech, occupational, and physical therapy. Laboratory analysis of cerebral spinal fluid (CSF) obtained on hospital day 3 found a perampanel concentration of 67 ng/mL.

Conclusion: Perampanel is a novel, non-competitive, amino-3-hydroxy-5-methyl-4-*isoxazolepropionic* acid (AMPA) glutamate receptor antagonist that was approved for use in 2012 as an adjunctive therapy for the treatment of partial-onset seizures [1]. Prior studies have shown that a supratherapeutic dose of 24 and 36 mg produces euphoria and dissociation similar to ketamine

10 mg. This is the first case report demonstrating an acute overdose of perampanel associated with a prolonged dissociated state with confirmation of an elevated perampanel concentration in CSF.

Reference

[1] Frampton JE. Perampanel: a review in drug-resistant epilepsy. Drugs. 2015;75:1657–1668.

149. Predicting clinically relevant drug-induced liver injury

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Objective: Although drug-induced liver injury (DILI) is the most common cause of acute liver failure in developed countries, it is still a diagnosis of exclusion. Reactions are predominantly idiosyncratic and mechanisms of injury vary widely. We attempted to create a computer-based model to link molecular structure with clinically relevant DILI in patients.
Methods: We performed a literature screen for DILI cases diagnosed with the Roussel Uclaf Causality Assessment Method (RUCAM) [1]. Our final dataset included 394 hepatotoxic and 194 non-hepatotoxic small molecule drugs (total $n = 588$). We then derived physico-chemical descriptors (such as weight, lipophilicity, structural complexity) from the structures and used several machine learning paradigms (support vector machines [SVM], k-nearest neighbors [kNN], decision tree induction [DTI]) to uncover associations between structures and hepatotoxicity. Models were learned with 10-fold cross-validation to avoid overfitting and increase generalizability. Additionally, we created a network of drugs and enzymes, transporters, and carriers by matching our dataset to DrugBank [2] ($n = 417$) to find correlations with pharmacokinetic fate and DILI.
Results: Our best performing model was a chi-squared automatic interaction detector (CHAID) decision tree with an accuracy of 89.6% (sensitivity 94.9%, specificity 78.9%). Other paradigms (SVM, kNN) fell far behind, mostly due to poor specificity. Network analysis showed significant differences in the interaction with certain cytochrome P_{450} (CYP) isoforms (CYP3A5/A7, 2C8, and a trend to CYP3A4 metabolism), serum albumin, and organic anion transporter (OAT1).
Conclusion: There is a clear link between structure and hepatotoxicity for many small molecule drugs, and a higher degree of metabolism and transport seems to be associated with DILI as well. While our models, however, do not explicitly reflect different modes of hepatotoxicity, they could be a valuable tool in the evaluation of clinical DILI and in drug development.

References

[1] Danan G, Benichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993;46:1323–30.
[2] Law V, Knox C, Djoumbou Y, et al. DrugBank 4.0: shedding new light on drug metabolism. Nucleic Acids Res. 2014;42:D1091–D1097.

150. Take a big GuLP: recurrent hypoglycemia from liraglutide responds to octreotide

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Objective: Liraglutide is a glucagon-like-peptide (GLP-1) receptor agonist that was originally marketed for diabetes at a dose of 1.2–1.8 mg injected subcutaneously daily. With the growing worldwide obesity epidemic, more patients are resorting to medication-assisted weight loss. High-dose liraglutide (up to 3 mg subcutaneously weekly) was recently approved for weight loss. We present a case of prolonged, recurrent hypoglycemia following an injection of liraglutide, which was treated successfully with octreotide.
Case report: A 22-year-old woman with no past medical history presented to the emergency department with a chief complaint of vomiting one day after receiving a 3 mg injection of liraglutide from a weight loss clinic. Her vital signs upon arrival were blood pressure 107/76 mmHg, heart rate 80/min, respiratory rate 18/min, oxygen saturations 100% (room air), temperature 36.9 °C and point-of-care blood glucose 2.2 mmol/L (40 mg/dL). Other than the vomiting, her examination was within normal limits. She was given a 50 mL bolus of 50% dextrose and her repeat blood glucose improved to 4.4 mmol/L (80 mg/dL). Her vomiting resolved, she was able to eat and was started on an infusion of 10% dextrose. Over the next 10 hours, she developed numerous episodes of hypoglycemia requiring treatment with dextrose boluses. After 10 hours of hospitalization, octreotide 50 µg subcutaneously was administered and the patient had no further episodes of hypoglycemia. Her maintenance infusion was then switched to 5% dextrose in normal saline. She was discharged home the next day with no complications.
Conclusion: Liraglutide stimulates insulin release, decreases glucagon secretion, and causes anorexia via a central mechanism. Although the recommended dose for weight loss is 0.6 mg increased weekly to a maximum of 3 mg, this patient received 3 mg as her first dose. As more non-diabetic patients use liraglutide and other GLP agonists for weight loss, we anticipate a rise in the number of hypoglycemic presentations. Since octreotide, a somatostatin analogue, inhibits insulin release, its use is reasonable in patients who present with recurrent hypoglycemia following administration of liraglutide.

151. The catechol-O-methyltransferase inhibitors tolcapone and entacapone uncouple and inhibit the mitochondrial respiratory chain in HepaRG cells

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Objective: Tolcapone is a catechol-O-methyltransferase (COMT) inhibitor associated with hepatotoxicity and mitochondrial damage in animal models. We aimed to study the interaction of tolcapone with the mitochondrial respiratory chain and to compare the findings with the structurally-related entacapone in a human hepatocyte cell line and in isolated mouse liver mitochondria.

Methods: Differentiated HepaRG cells (human hepatocyte cell line) were treated with different concentrations of tolcapone and entacapone (10–200 μM) for 24 hours.
Results: In HepaRG cells (a human hepatocyte cell line), tolcapone decreased the adenosine triphosphate (ATP) content (IC_{50} 100 ± 25 μM) and was cytotoxic (IC_{50} 333 ± 45 μM), whereas entacapone was not cytotoxic up to 200 μM. Cytochrome P450 induction did not increase the toxicity of the compounds. In permeabilized HepaRG cells, tolcapone, but not entacapone, inhibited maximal complex I- and complex II-linked oxygen consumption. In isolated, intact mouse liver mitochondria, tolcapone stimulated state 2 complex II-linked respiration and both compounds inhibited state 3 respiration of complex IV. Uncoupling of oxidative phosphorylation could be confirmed for both tolcapone and entacapone by stimulation of complex I-linked respiration in the presence of the ATPase inhibitor oligomycin. Inhibition of complex I, II and IV for tolcapone and of complex I and IV for entacapone could be directly demonstrated in disrupted mouse liver mitochondria. At similar concentrations, tolcapone inhibition of mitochondrial respiration was more pronounced than entacapone, as evidenced by increased lactate and mitochondrial reactive oxygen species production and hepatocyte necrosis.
Conclusion: Both tolcapone and entacapone uncouple oxidative phosphorylation and inhibit enzyme complexes of the respiratory chain. At similar concentrations, tolcapone exhibits a more pronounced mitochondrial toxicity than entacapone. Mitochondrial toxicity is a possible mechanism for tolcapone-associated hepatotoxicity in susceptible patients.

152. The impact of polypharmacy and drug interactions on the onset of adverse drug reactions

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Objective: Pharmacovigilance is indispensable in order to monitor adverse drug reactions (ADRs) but little is known about the impact of polypharmacy and drug interactions on their onset. The objective of this study was to assess this aspect considering known interactions and triggering events.
Methods: Inclusion criteria: adverse drug reactions (ADRs) occurring in our hospital between 2005 and 2015. Exclusion criteria: incomplete data, concomitant medical errors, intentional exposure or due to incapacity events. Data were retrieved from our Poison Center database and integrated with clinical information collected from the medical records. Data about the number of drugs used by the patient, the active ingredients, the Anatomical Therapeutic Chemical (ATC) classes, and the presence of comorbidities were taken into account to identify drug interactions and precipitating factors. Each patient's therapy regimen was analyzed using Drug-Reax® (Micromedex®) and Embase® to verify all known or suspected drug interactions.
Results: Overall 135 cases (134 patients) met the inclusion criteria; 62 males (46.3%), 70 females (52.2%), and 2 unknown (1.5%). The median age was 40 years among males, 57 among females. In total 19% of patients were on single drug therapy; 28% were on polytherapy with no known pharmacological interactions; 40% experienced ADRs caused by interacting drugs, while the remaining 13% suffered from ADRs not related to the drug interactions. Overall 53% of patients were on a polytherapy regimen that included at least one known interaction and among these three-quarters experienced an ADR. Overall, 40% of ADRs were due to a drug interaction, even if the clinical benefit was higher than the risk. Considering co-morbidities and precipitating events, kidney failure was reported in 19.3% of cases, liver disease in 13.3%, cardiovascular disease in 8.6%, and 3% of patients were HIV positive. The drugs most frequently involved in the ADRs without known interactions were neurologic drugs ($n = 43$, 50.6%), followed by gastrointestinal and metabolism drugs (ATC A) ($n = 11$, 12.9%). Also among cases with known interactions, the drugs most frequently involved were neurologic drugs ($n = 45$, 55.6%), followed by cardiovascular drugs ($n = 12$, 14.8%). The drugs most frequently involved in interactions were digoxin ($n = 28$), lithium ($n = 14$), and beta-blockers ($n = 11$). The pharmacological interactions severity presented as follows: 2.4% minor, 61% moderate, 34.7% major and 1.9% contraindicated.
Conclusion: Our records showed that 40% of ADRs were due to drug interactions. In particular, the number of drugs is a major risk factor for interactions, therefore a reduction in the use of unnecessary drugs and a periodic check of complex therapeutic regimens should be considered.

153. Acute "bath salts" intoxications: analytical findings and clinical features

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Objective: The use of "bath salts", chemically phenylethylamine derivatives (PD), is increasing. The multiplicity of new upcoming substances is challenging since many effects and complications are yet unknown. We describe typical clinical features, perform detailed analytics and test if there are typical symptoms corresponding with distinct PD.
Methods: A single centre retrospective cohort study enrolling patients with analytically confirmed intoxication due to phenylethylamine derivatives from January 2012 to July 2015. Urine samples were analysed with gas chromatography–mass spectrometry after acid hydrolysis and acetylation.
Results: Overall 63 patients, predominantly male (77.8%), mean age 31.1 (± 7.9) years, fulfilled the inclusion criteria. The severity of the intoxication according to the Poison Severity Score was mainly moderate ($n = 22$) or severe ($n = 22$). Most symptoms were neuropsychiatric (26 moderate, 15 severe) in the form of aggressiveness, agitation or unconsciousness but also muscular (5 moderate, 5 severe) in the form of rhabdomyolysis. In total 52.4% patients were discharged after ≤1 day (median 1 day [0–65]). Patients with severe muscular symptoms required longer treatment (median 5 days [0–5]). Analytically, a total of 336 substances (133 unique substances) were found, out of which 140 were PD (48 unique). On average 7 (0–15) substances were detected for each patient, 2 (0–6) of them being PD. The largest groups of PD were methylendioxypyrovalerone (MDPV, $n = 20$; mainly detected in 2013), 3-methylmethcathinone (3-MMC, $n = 14$; predominantly after 2013) and methylone ($n = 7$), but also traditional drugs such as 3,4-methylendioxy-N-methylamphetamine (MDMA, $n = 9$), amphetamine ($n = 8$), and methamphetamine ($n = 7$) were detected. Some exotic PD, among others, were e.g., 2,5-dimethoxy-4-ethylphenethylamine (2C-E, $n = 4$), alpha-pyrrolidinopentiophenone (alpha-PVP, $n = 4$), methoxamine ($n = 3$), 1-(benzofuran)-N-methylpropan-2-amine (MAPB, $n = 2$), 2,5-dimethoxy-4-ethoxyamphetamine ($n = 2$), methiopropamine ($n = 2$), 3,4-dimethylmethcathinone (3,4-DMMC, $n = 1$), methyl-alpha-pyrrolidinobutiophenone (MPBP, $n = 1$), 2,5-dimethoxy-4-propylphenethylamine (2C-P, $n = 1$) or N-methyl-N-isopropyltryptamine (5-MeO-MIPT, $n = 1$). Amphetamine was usually co-ingested with MDMA ($p < .005$) or methamphetamine ($p < .005$), and methylone

with MDMA ($p = .02$). Amphetamine and MDPV were never ingested simultaneously ($p < .005$). The most co-ingested non-PD were benzodiazepines ($n = 42$), opiates ($n = 30$) and tetrahydrocannabinol (THC, $n = 7$). Compared with other PD, MDPV was more often found in intravenous users ($p = 0.01$) and caused more muscular complications ($p < .005$), longer lasting hallucinations ($p = .02$), and longer hospital stays (median 4.5 days [0–65], $p = .03$).

Conclusion: Bath salt users are typically intoxicated with multiple substances and have moderate to severe symptoms. The duration of intoxication is usually short except in patients with muscular complications. Due to the multiplicity of the substances and rare mono-intoxications, it is difficult to predict symptoms. Among PD, MDPV seems particularly harmful.

154. Acute effects after consumption of the novel synthetic cannabinoids 5F-ADB

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Objective: We report five cases of synthetic cannabinoid acute use with analytical confirmation.

Case series: Three 17-year-old boys with agitation (Cases 1, 2 and 3), a 14-year-old girl (Case 4) with altered consciousness and headache, and a 21-year-old male (Case 5) with agitation and attempted suicide were brought to an ED on separate days. The three boys had smoked a joint of what they believed was "Spice" an hour previously. They presented psychomotor agitation, confusion, anxiety, psychosis and tachycardia. Case 2 also showed mydriasis and sinus tachycardia. None required treatment and were discharged after 3 hours. Case 4 was hypoactive, but reactive to stimuli, with tendency to stupor and bilateral reactive mydriasis. She confessed that after smoking marijuana with a substance called "Cherry Bomb, formula 6A" she had noticed discomfort, severe headache and dizziness. She was treated with intravenous fluid therapy and discharged 4 hours later. Case 5 smoked cannabis and "Spice" the previous night. He had daily consumption of cannabis and sometimes "Spice". He presented with extensive vomiting, agitation, altered language, slow thought and speech and mydriasis. He required intravenous fluid therapy and was discharged after 8 hours but 6 days later he represented agitated, with altered language and slow thought and speech after smoking "Spice". A package called "Volume 2, formula 6A" was collected. After 6 hours, he was awake, with coherent speech and not aggressive, so was discharged. The analytical results are summarized in Table 1.

Conclusion: We describe for the first time acute adverse reactions after recreational use of 5F-ADB (or 5F-MDMB-PINACA) an indazole-based synthetic cannabinoid. In all cases 5F-ADB metabolites were detected; moreover in two cases 5F-ABICA and MMB-2201 metabolites and in one case 5F-AKB48 metabolites were also detected.

155. Acute health problems due to recreational drug use in patients presenting to an urban emergency department in Switzerland

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Objective: To describe the frequency and acute medical problems due to recreational drug use in patients presenting to an emergency department in Switzerland during a 4-year period with a focus on novel psychoactive substances.

Methods: Retrospective analysis of cases presenting from May 2012 to April 2016 at the emergency department of the University Hospital of Bern with symptoms/signs consistent with acute toxicity due to self-reported or suspected recreational drug use. The cases were retrieved using a comprehensive full-text search algorithm. Isolated ethanol intoxications were excluded.

Results: During the study period, 503 of the 157,328 emergency department attendances were directly related to acute toxicity of substances used recreationally. The mean patient age was 33 years (range 16–74) and 68% were male. Alcohol co-ingestion

Table 1. Toxicological analysis results of 5 patients with synthetic cannabinoid use.

Case	Urine THC (Imunoassay screening)	Urine THC-COOH (ng/mL) GC-MS	Herbal blend (GC-MS)	Substance	Urine positive metabolites (LC-MS/MS)
Boy 1	+	555.5	NA	5F-ADB	5F-ADB 5-OH-pentyl 5F-ADB Valine
Boy 2	+	38.3	NA	5F-ADB	5F-ADB 5-OH-pentyl 5F-ADB Valine
Boy 3	–	6.2	NA	5F-ADB	5F-ADB 5-OH-pentyl 5F-ADB Valine
Girl 4	+	NA	5F-ADB	5F-ADB	5F-ADB 5-OH-pentyl 5F-ADB Valine
			5F-ABICA/MMB-2201	5F-ABICA/MMB-2201	5F-ABICA/MMB-2201 Valine[a]
Boy 5	+	21.3	5F-ADB	5F-ADB	5F-ADB 5-OH-pentyl 5F-ADB Valine
			5F-AKB48	5F-AKB48	AKB48 5-OH-pentyl AKB48 Acid 5F-AKB48 Adamantyl-OH AKB48 Carboxylated, Mono-OH 5F-AKB48 Adamantyl-Di-OH
			5F-ABICA/MMB-2201	5F-ABICA/MMB-2201	5F-ABICA/MMB-2201 Valine[a]

NA: not available; GC-MS: gas chromatography-mass spectrometry; LC-MS/MS: liquid chromatography-tandem mass spectrometry; THC: tetrahydrocannabinol, THC-COOH: 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol.

[a]Both substances have the same main metabolite and cannot clearly be distinguished from one another.

was reported in 54% of the cases. Use of more than one recreational drug was reported in 37% of the cases and in 35% of the cases more than one substance was analytically detected. Most presentations were related to cocaine (29%), cannabis (26%), heroin (20%) and benzodiazepines/sedatives (18%). Excluding opioids and benzodiazepines, the most common recreationally used prescription drugs were methylphenidate (3%), antipsychotics (1%), dextromethorphan (1%), antidepressants (1%), monoamine oxidase inhibitors (1%), and antihistamines (0.6%). Urine drug screening using an immunoassay was available in 277 cases (55%). The most frequently detected substances were cannabis (29%), cocaine (22%), benzodiazepines (21%) and opioids excluding methadone (20%). There were only two intoxications with novel substances: One case with methylone (self-reported, immunoassay negative) and one with 2,5-dimethoxy-4(n)-propylphenethylamine (2C-P) sold as 2,5-dimethoxy-4-bromophenethylamine (2C-B) (immunoassay negative, 2C-P detected with liquid chromatography-mass spectrometry), both of moderate severity. The majority of patients (58%) had impaired consciousness (Glasgow Coma Scale (GCS) <15) upon presentation and/or prehospital, 21% were unconscious (GCS <8). Other frequent symptoms were agitation (36%), tachycardia (29%), and anxiety (24%). Severe complications included two fatalities (one cerebral hypoxia after methadone intake and one cerebral infarction with analytical confirmation of cocaine and cannabis), three acute myocardial infarctions, two intracranial hemorrhages, as well as psychosis and seizures in 71 and 26 cases, respectively.

Conclusion: Most medical problems related to recreational drug use were related to cocaine and cannabis use and were mainly characterized by central nervous system depression, sympathomimetic toxicity and/or psychiatric disorders. Acute toxicities related to novel psychoactive substances appear to be uncommon.

156. Acute intoxication involving the new psychoactive substance alpha-pyrrolidinobutiophenone (α-PBP): results from the Swedish STRIDA project

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Objective: Despite the severe burden to individuals and society caused by new psychoactive substances (NPS), the availability of new structural analogues has not been hampered. Most NPS fall into two chemical classes, synthetic cathinones and cannabinoids. The pyrovalerone-related cathinones MDPV and α-PVP were analytically confirmed in many patients in the STRIDA project. One NPS cathinone that followed methylenedioxypyrovalerone (MDPV) and alpha-pyrrolidinovalerophenone (α-PVP) is alpha-pyrrolidinobutiophenone (α-PBP). This study summarizes the results of analytically confirmed α-PBP cases presented at Swedish hospitals.

Methods: Blood and/or urine samples were collected from patients with suspected intake of NPS at emergency departments or intensive care units (ICU). α-PBP exposure was confirmed using multi-component liquid chromatography-mass spectrometry. Basic demographic details and clinical data were collected during Poisons Information Centre (PC) consultations and retrieved from medical records.

Results: From April 2013 to November 2015, 43 patients in the STRIDA project tested positive for α-PBP; 60% of the cases occurred in 2014. However, the enquiries at PC consultation never related specifically to α-PBP and use of α-PBP was confirmed analytically by detection in urine ($n = 37$) or, when urine was unavailable, in serum ($n = 6$). The α-PBP concentration in urine ranged from 2.0 to 13194 ng/mL and in serum from 2.0 to 436 ng/mL. The age range of patients was 19–57 (mean 34) years, 81% were men, and 73% had a documentation of drug abuse. α-PBP was the only psychoactive substance detected in 3 cases (7%). In 40 cases (93%), α-PBP was detected together with new and/or conventional central nervous system (CNS) stimulants, with MDPV, α-PVP, and other pyrovalerone analogues being the most common substances, present in 31 cases (72%). CNS depressants were detected in 28 cases (65%), with benzodiazepines (16 cases) being most frequent. The main clinical characteristics in α-PBP-positive patients were agitation/anxiety (59%), tachycardia (54%), hypertension (37%), dilated pupils (24%), and decreased consciousness (17%). Fourteen patients required intensive care monitoring of which 8 were graded as severe intoxications. No fatalities were reported.

Conclusion: The clinical features and patient characteristics in intoxications involving α-PBP resembled those observed in MDPV- and/or α-PVP-positive cases in the STRIDA project. The high number of other stimulants detected besides α-PBP is likely to contribute to both the symptomatology and severity grade. The fact that the patients rarely declared α-PBP intake on admission, and the high number of polysubstance intoxications, suggests that this group of drug users is more interested in the general stimulatory effect, rather than α-PBP specifically.

157. Addressing the public health impact of new psychoactive substances: early analysis of the effects of the UK's Psychoactive Substances Act on poisons centre enquiries related to drugs of misuse

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Objective: Hospital presentations with toxicity after recreational use of novel psychoactive substances (NPS, sometimes termed "legal highs") have recently increased in many countries. Legislation based on chemical structure is of limited value because suppliers can make molecular changes to evade this. Attempting to overcome this, the UK Psychoactive Substances Act (PSA), introduced on 26 May 2016, made it an offence to supply any psychoactive substance if the substance is likely to be used for its psychoactive effects. Exceptions include alcohol, nicotine, caffeine and medicines. This study examined the patterns of enquiries made to the UK National Poisons Information Service (NPIS) about drugs of misuse before and after this legislative change.

Methods: Monthly numbers of telephone enquiries relating to NPS and common established drugs of misuse (cocaine, amphetamines, ecstasy, heroin and cannabis) were obtained for the period 1 March 2015 to 30 September 2016. Because of seasonal changes in activity, the primary analysis used was the numbers of calls for the 4 months after the legislation change in 2016

Table 1. TOXBASE access and NPIS telephone enquiry numbers for selected drugs of misuse for the period June to September 2013–2016.

	TOXBASE accesses					Telephone enquiries		
Drug type	Jun-Sep 2013	Jun–Sep 2014	Jun–Sep 2015	Jun–Sep 2016	% Change	Jun–Sep 2015	Jun–Sep 2016	% Change
NPS	4520	4463	7606	2882	−62%	218	50	−77%
Cocaine	3108	2977	3821	4121	8%	48	52	8%
Amphetamines	2129	2231	3227	2011	−38%	17	12	−29%
Ecstasy/MDMA	2082	2606	3030	2890	−5%	56	60	7%
Heroin	1773	1866	2200	1877	−15%	28	23	−18%
Cannabis	1220	1213	1584	1226	−23%	36	40	11%
All drugs of misuse	21,393	21,326	26,143	20,846	−20%	618	303	−51%

compared to the same 4 month period in 2015. TOXBASE® accesses to the same substances were obtained for the same 4 month period for 2013–2016.
Results: Numbers of TOXBASE accesses and telephone enquiries about NPS substantially reduced comparing 2016 with the equivalent period in 2015. Smaller reductions were seen for amphetamines and heroin. For cannabis and ecstasy, TOXBASE accesses reduced while telephone enquiries increased. Cocaine activity increased slightly comparing 2016 with 2015 (Table 1).
Conclusion: These preliminary data demonstrate reductions in NPS-related activity comparing the summer of 2016 with that of 2015. These data should be interpreted with caution; the findings could be consistent with an impact from the PSA, but other reasons for temporal changes in activity are possible. Further data collection over a longer period and more detailed statistical analysis are needed.

158. An example of a new toxicological disease and a new social problem related to the abuse of and addiction to new psychoactive substances

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Objective: A new disease has arisen with the tidal wave of new psychoactive substances (NPSs) available to abusers and this has created a new challenge for clinicians. Due to the difficulty in diagnosis and clinical management, NPS-abusers force clinicians to search for better ways to manage poisoned patients. To manage acute intoxication, potential addiction and possible long-term sequelae, it is increasingly evident that a multidisciplinary approach is mandatory. Particularly, NPS-induced psychoses are frequently treated as an organic psychosis, but this is associated with therapeutic failure. We describe a case of a "human-tester" of different NPS presenting repeatedly with severe acute toxic effects and long-term psychiatric consequences.
Case report: A clinical course of a 27-year-old male (chemist) with positive history of cannabis, 3,4-methylenedioxymethamphetamine (MDMA) and ketamine abuse is described. Over 4 years (2012–2016) the patient was hospitalized (intensive care [ICU] and/or psychiatric wards) 7 times for severe acute intoxication due to NPS abuse. NPS were carefully chosen for their dissociative effects and were purchased on the Internet. The length of stay of each hospitalization varied from 4 days to 11 weeks. For severe conditions, during an ICU stay the patient underwent renal depurative treatments for 3 weeks. The main clinical manifestations (during the acute phase) were severe psychomotor agitation, aggressiveness, delirium, hallucinations and dissociative state. Psychosis was unsuccessfully treated with haloperidol, clotiapine, aripiprazole, valproic acid and promazine. NPS detected in biological samples during the different hospitalizations included dextromethorphan, methoxamine (MXE), MXE-bromo-derivative, ethylketamine, ethylnorketamine, norketamine, deschloroketamine, phencyclidine, 3-OH-PCP, 3-MeO-PCP, methoxyphencyclidine, dyphylline, methylphenidate, methoxphenidine and 5F-ADB. Brain positron emission tomography (PET) scan revealed a severe diffuse widespread metabolic deficit as a cerebral "age" of about a 70 years old subject. At present, the addiction behavior is still "active" and psychosis is pharmacology-resistant.
Conclusion: NPS-addicted patients give rise to different problems compared to abusers of classic substances. NPS-related psychosis has peculiar clinical aspects, and seems to be less responsive to standardized pharmacological treatments. As future perspectives, a multidisciplinary collaboration is necessary in order to identify optimal and appropriate management in these patients. To better understand all the crucial aspects of these novel toxicological diseases, experimental and clinical research on acute and chronic toxicity of NPS is needed.

159. An online survey on misuse of benzodiazepines and "Z drugs" in Singapore

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Objective: There is increasing concern regarding misuse of benzodiazepines and "Z-drugs". The aim of this study was to establish awareness and misuse prevalence of these drugs in Singapore.
Methods: An online survey was delivered through a market research company in September 2015 and June 2016. Demographic data and data on whether individuals had heard of a range of benzodiazepines/"Z drugs" and if so, whether they had ever misused them were collected; misuse was defined as use for reasons other than as directed by a doctor or pharmacist. Differences in proportions by year were tested using Fisher's

Table 1. Results of an online survey on misuse of benzodiazepines and "Z drugs" in Singapore.

	Number (%) of respondents who had heard of the drug			Number (%) of respondents who had ever misused the drug		
Drug Name	2015	2016	*p*-Value	2015	2016	*p*-Value
Diazepam	349 (34.9%)	376 (37.6%)	.227	27 (7.7%)	37 (9.8%)	.360
Alprazolam	183 (18.3%)	225 (22.5%)	.023	9 (4.9%)	16 (7.1%)	.411
Lorazepam	151 (15.1%)	189 (18.9%)	.028	10 (6.6%)	16 (8.5%)	.547
Midazolam	146 (14.6%)	188 (18.8%)	.014	8 (5.5%)	20 (10.6%)	.112
Clonazepam	88 (8.8%)	113 (11.3%)	.074	4 (4.5%)	9 (8.0%)	.396
Nitrazepam	78 (7.8%)	98 (9.8%)	.134	7 (9.0%)	15 (15.3%)	.255
Bromazepam	75 (7.5%)	99 (9.9%)	.068	5 (6.7%)	6 (6.1%)	1.000
Zolpidem	86 (8.6%)	116 (11.6%)	.031	7 (8.1%)	11 (9.5%)	.807
Zopiclone	67 (6.7%)	97 (9.7%)	.018	4 (6.0%)	9 (9.3%)	.562

exact test due to small cell counts in a post-hoc analysis (Bonferroni-adjusted $p < .006$).

Results: There were 999 respondents in 2015: 50.1% male, 49.8% female, 0.1% transgender; median (IQR) age 35 (29–45) years; 82.6% were Chinese, 8.2% Indian, 5.3% Malay, 0.8% Eurasian, 3.1% other race/ethnicity; 85.4% were employed, 11.3% unemployed, 3.3% students. There were 1000 respondents in 2016: 50.0% male; median (IQR) age 36 (30–45) years; 83.9% were Chinese, 6.8% Indian, 5.7% Malay, 0.6% Eurasian, 3.0% other race/ethnicity; 86.6% were employed, 10.1% unemployed, 3.3% students. Diazepam was the most commonly heard of drug; of those who had heard of the drugs, misuse ranged from 4.5–15.3% (Table 1). There was an increase in the awareness of the drugs but not in their misuse from 2015 to 2016.

Conclusion: This study suggests that the misuse prevalence of these drugs is similar to that in the UK [1] and USA [2]. Further work is needed to understand this problem to inform public health initiatives to address this issue.

References

[1] Kapil V, Green JL, Le Lait C, et al. Misuse of benzodiazepines and Z-drugs in the UK. Br J Psychiatry. 2014;205:407–408.

[2] Goodwin RD, Hasin DS. Sedative use and misuse in the US. Addiction. 2002;97:555–562.

160. Ayahuasca intoxication: two case reports

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Objective: Ayahuasca, a plant-based psychotropic beverage utilized for medicinal and religious purposes by Amazon and Orinoco shamans, is gaining advocates worldwide. The main species of plants used in its preparation are *Banisteriopsis caapi* and *Peganum harmala*. Both plants contain various alkaloids including beta-carboline, harmine, tetrahydroharmine and N,N-dimethyltryptamine (DMT). Onset of action after ingestion of the tea is relatively rapid – within the first 30–40 minutes. The user experiences intense mental activity characterized by introspection with strong visual-perceptual alterations (hallucinations involving geometric shapes, bright colors and moving lights) and a range of emotions spanning sadness, fear, euphoria, and uncontrolled laughter. These phenomena are associated with an increase in associative processes and inability to focus attention with enhanced ability to recall memory of past events. Systemic effects are limited to vomiting, tachycardia and mydriasis. Clinical effects intensify during the first two hours after ingestion and subside gradually in about six hours. Recent work shows effects after a single dose in depressed subjects may persist for weeks. Other studies indicate that use may help opioid addiction. We report two cases.

Case reports: Case 1: A 45-year-old male former heroin addict and habitual cannabis user began visiting Santo Daime and regularly traveled to one of the two Italian locations where ayahuasca is available. He drank ayahuasca on multiple occasions between mid-August to early October. Several months prior to drinking ayahuasca, he had stopped treatment with methadone, but denied heroin or other opioid use. In mid-September he began experiencing episodes of abnormal behaviors with paranoid ideations culminating in uncontrollable aggression requiring police intervention and hospitalization. His treating physician opined that although the patient had previously demonstrated abnormal behavior, he now showed marked symptomatology. Case 2: A 29-year-old male methadone patient presented to hospital with marked agitation and uncontrollable aggression. Blood was positive for amphetamines and urine testing reported DMT. The poison center suspected ayahuasca ingestion. High performance liquid chromatography-mass spectrometry (HPLC-MS) urine testing revealed: 2,5 dimethoxy-4-methyl-phenethylamine (2C-D), 2,5-dimethoxy-4-ethylphenethylamine (2C-E), 2,5-dimethoxy-4-ethyl-amphetamine (DOET), caffeine, and lidocaine.

Conclusion: The clinical effects of ayahuasca may be over in hours but can last for days. Multiple doses may prolong the effects. Individuals with pre-existing psychological and drug-seeking disorders such as opioids may be more at risk for adverse events than the general population. Combative psychosis has not generally been reported. Ayahuasca use should be considered in the differential diagnosis of patients who present with psychomotor agitation and hallucinations or who have a history of addictive disorders. Effects may be prolonged.

161. Baclofen poisoning in France reported to French Poison Centers: a five-year retrospective study

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Objective: Baclofen, a gamma-aminobutyric acid B receptor agonist, seems to be a promising treatment for alcohol dependence and in France the off-label use of baclofen for this indication has greatly increased since 2008. In March 2014, the National Safety Agency for Medicines and Health Products issued a Temporary Recommendation for Use (TRU) of baclofen up to the dose of 300 mg/day. The French Poison Centers were asked

to carry out a national retrospective survey to give an overview of self-poisoning with baclofen as alcohol-dependent patients usually exhibit psychiatric comorbidities [1].
Methods: A national retrospective study from January 2008 to December 2013, focused on self-poisoning with baclofen in alcohol-dependent patients managed by the nine French poison control centers. Data collected included date of occurrence, patient demographics (age and gender), details of the overdose (estimated dose and co-ingestants), neurological clinical signs (Glasgow Coma Scale [GCS], seizures, delirium, decrease of consciousness), hemodynamic changes (blood pressure, heart rate), and past psychiatric history.
Results: In total 220 suicide attempts with baclofen were recorded. The mean age of patients was 40.5 years (range 14–64 years), with a sex-ratio of 1.2. Psychiatric disorders (50.5%) and previous suicide attempts by self-poisoning were the most frequent comorbidities (20.5%). The mean supposed ingested dose was 480.7 mg (range 8–6000 mg). A quarter of the patients had drowsiness ($n = 55$, 25.5%), 21.8% had a GCS between 4 and 8 ($n = 47$), and 20.8% of patients were agitated ($n = 45$). Baclofen was associated with other drugs in 172 cases, most commonly benzodiazepines ($n = 87$, 50.5%), alcohol ($n = 84$, 48.8%), and illicit drugs ($n = 4$, 2.3%). Nine deaths were recorded, with a mean blood baclofen concentration of 1.7 mg/L (range 1–36.9 mg/L).
Conclusion: Self-poisoning with baclofen in alcohol-dependent patients remains a serious concern for physicians. Psychiatric comorbidities should be assessed before prescribing baclofen to these patients. Treatment is supportive and most patients with baclofen overdose have a good outcome [2].

References

[1] Franchitto N, Pélissier F, Lauque D, et al. Self-intoxication with baclofen in alcohol-dependent patients with co-existing psychiatric illness: an emergency department case series. Alcohol Alcohol. 2014;49:79–83.
[2] Leung NY, Whyte IM, Isbister GK. Baclofen overdose: defining the spectrum of toxicity. Emerg Med Australas. 2006;18:77–82.

162. Capsaicin cream in the treatment of cannabinoid hyperemesis syndrome: relief from the "joint" pain

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Objective: The objective is to demonstrate the efficacy of capsaicin cream in the treatment of cannabinoid hyperemesis syndrome in a large-volume, urban emergency department (ED) setting.
Case series: Four patients (three males, one female) presented to the ED with nausea, vomiting, and severe abdominal pain (rated 10/10 in three and 8/10 in one). Laboratory tests were non-diagnostic. Each received ondansetron and IV fluids. Two received prochlorperazine, and one received repeated doses of morphine prior to discharge. Each patient returned within 12 hours to 3 days with similar complaints and again received ondansetron and IV fluids; two also received prochlorperazine. ED physicians suspected cannabinoid hyperemesis syndrome. Three patients admitted to daily cannabis use, and one had a urine drug screen positive for cannabis on both visits. Each patient received capsaicin 0.075% topical cream applied to the abdomen. All four patients improved and were discharged within hours of receiving capsaicin cream and have not returned.
Conclusion: Cannabinoid hyperemesis syndrome (CHS) is a well-recognized, though, arguably under-diagnosed syndrome of recurrent emesis with patients who regularly use marijuana [1,2]. CHS patients frequently report taking long, hot showers as the only way to relieve their nausea and vomiting [2]. Typical antiemetics such as phenothiazines (prochlorperazine), 5HT-3 antagonists (ondansetron), and dopamine agonists (metoclopramide) are often ineffective. The exact mechanism of action of capsaicin is unclear, but likely involves its antagonism of transient receptor potential cation channel subfamily V member 1 (TrpV1) receptors [3,4]. We present a unique case series in which 4 patients with suspected cannabinoid hyperemesis syndrome resulting in repeated ED visits had successful treatment with topical capsaicin cream.

References

[1] Parekh JD, Wozniak SE, Khan K, et al. Cannabinoid hyperemesis syndrome. BMJ Case Rep. 2016;pii:bcr2015213620.
[2] Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53:1566–1570.
[3] Lapoint J. Capsaicin cream for treatment of cannabinoid hyperemesis syndrome. Clin Toxicol. 2014;52:707.
[4] Biary R, Oh A, Lapoint J, et al. Topical capsaicin cream used as a therapy for cannabinoid hyperemesis syndrome. Clin Toxicol. 2014;52:787.

163. Clinical features following analytically confirmed use of 5F-ADB, a synthetic cannabinoid receptor agonist. A report from the UK IONA study

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Objective: Synthetic cannabinoid receptor agonists (SCRAs) have been encountered increasingly frequently in recent years and can cause severe toxic effects. Here we describe the clinical characteristics of patients with analytically confirmed exposure to 5F-ADB, an indazole-3-carboxamide SCRA.
Methods: The UK Identification Of Novel psychoActive substances (IONA) study aims to identify new psychoactive substances (NPS) involved in episodes of severe acute toxicity presenting to participating hospitals and to link detected substances with the reported clinical features of toxicity. With ethical approval, consenting adults (≥16 years) with severe acute toxicity (according to specific definitions) presenting to participating hospitals after suspected NPS use exposure can be recruited. Blood, and/or urine samples are collected and clinical features recorded using a structured form. These are transferred to Newcastle in linked anonymised format with the code held by the local clinical team. Biological samples are analysed by liquid chromatography-tandem mass spectrometry.
Results: From 54 patients presenting during 2016, for which analytical data are available, a SCRA was identified in 24 and 5F-ADB

in 14 (10 male, age range 18–47, median 32 years) with the first presenting in January 2016. The methods of use were smoking ($n = 12$), ingestion ($n = 1$) and not known ($n = 1$). Reported drug products used were "Spice" ($n = 7$), "Pandora's Box" ($n = 2$), "Cherry Bomb" ($n = 1$) or unknown ($n = 4$). When reported (12 cases), drug product had been supplied by a friend ($n = 6$), shop ($n = 3$) or street-level dealer ($n = 3$). Comparing 8 cases with analytical evidence of exposure to other recreational drugs (including other SCRAs [$n = 6$], methadone [$n = 5$], diazepam and methylamphetamine) with 6 cases where no other substances were identified, clinical features most commonly recorded included confusion (5/8 and 4/6), paranoid ideation (4/8 and 4/6), reduced level of consciousness (7/8 and 3/6), convulsions (1/8 and 3/6), hallucinations (2/8 and 2/6), bradycardia (2/8 and 2/6), tachycardia (2/8 and 2/6), chest pain (1/8 and 2/6), agitation (4/8 and 2/6) and raised plasma lactate (1/8 and 2/6). All patients with isolated 5F-ADB exposure recovered rapidly without specific treatment and were discharged within 10 hours of presentation.

Conclusion: Human exposure to 5F-ADB was first reported after analysis of autopsy specimens from a male patient in Japan in 2014. It has been the most common SCRA identified in samples from UK IONA participants during 2016. As with other SCRAs, clinical effects reported include confusion, paranoia, reduced level of consciousness and convulsions.

164. Clinical features in emergency department patients with analytically confirmed intake of ADB-CHMINACA: a case series from the prospective study SPICE II plus

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Objective: The synthetic cannabinoid (SC) ADB-CHMINACA, an indazole-based valine derivative carrying a cyclohexylmethyl side chain, appeared on the European drug market in 2015. The compound is an agonist with high affinity at the cannabinoid receptor type 1 (CB_1) receptor ($K_i = 0.3$ nM), therefore posing the risk of acute side effects. We describe clinical features of patients with analytically confirmed intake of ADB-CHMINACA.

Methods: Cases are from a prospective observational study of patients treated in emergency departments (ED) after recreational use of SC. Patients were recruited after informed consent was obtained. Clinical features were recorded using a structured questionnaire. Serum and/or urine specimens were analyzed using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) for SC and their metabolites. Only cases with analytically confirmed intake of ADB-CHMINACA were included. Severity of poisoning was evaluated according to the Poisoning Severity Score (PSS).

Results: There were 14 patients (12 male, 2 female, 17–46 years), treated in the ED because of acute adverse effects. ADB-CHMINACA was identified in 13 (10) serum (urine) samples from March 2015 to May 2016. Concentration in serum varied from 0.22 to 31 ng/mL (median 0.49 ng/mL). In 7 cases more than one SC was found (4 times in urine samples only). Amphetamine derivatives were detected in 6 cases. PSS was moderate (8) or severe (6). Ten patients reported panic attacks (predominantly within 2–30 minutes after intake). Clinical features included tachycardia ($n = 9$), recurrent vomiting ($n = 7$), agitation ($n = 7$), somnolence, disorientation, aggressiveness and shivering (each 6), dyspnea ($n = 5$), seizures ($n = 2$), bradycardia ($n = 2$), double vision ($n = 1$), and psychosis ($n = 1$). Elevation of creatine kinase (CK, $n = 6$) and of creatinine ($n = 4$), hyperkalemia ($n = 2$), and hypoglycemia (47 mg/dL, $n = 1$) were also recorded. One patient developed posterior reversible encephalopathic syndrome (PRES), with recovery after 4 days. Extreme agitation and rioting was followed by muscle hematomas, rhabdomyolysis (maximum CK 166,000 U/L) and renal impairment (creatinine 1.7 mg/dL) in one case. A 25-year-old required mechanical ventilation after aspiration. All patients recovered.

Conclusion: Clinical features in patients with analytically confirmed intake of SC are similar to former reports, but there are also differences like the predominance of panic attacks (71%). In addition, the frequency of aggressiveness, agitation and shivering (each 43%) is unexpectedly high. In contrast to former reports of hypokalemia and hyperglycemia after SC use, our patients had hyperkalemia and hypoglycemia. Furthermore, PRES has yet not been described after SC consumption. ADB-CHMINACA seems to have a higher potential of toxicity than first generation SC of the aminoalkylindole type.

165. Clinical features of severe intoxications associated with analytically confirmed use of NBOMe

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Objective: A novel class of synthetic hallucinogens called NBOMe have emerged as new psychoactive substances (NPS) since 2009. NBOMe substances are N-2-methoxybenzyl analogues of the respective 2C-X substituted phenethylamines, and were first synthesized as 5-HT2A receptor activators at the Free University of Berlin in 2003 [1]. We evaluate the prevalence and the clinical features of analytically confirmed intoxications by NBOMe substances over the last two years (2014–2015).

Case series: Among the consecutive cases referred to our Poison Control Centre (as reference Centre in Italy) for suspected/confirmed poisoning by NPS between 2014 and 2015, 11 cases of NBOMe intoxication were evaluated (age range 16–27 years; 82% males). Specific laboratory investigations (liquid chromatography-mass spectrometry) were performed in all cases on urine and/or blood specimens; 7 patients were positive for 25I-NBOMe, 2 for 25B-NBOMe, 1 for 25C-NBOMe and 1 for 25I- and 25H-NBOMe. Urine samples were also positive for 2C-I (7 cases), tetrahydrocannabinol (THC) (7), amphetamines (3), 3,4-methylenedioxymethamphetamine (MDMA) (2) and ketamine (1 case). The patients declared use of LSD or another hallucinogenic substance ($n = 6$), mescaline ($n = 1$), other or unknown substances of abuse ($n = 3$) or no drug use. Three patients (27%) took part in a rave party. The most common clinical manifestations were severe psychomotor agitation (91%), tachycardia (64%), seizures and rhabdomyolysis (45%), confusion (36%), hyperthermia (27%), coma, mydriasis, hallucinations and violent behavior (18% each).

No lethal cases were registered. Treatment included sedation with benzodiazepines (6 cases), intubation and respiratory support (5 cases). Hospital stay ranged from 10 hours to 11 days for patients needing intensive care treatment.
Conclusion: This case series confirms the presence of at least 4 types of NBOMe molecules (25I-, 25B-, 25C- and 25H-NBOMe) in the Italian territory. Seven patients were positive for 25I-NBOMe and 2C-I, and this may be due to the metabolism of NBOMe to 2C analogues, or to the simultaneous abuse of 25I-NBOMe and 2C-I. Clinicians should be aware of the presence of these new psychoactive substances and their potential for toxicity, and they should suspect possible NBOMe usage in patients reporting the recent use of LSD or other hallucinogens. All the cases have been reported to the National Early Warning System.
Acknowledgements: Study carried out with the support of Antidrug Policy Department, Italian Presidency of the Council of Ministers.

Reference

[1] Kyriakou C, Marinelli E, Frati P, et al. NBOMe: new potent hallucinogens – pharmacology, analytical methods, toxicities, fatalities: a review. Eur Rev Med Pharmacol Sci. 2015;19:3270–3281.

166. Cocaethylene formation following ethanol and cocaine use: a case report

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Objective: Ethanol alters the hepatic biotransformation of cocaine, resulting in trans-esterification to an active metabolite, cocaethylene (ethylbenzylecgonine). Cocaethylene is metabolized along the same pathway of cocaine and both alcohol and cocaine decrease the clearance of cocaine by 47% and 26%, respectively, thus prolonging cocaine toxicity and behavioural changes.
Case report: A 23-year-old male with history of cocaine and alcohol abuse on a daily basis, was brought by ambulance to the First Aid Unit of the Careggi Hospital, Florence (Italy) as he was found in the street in a state of psychomotor agitation. He had epistaxis and referred chest pain, palpitations and nose pain and reported that he had been sniffing cocaine for the past 3 days. The electrocardiogram (ECG) showed tachycardia and non-specific alterations. He had no blood markers of chronic alcohol abuse and the toxicological screening of urine was positive for cocaine (benzoylecgonine >6 mg/L), tetrahydrocannabinol (THC) (223 µg/L); blood alcohol was negative (<0.2 g/L). A blood sample was sent to the Forensic Toxicology Unit for cocaethylene detection using a selective and sensitive gas chromatography-mass spectrometry (GC-MS) method. The determination revealed a positive value of 84.178 ng/mL. The patient was transferred to the Short-Stay Toxicological Observation Unit, where, apart from an episode of epistaxis about 6 hours after admission, he had no other complications. Cardiovascular parameters remained normal during the whole hospital stay, while an otorhinolaryngological visit revealed a hyperemic septal mucosa and signs of ischemia of the mucosa of the ala nasi bilaterally. Since he had no further toxicological signs, he was discharged the day after admission.
Conclusion: From epidemiological and toxicological data, it has been suggested that the combination of alcohol and cocaine produces an increased cardiac toxicity with respect to cocaine alone, in addition to behavioral changes. However cocaine and cocaethylene appear to differ in some respects, including the relative potency of their actions on the dopamine and serotonin transporters and on behavioral alterations. In this patient, although he had positive blood results for benzoylecgonine, the metabolite of cocaine, and of cocaethylene, parameters that are not frequently revealed together, he developed psychomotor agitation but no cardiotoxic effects.

167. Comparison of prevalence of illicit recreational drug use in the annual Crime Survey England and Wales and the UK Survey of Non-Medical Use of Prescription Drugs Programme between 2014 and 2016

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Objective: To compare lifetime and annual prevalence of illicit/recreational drug use reported in the annual Crime Survey England and Wales (CSEW), a population level survey, to that reported in the UK Survey of Non-Medical Use of Prescription Drugs (NMURx); this is a repeated online survey conducted to determine the prevalence of non-medical use of a range of prescription/over-the-counter drugs.
Methods: Data was extracted from CSEW for 2013–14, 2014–15 and 2015–16 on the percentage of respondents reporting lifetime and last year use of any illicit/recreational drug and of cannabis, the most commonly reported drug. Similar data was extracted for respondents from England and Wales for the NMURx surveys in 2014, 2015 and 2016; since CSEW data is for those aged 16–59 years old, the same age range was used for the NMURx dataset.
Results: In total 62,510 respondents completed the CSEW surveys and 14,449 respondents aged 16–59 years in England and Wales completed the NMURx surveys during the study period. As shown in Table 1, lifetime and last year prevalence of use of any illicit/recreational drug and of cannabis were comparable between the two datasets over the three year time period.
Conclusion: Prevalence of lifetime and annual use of any illicit/recreational drug and of cannabis was comparable between CSEW and NMURx over this 3-year period. The CSEW is

Table 1. Percent of respondents aged 16–59 years old reporting last year and lifetime use of cannabis and of any illicit/recreational drug in the Crime Survey England and Wales (CSEW) and the UK Survey of Non-Medical Use of Prescription Drugs (NMURx).

	CSEW			NUMRx		
Drug	2013–14	2014–15	2015–16	2013	2014	2016
Cannabis						
Last year	6.6%	6.7%	6.5%	7.4%	7.2%	8.0%
Lifetime	29.9%	29.1%	29.4%	31.1%	30.9%	30.5%
Any drug						
Last year	8.8%	8.6%	8.4%	8.9%	9.0%	10.3%
Lifetime	35.7%	34.7%	35.0%	32.8%	32.8%	33.0%

considered the "gold standard" indicator of population prevalence of illicit/recreational drug use in England and Wales. Therefore, this study suggests that since the NMURx survey has a comparable prevalence of illicit/recreational drug use to CSEW, data on the non-medical use of prescription drugs from the NMURx could be considered representative of population-level data.

168. Confirmed intoxication by 2-methoxphenidine and flubromazepam mimicking ischemic cerebral disease

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Objective: Intoxications by new psychoactive substances (NPS) are frequently associated with unexpected and unpredictable clinical manifestations. Flubromazepam and methoxphenidine have recently appeared on the illegal drug market and there is very limited information about analytical evaluations on biological samples and acute toxicity profile of these substances [1,2]. We report a case of analytically confirmed intoxication by methoxphenidine and flubromazepam.
Case report: A 25-year-old male was brought to the emergency department (ED) 20 hours after an episode of syncope with secondary head trauma and a wound to the right orbital region. On arrival, he had excitatory behaviour, severe psychomotor agitation, confusion, dysarthria and aphasia, mild hypertension (150/100 mmHg) and slight tachycardia (85 bpm). He was unable to maintain an upright position, and had lower limb hyposthenia. He denied any pharmacological therapy. A cranial computerised tomography (CT) scan for suspected cerebral ischemia was negative. He remained confused, seriously agitated and hypertensive (BP 180/100 mmHg), with a weakness on the left side of the body, so he underwent perfusional and angiographic cerebral CT scans; both were normal. During the first hours of hospitalization, he required massive sedation therapy with high doses of midazolam and propofol. Immunoenzymatic urinary tests were positive for tetrahydrocannabinol (THC) and benzodiazepines. He was discharged two days later with a prescription for paroxetine. His parents brought in some pills and a powder purchased on the Internet and labelled "flubromazepam" and "2-methoxphenidine", respectively. Urine, blood and product samples were analysed by gas chromatography-mass spectrometry and liquid chromatography with tandem mass spectrometry. The products contained the declared compounds and blood samples flubromazepam (247 ng/mL) and methoxyphenidine (411 ng/mL).
Conclusion: Standard urine screen tests are insufficient to make a correct diagnosis when NPS are taken. In patients with unusual symptomatology onset (e.g., for age and/or history) it is advisable to suspect the consumption of NPS. Considering the wide variety of NPS and the attitude of users to mix substances that may act in different ways, the use of advanced techniques for the detection of specific substances and their quantification in serum are fundamental tools in order to support a correct diagnosis and undertake an effective therapy.

References

[1] Moosmann B, Huppertz LM, Hutter M, et al. Detection and identification of the designer benzodiazepine flubromazepam and preliminary data on its metabolism and pharmacokinetics. J Mass Spectrom. 2013;48:1150–1159.
[2] Hofer KE, Degrandi C, Müller DM, et al. Acute toxicity associated-with the recreational use of the novel dissociative psychoactive substance methoxphenidine. Clin Toxicol. 2014;52:1288–1291.

169. Does one affect the other? A 5-year characterization of US Poison Center data comparing human marijuana and synthetic cannabinoid exposures

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Objective: An increasing number of US states are considering legalizing recreational marijuana, while synthetic cannabinoid outbreaks continue to occur. We sought to compare trends of US Poison Center marijuana exposures to synthetic cannabinoids exposures over a 5-year period.
Methods: We queried the National Poison Data System (NPDS) for US aggregate poison center data involving closed, human exposures to marijuana and synthetic cannabinoids (SCs) from 2011 to 2015 using American Association of Poison Control Center (AAPCC) generic codes 0083000 (marijuana) and 0200617 (SCs). Cases for inclusion were not limited to single-substance exposures. Parameters evaluated were age, clinical effects, gender, management site, medical outcome, reason, route, and therapies. Descriptive statistics were used.
Results: Nationally, NPDS reported 27,578 exposures to marijuana from 2011 to 2015; 17,076 (62%) were male. Marijuana exposures have risen since 2012 ($n = 4934$) to 2015 ($n = 6600$). The age range with the most number of exposures was 15–21 years ($n = 10,906$ representing 40% of the total number of exposures over the 5-year period). A majority ($n = 20,768$, 75%) were already in or en route to a healthcare facility when the poison center was called; 11% ($n = 2926$) were managed on site (non-healthcare facility). The 10 most frequently reported clinical effects were drowsiness, tachycardia, agitation, confusion, hypertension, vomiting, hallucinations, nausea, mydriasis, and slurred speech. Overall 36% ($n = 10,041$) of exposures reported minor or no effects; 34% ($n = 9421$) had moderate effects, and 6% ($n = 1527$) had major effects. There were 118 deaths (combined indirect and direct reports). Regarding SC exposures, there were 26,345 exposures from 2011 to 2015. A majority (76%) were male. SC exposures dropped from 6968 in 2011 to 2668 in 2013. But in 2015 there were 7797 SC exposures nationwide (surpassing marijuana exposures). Age distribution was similar to marijuana (age 15–21 years comprised 42% of total exposures); 94% ($n = 24,714$) of exposures were referred or already in a healthcare facility. The most frequently reported clinical effects were similar to marijuana; 33% ($n = 8722$) of exposures reported minor/no effect, 41% ($n = 10,900$) had moderate effects, 7% had major effects, and 77 deaths were reported.
Conclusion: Ever-changing federal and state laws governing marijuana and SCs are reflected in yearly changes to abuse patterns. We compared US poison center data involving marijuana

and synthetic cannabinoid exposures over a 5-year period and found similarities: the age group with the heaviest use was 15–21 years, male > female, and clinical effects and outcomes were similar. As more states adopt medical and recreational marijuana, these trends will likely change.

170. Drowning in bath salts: MDPV in northern Germany

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Objective: 3,4-Methylenedioxypyrovalerone (MDPV) is a substituted cathinone belonging to the class of α-pyrrolidinophenones that have become increasingly popular as psychostimulants in recent years. MDPV is sold via the Internet under different slang names such as bath salts, flex and others.
Methods: For the period 2008–2016 all enquiries regarding hospitalisations due to intoxication with MDPV were identified in the GIZ-Nord database. Mono-intoxications, co-ingestants, symptoms and severity, annual distribution and ToxIndex were analysed for the cases retrieved.
Results: The MDPV epidemic in northern Germany began in 2008, peaked in 2014 and has been on the decline since. During this period GIZ-Nord received 33 enquiries regarding hospitalised patients intoxicated with this substance. Of these 22 were mono-intoxications and 11 combined intoxications. All patients were male with an average age of 32 years. The leading symptoms were psychomotor agitation (42%), somnolence or coma (24%), alternating somnolence with agitation (9%) and hallucinations (12%). One patient developed serotonin syndrome and another had to be resuscitated because of ventricular fibrillation. Both were mono-intoxications and the patients survived. According to the Poisoning Severity Score 33% had minor, 49% moderate and 12% severe symptoms (6% were not well documented). No fatalities occurred. The ToxIndex is defined as the sum of all cases classified as lethal, severe or moderate related to the number of all exposure cases. This index of 60% in this analysis is very high and indicates the hazardous nature of MDPV.
Conclusion: After a century of a more or less consistent spectrum of drugs, Europe now faces a new drug problem, called new psychoactive substances (NPS). Synthetic cathinones play an increasing role among these mind-altering substances. The example of MDPV shows the unpredictable danger of these new substances. Although the figures of MDPV have declined, dozens of similar substances are ready to take over.

171. Gamma-hydroxybutyrate intoxication in Italy related to a pharmaceutical preparation

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Objective: In Italy, gamma-hydroxybutyrate (GHB) is used to control withdrawal symptoms in the treatment of alcohol dependence. It is available in 10 or 240 mL bottle of 17.5% solution. This study evaluates a case series of patients with voluntary intoxication by GHB as the pharmaceutical formulation referred to Italian Emergency Departments (EDs) and our Poison Control Centre, in order to identify the characteristics of this intoxication in our country.
Methods: A retrospective analysis of all cases of pharmaceutical-GHB intoxication referred to our Poison Control Center over a nine-year period (2007–2015). All cases of admission to EDs for a confirmed and voluntary GHB poisoning were evaluated, while accidental intoxications (e.g., therapeutic error) were excluded. Characteristics of the poisoned patients and clinical features were evaluated.
Results: Overall 466 of the 539 cases of pharmaceutical-GHB intoxication met the inclusion criteria (M/F ratio 1.39), aged from 16 to 78 years (median age 39.45 ± 9 years). The average dose taken (known in 318/466 patients) was 76.62 mL (13.4 g, range 1.75–49 g); 26.1% of the patients were admitted to the EDs during the weekend. In total 41% of patients ($n = 191$) ingested only pharmaceutical-GHB, while other agents were co-ingested in 275 cases (59%). Among these, the main co-ingestants were sedative-hypnotics (30%), antidepressants (19%), ethanol (26%), methadone (5%), substances of abuse (8%) and other drugs for the treatment of alcohol abuse (7.6%). Severe neurological impairment (Glasgow Coma Score <9) was present in 56.2% of all the cases (276/466), and in 36.3% of the pharmaceutical-GHB pure intoxications (121/191). Twenty-one patients (4.5%) needed endotracheal intubation and supported ventilation (4.1% in pure intoxication and 4.7% in mixed intoxications).
Conclusion: Compared to the previously published studies on GHB intoxication, this case series of pharmaceutical-GHB intoxication shows some peculiarities such as (i) higher average age, (ii) high percentage of co-ingestion of medications and ethanol, (iii) lower percentage of excitatory symptoms and (iv) a homogeneous distribution of the cases during the week. The use of GHB in Italy for the treatment of alcoholism results in an easier availability for patients at risk of abuse and could explain the peculiarities of our case series.

172. Increase in Emergency Department presentations in Europe related to the use of synthetic cannabinoid receptor agonists

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Objective: There is increasing concern about the availability, use and acute harms related to the use of synthetic cannabinoid receptor agonists (SCRA) in Europe. This study aimed to determine whether prevalence of SCRA-related acute harm in Europe has changed.
Methods: The Euro-DEN Plus project collects longitudinal data from 16 sentinel centres in 10 European countries on Emergency Department (ED) presentations with acute recreational drug toxicity. The Euro-DEN database was searched for presentations involving the use of SCRAs between October 2013 and September 2015. The following data were extracted from

identified cases: demographics, SCRA and co-used substances and outcome.
Results: There were 104 presentations reporting use of one or more SCRA. The majority of these were male (80, 83%) and the median (IQR) age was 22.5 (17–32) years. SCRA cases were reported in only 6 of the 16 Euro-DEN Plus countries (Germany, Ireland, Norway, Poland, Spain and the UK). There was a significant increase in the SCRA presentations from year 1 (October 2013 to September 2014) to year 2 (October 2014 to September 2015) from 26 to 78; in particular this increase was seen in three countries (Germany 1 to 17; Poland 1 to 8; UK 18 to 49, in the UK this increase was seen in all three Euro-DEN Plus centres [London 2, York 1]). The majority of SCRAs used were either branded ($n = 30$, 29%), "SCRA not known" ($n = 25$, 24%) or "Spice" ($n = 45$, 43%); only a minority of patients reported use of specific SCRA compounds: MAM-2201 ($n = 2$, 2%); MDMB-CHMICA ($n = 1$, 1%); AB-PINACA ($n = 1$, 1%); and UR-144 ($n = 1$, 1%). The majority of presentations involved lone SCRA use with/without ethanol ($n = 79$, 76%). The most common co-used substance was cannabis ($n = 12$, 11.4% presentations); co-used novel psychoactive substances (NPS) were fluoroamphetamine ($n = 2$), AMT ($n = 1$), ethylphenidate ($n = 1$) and mephedrone ($n = 1$). The majority of patients ($n = 82$, 79%) were medically or self-discharged from the ED and the median (IQR) length of hospital stay was 4 hours 11 minutes (2 h 44 m to 15 h 13 m); no patients were admitted to critical care and there were no deaths.
Conclusion: This data demonstrate a significant increase in ED presentations related to the use of SCRAs to the Euro-DEN Plus network across Europe between 2013 and 2015. This mirrors the increasing detection and reported use of SCRAs across Europe and greatest numbers of Euro-DEN Plus SCRA-related presentations were seen in countries where other indicators suggest more prevalent use of SCRA products. Further harm reduction work is required to reduce the availability and use of these products.

173. Moderate and severe carbon monoxide intoxication related to waterpipe use

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Objective: Narghile (waterpipe, hookah) is a traditional method of tobacco use. In recent years, its use has increased worldwide, especially among young people. Compared to cigarettes, narghile smoking can result in a greater exposure to several volatile compounds, including carbon monoxide (CO) [1]. We evaluate waterpipe-related CO-poisoning to assess the severity of the intoxication.
Methods: All cases referred to our Poison Control Centre in a eight year period (April 2008 to April 2016) for CO intoxication were retrospectively reviewed, and narghile-related cases were selected and evaluated for (i) patient data, (ii) clinical manifestations, (iii) carboxyhemoglobin (COHb) concentration at admission, (iv) treatment and (v) outcome.
Results: Sixteen patients (M/F 13/3), aged from 17 to 47 years, were identified with waterpipe-related CO poisoning. Half the patients had smoked alone, and half smoked with other people. Most (15/16) patients had smoked tobacco, while only one had smoked hashish. Ten patients were seen in an emergency department because of symptoms: syncope (5/10), headache (7/10), dizziness (2/10), vomit (3/10), diarrhea (1/10), and dyspnea (3/10). COHb concentrations in symptomatic patients at admission ranged from 5.3 to 23.2% (average 14.2 ± 7%). Six patients were asymptomatic and underwent medical evaluation because they smoked with symptomatic patients; their COHb concentrations on admission ranged from 5.6 to 18.3% (average 8.4 ± 5%). Five of six asymptomatic patients were discharged in 12 hours after cardiac evaluation and normobaric oxygen treatment. Eleven patients were hospitalized for further clinical evaluations and for normobaric (7/11) or hyperbaric oxygen treatment (4/11). All patients were discharged without sequelae. A 40 day clinical follow-up was performed. The symptomatic patient who smoked hashish manifested syncope with short pseudoparesis of limbs; his COHb level was 11.5% three hours after smoking.
Conclusion: Narghile smoking exposes users to the same harmful substances as cigarette smoking (including CO), but in greater quantity due to the duration of smoking/inhalation (approximately 5 minutes for cigarettes, 50 minutes for narghile) and the combustion temperature. The amount of CO in smoke is mostly related to waterpipe size and tobacco type. Moreover, waterpipe smokers inhale CO as a result of the charcoal combustion. CO intoxication, even severe, may occur, and it is reasonable to believe that these cases are underestimated. This diagnosis should be considered in case of non-specific neurological symptoms.

Reference

[1] Shihadeh A, Salman R, Jaroudi E, et al. Does switching to a tobacco-free waterpipe product reduce toxicant intake? A crossover study comparing CO, NO, PAH, volatile aldehydes, "tar" and nicotine yields. Food Chem Toxicol. 2012;50:1494–1498.

174. Necessity of vigilant supervision of body stuffers: a case report

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Objective: In Lithuania body packaging and body stuffing is not common, however in recent years the number of "body packers" in other countries is increasing [1]. The aim of this case report is to emphasize the necessity of vigilant supervision of body stuffers despite other available diagnostic tools.
Case report: A 42-year-old woman was delivered to the Emergency Department (ED) of the Hospital of Lithuanian University of Health Sciences "Kauno klinikos" by police officers. During questioning at the patient's home the police officers noticed a little red packet in her hand, but after a few moments it disappeared. Illicit drug concealment was suspected and for further observation and investigations the patient was admitted to the ED. Physical examination revealed no pathological signs. During diagnostic gastroscopy a red packet filled with an unknown substance was seen in stomach. It was not taken out due to risk of rupture and laxatives were chosen for therapy. Diagnostic gastrointestinal passage and then a computerised tomography (CT) scan were performed with the aim of identifying the location of the drug package, but these investigations were not informative. After 24 hours it was decided to perform a fibrocolonoscopy and the anesthesiologist found the package in the patient's mouth. How the package reached the patient's mouth remains unknown, there were two possibilities: regurgitation from the stomach or the patient retrieved it from faeces. The main reason for this situation was negligent supervision of the patient; she was observed by two policemen at all times, but both police officers were sitting behind her most of time and even left the patient alone for several short periods.

Conclusion: People who perform illegal actions employ all possible methods to avoid the law [2]. This case report emphasizes the need for good supervision which does not depend entirely on medical staff.

References

[1] Markovits N, Kurnik D, Halkin H, et al." Body packers "in Israel: a case series. Isr Med Assoc J. 2013;15:639–645.

[2] Booker RJ, Smith JE, Rodger MP. Packers, pushers and stuffers – managing patients with concealed drugs in UK emergency departments: a clinical and medicolegal review. Emerg Med J. 2009;26:316–320.

175. Non-medical use of loperamide in the UK

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Objective: There have been increasing anecdotal reports of non-medical use of loperamide in the US; there is interest in this issue in Europe but no data. The aim of this study was to determine the prevalence of non-medical use of loperamide in the UK.

Methods: An online survey of adults aged 16–100 years living in the UK was delivered through a market research company in August 2016. Non-probability quota sampling was used to provide a proportional distribution of respondents across the UK regions and an approximately equal gender distribution within each region. Data collected were: demographics (age, gender, place of residence), lifetime use of loperamide and lifetime non-medical use of loperamide. If they reported non-medical use, respondents also completed the Drug Abuse Screening Test (DAST-10) and their reason for non-medical use. Non-medical use was defined as ever using loperamide for any reason other than what was recommended by a doctor/dentist/pharmacist/the package insert. Statistical comparisons were made using Fisher's exact test for categorical variables and t-test for continuous variables.

Results: Overall 10,013 individuals completed the survey: mean ± SD age 46.8 ± 15.6 years, 50.0% female; 13.4% were from London, 70.8% elsewhere in England, 4.8% Wales 8.3% Scotland and 2.8% Northern Ireland. In total 2919 (29.2%) reported lifetime use of loperamide; 135 (1.3% of all survey respondents, 4.6% of those with lifetime loperamide use) reported lifetime non-medical use of loperamide. Those respondents were younger (41.7 ± 15.1 versus 46.9 ± 15.6, $p < .001$) than those not reporting non-medical use of loperamide, were more likely to live in London (31.1% versus 13.1%, $p < .001$), were more likely to report lifetime illicit drug use (40.7% versus 28.9%, $p = .004$) and had a higher risk of problematic drug use as reflected in their DAST-10 (25.9% versus 7.5% DAST-10 ≥ 3, $p < .001$; mean ± SD DAST-10 (2.0 ± 2.5 versus 0.9 ± 1.6, $p < .001$). There was no difference in gender between these groups (48.9% versus 50.1% female, $p = .80$). Common reasons for non-medical use of loperamide were to self-treat pain (53.3%), to self-treat a medical condition other than pain (53.3%), for "enjoyment" or" to get high" (20.7%), to "come down" (14.1%) and to prevent/treat withdrawal symptoms (13.3%).

Conclusion: Non-medical use of loperamide was reported by a small but significant minority in this large online UK survey, most commonly amongst those reporting use of illicit drugs and in those with a DAST-10 indicating a risk of problematic drug use. Further work is required to investigate this issue to design appropriate public health interventions.

176. Novios muertos: two confirmed fatalities from U-47700

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Objective: 3,4-Dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide, otherwise known as U-47700, is a synthetic opioid and research chemical that has been available since its development by Upjohn in the 1970s. It is a potent μ-opioid receptor agonist that has been described in animal models as being 7.5× more potent than morphine [1]. Due to these characteristics and its ready availability on the Internet, it is concerning as a drug of abuse. Although use is well reported, fatalities are uncommon. We present two cases of clinical opioid fatalities related to this uncommonly fatal synthetic opioid.

Case reports: A 26-year-old female was discovered in bed by her boyfriend, surrounded by vomitus and agonally breathing. She suffered an asystolic cardiac arrest during emergency medical services (EMS) transport to hospital. Chest compressions, intubation, and epinephrine achieved return of spontaneous circulation. No medications were required for intubation. She was acidemic on arrival (pH 7.34, PCO_2 32 mmHg, PO_2 338 mmHg, bicarbonate 17.2 mmol/L, lactate of 15), and unresponsive to all stimuli. Electrocardiogram (ECG) showed a heart rate of 118 beats/min with a QTc of 611 ms and marked evidence of cardiac damage (lateral ST depressions). Urine toxicology was positive for benzodiazepines only. Computerised tomography (CT) imaging of the brain demonstrated marked cerebral edema, most likely due to anoxic brain injury. The patient's boyfriend returned home that evening and was found deceased in the shower the following morning. The index patient was pronounced dead 6 days after initial presentation. Comprehensive toxicology performed by the medical examiner demonstrated the presence of only U-47700 and cotinine in both decedents' blood.

Conclusion: These cases represent uncommon fatal exposures to a synthetic opioid that is still readily available via the Internet. Given the current climate of opiate abuse and misuse, this work presents a particular risk to opioid users. As such, practitioners should be aware of this as a potential additive in illicit opioid supplies as well as a primary drug of abuse.

Reference

[1] Cheney VB, Szmuszkovicz J, Lahti RA, et al. Factors affecting binding of trans-N-[2-(Methylamino)cyclohexyl]benzamides atthe primary morphine receptor. J Med Chem. 1985;28:1853–1864.

177. Patients self-discharging during treatment for acute poisoning by substances of abuse

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Objective: We charted characteristics of patients self-discharging during treatment for acute poisoning by substances of abuse and looked for associations between self-discharge and multiple presentations.
Methods: All patients 12 years and older treated for acute poisoning with substances of abuse at an emergency outpatient clinic in Oslo, Norway, were included consecutively from October 2011 through September 2012. We collected data on gender, age, main toxic agent, suicidal intention, homelessness, history of severe psychiatric condition, and whether the patient self-discharged. The main toxic agent for a patient was defined as the most frequently diagnosed main toxic agent in that patient's poisoning episodes. We performed a multiple logistic regression analysis to identify factors associated with multiple presentations with acute poisoning by substances of abuse during the inclusion period.
Results: During one year 1731 patients were treated for 2343 episodes of acute poisoning with substances of abuse. Of these, 1136 (66%) patients were male. In total 266 (15%) patients self-discharged during at least one poisoning episode. Self-discharging patients were older (median age 39 years versus 32 years, $p < .001$), more frequently homeless (20/266 [8%] versus 63/1465 [4%], $p = .035$), and the main toxic agent more frequently was an opioid (82/266 [31%] versus 282/1465 [19%], $p < .001$), and less frequently a benzodiazepine (12/266 [5%] versus 132/1465 [9%], $p = .020$). Self-discharging patients more often had multiple presentations with acute poisoning by substances of abuse (89/266 [33%] versus 186/1465 [13%], $p < .001$). Self-discharge was an independent risk factor for presenting more than once, adjusted odds ratio (AOR) 2.9 (95% CI 2.1–4.0). The association was even stronger for presenting more than twice, AOR 4.9 (2.3–7.4).
Conclusion: Self-discharge is associated with frequent poisonings with substances of abuse. Self-discharging patients might benefit from special attention, for instance by way of follow-up from outreach services.

178. Patterns of use of licensed medicines in Emergency Department acute recreational drug toxicity presentations reported to the European Drug Emergencies Network Plus (Euro-DEN Plus)

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Objective: There is little published data on the recreational use of licensed medicines in Europe; therefore we investigated the pattern of presentations to the European Drug Emergencies Network Plus (Euro-DEN Plus) involving recreational use of licensed medicines.
Methods: The Euro-DEN Plus project collects longitudinal data from 16 sentinel centres in 10 European countries on Emergency Department (ED) presentations with acute recreational drug toxicity. The Euro-DEN Plus database was searched for presentations involving reported recreational use of licensed medicines (defined as registered medicines available on prescription or over the counter); these were divided into presentations involving a licensed medicine together with an illicit/established recreational drug and/or novel psychoactive substance (NPS) and those presentations involving only a licensed medicine.
Results: Between October 2013 and September 2015 there were 10,956 Euro-DEN Plus presentations involving 16,986 drugs; 3139 (28.6%) presentations involved the reported recreational use of at least one licensed medicine. The five most commonly reported were clonazepam (626 reports), "unknown benzodiazepine" (527), methadone (467), diazepam (423) and "unknown opioid" (307). In 1426 (13.0% of all presentations and 45.4% of those involving a licensed medicine) only licensed medicines had been used: methadone was most commonly reported (245 reports), followed by "unknown opioid" (209), "unknown benzodiazepine" (199), diazepam (188) and clonazepam (160). In the licensed medicines only presentations, 979 (68.7%) were male and the median (IQR) age was 37 (28–46) years. The majority (756, 53.0%) were medically discharged from the ED and 61 (4.3%) were admitted to critical care. The median (IQR) length of hospital stay was 6 hours 9 minutes (3 h 21 m to 14 h 51 m). There were nine fatal cases in the licensed medicine only presentations, seven of which involved an opioid. The extent of licensed medicine recreational use varied between Euro-DEN Plus centres. They accounted for between 5.1 and 57.8% of the drugs reported in individual centres, with five centres reporting over 40% (Drogheda, Tallinn, Paris, Munich and Pärnu). In 10 centres, licensed medicine only presentations were <10% (3.3–9.6%) of the total presentations to the centre, in six centres 10–25% (10.3–22.4%), 33.0% in Paris, 33.8% in Tallinn and 57.5% in Pärnu.
Conclusion: Recreational use of licensed medicines was common in acute recreational drug toxicity presentations to Euro-DEN Plus centres and 13.0% of presentations involved only licensed medicines, with opioids and benzodiazepines being most frequently reported. This suggests significant morbidity related to the recreational use of licensed medicines in Europe and the need for work to address this issue.

179. Pregabalin misuse and abuse reported to US Poison Centers

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Objective: Anticonvulsant medications are commonly prescribed for several conditions including epilepsy, neuropathic pain, and mood disorders. Among them, pregabalin is widely prescribed for neuropathic pain analgesia and general anxiety disorder with the presumption that it has a very low abuse and misuse potential. Pregabalin abuse and misuse, however, is reported. Therefore, the purpose of this study is to characterize cases of intentional pregabalin abuse and misuse reported to US Poison Centers using the National Poison Data System (NPDS).
Methods: All pregabalin exposures reported to the National Poison Data System specifically as intentional abuse or misuse from 2006 to 2015 were extracted from the National Poison Data System. System generic codes and product codes for pregabalin were used. All cases as the major category were analyzed. Descriptive statistics were generated for demographic data, route or administration, clinical effects, treatments administered, level of healthcare facility, and medical outcomes.
Results: During the 10-year study period, there were 28,920 cases involving pregabalin exposure reported to the NPDS. The mean age was 41.9 years. Females were involved in the majority of cases ($n = 18,191$; 62.9%). The most common route of exposure was ingestion ($n = 28,691$, 99.2%). Intentional abuse or

misuse was involved in 2446 (8.5%). The most common clinical effects were drowsiness/lethargy ($n = 10,603$; 36.7%), tachycardia ($n = 3619$, 12.5%), and agitation/irritability ($n = 1,984$; 6.9%). Respiratory depression was reported in 1267 patients (4.4%), hypotension in 1992 patients (6.9%) and cardiac arrest in 106 patients (0.4%). Patients were treated and released ($n = 6,006$; 20.8%) or admitted to a critical care setting ($n = 6233$; 21.6%) in many scenarios. Medical outcomes were no effect ($n = 5585$; 19.3%), 6759 minor (23.4%), 5869 moderate (20.1%), and 1656 major (5.7%) effects. The most common therapeutic interventions were intravenous fluids ($n = 8,425$; 29.1%), supplemental oxygen ($n = 3926$, 13.6%), intubation ($n = 2,139$, 7.4%), and benzodiazepines ($n = 1933$, 6.7%). There were 106 (0.37%) deaths.
Conclusion: Females were involved in the majority of cases involving pregabalin exposure. Most exposures resulted in no effect, minor effects, or moderate effects not requiring treatment, although a minority of exposures resulted in more severe effects, including respiratory depression and cardiac arrest requiring intubation. Likely to become more frequent, healthcare providers should be aware of the abuse of antiepileptic medications including pregabalin as a relatively new and important trend.

180. Recreational carfentanil: the devil in disguise

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Objective: Recreational use of potent fentanyl derivatives is increasing and poses a serious threat to health and public safety [1]. The fentanyl derivative carfentanil, a large animal tranquilizer, is one of the most potent opioids known (10,000 times more potent than morphine) and can lead to severe or fatal intoxications even among opioid-tolerant users. Naloxone can be lifesaving in acute intoxications. The substance should be handled with utmost caution, as even inhalation, dermal or mucosal exposure can lead to intoxication [1]. We report a case of confirmed acute carfentanil intoxication in Switzerland in order to contribute to the scarce knowledge of its toxicodynamic properties in humans.
Case report: A 16-year-old male was admitted to the intensive care unit after sudden collapse, reportedly following the intake of an unknown drug via an unknown route. His regular medications were atomoxetine and mirtazapine. The patient was found unconscious (Glasgow Coma Scale 3/15), hypotensive (71/58 mmHg), tachycardic (126 beats per minute), apneic and cyanotic with peripheral oxygen saturation of 70%. Temperature and pupil findings were normal. After intubation, he was airlifted to the emergency department, where, after intravenous naloxone and flumazenil, he rapidly regained consciousness, becoming agitated and hypertensive. Other investigations including focused sonography, electrocardiogram, head computed tomography and laboratory analyses were normal except for mild respiratory acidosis. Urine drug screening immunoassay was negative twice. When a white powder along with a snorting tube were found in the patient's belongings, cocaine intoxication was suspected, but gas chromatography-mass spectrometry (GC-MS) and liquid chromatography combined with high resolution tandem mass spectrometry (LC-MS/MS) both identified the powder as carfentanil. Traces of carfentanil were also detected in blood using LC-MS/MS. According to the caretaking institution, the patient was known for online substance acquisitions for self-experimenting and trafficking. He was discharged the day after the event.
Conclusion: Recreational use of carfentanil caused sudden deep coma, hypotension and respiratory arrest responsive to naloxone. Immediate emergency care including antidote administration is vital but can be hampered by incomplete opioid toxidrome (e.g., because of sympathomimetic co-medication), confusion with other substances (e.g., cocaine), and lack of detection by standard drug immunoassays.

Reference

[1] Drug Enforcement Administration, Carfentanil: A Dangerous New Factor in the US Opioid Crisis, in Officer Safety Alert, U.S. Department of Justice, Editor. 2016.

181. Synthetic cannabinoid receptor agonist (SCRA) detection from pooled urine samples in central London

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Objective: SCRAs are an increasingly common group of new psychoactive substances (NPS) with more than 160 compounds currently being monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). In the UK, SCRAs were classified under the Misuse of Drugs Act 1971 in 2009 and 2013. New SCRAs have emerged to replace those covered by the generic classification; these are now covered under the 2016 UK Psychoactive Substance Act. This study aimed to evaluate the SCRAs detected in pooled urine samples from street urinals over a 3-year period in central London since the second legislative control in 2013.
Methods: Anonymised pooled urine samples were collected from street urinals in central London on the first Saturday each month from July 2013 to June 2016. Samples were analysed using full-scan accurate mass high-resolution liquid chromatography tandem mass-spectrometry. Data are presented as percentage of urinals positive per month for each SCRA; data on the detection of tetrahydrocannabinol (THC) are presented for comparison.
Results: THC was detected consistently in 79% of urinals over the 3-year period. SCRAs were not detected until March 2014 with 5F-AKB-48 present in 8.3% of urinals that month. Subsequently SCRAs were detected intermittently with variability in detection over time: 5F-AKB-48 and STS-135 in April 2014 (both present in 8.3% of urinals that month), AKB-48 in October 2014 (41.7% of urinals), 5F-AKB-48 in April 2015 (16.7% of urinals) and 5F-ADB in May 2016 (16.7% of urinals). However, 5F-PINACA was detected every month between January to June 2016 (16.7–66.7% of urinals per month). The SCRAs detected were all "third" generation: three incorporating an adamantyl group (5F-AKB-48, STS-135, AKB-48) and two indazole-based (5F-ADB, 5F-PINACA).
Conclusion: Analysis of pooled urine samples was effective at detecting SCRAs and has demonstrated the detection of only third generation SCRAs. Over the last 6 months of the study, 5F-PINACA was detected with increasing frequency. Further monitoring is required to triangulate this data with other indicators, and to follow SCRA trends over time which may help to assess the impact of the Psychoactive Substance Act in May 2016.

182. Synthetic cannabinoid receptor agonists identified in patients with severe clinical toxicity in England: a report from the Identification Of Novel psychoActive substances (IONA) study

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Objective: Recreational use of synthetic cannabinoid receptor agonists (SCRAs) has increased in recent years. Challenges in management include the numbers of substances involved, lack of information about their pharmacology and toxicology and the lack of knowledge about exact constituents of SCRA-containing products. The IONA study is identifying the new psychoactive substance (NPS) involved in episodes of severe toxicity in the UK and linking these to the clinical features documented. Here we describe characteristics of patients with analytically confirmed SCRA exposure.
Methods: Adults (≥16 years) presenting to participating English hospitals with severe acute toxicity after suspected new psychoactive substance exposure were recruited with consent or personal or professional representative agreement. Clinical features were recorded using a structured data collection sheet. Blood and urine samples were collected and analysed by liquid chromatography-tandem mass spectrometry.
Results: One or more SCRAs were identified in samples from 42 (32 male, 10 female; median age 33, range 16–61 years) of 91 patients where analytical information was available. These patients presented to hospitals in London, Newcastle, Blackpool, Liverpool and Manchester between March 2015 and September 2016. More than one SCRA was identified in 20, non-SCRA new psychoactive substances in 5 and established drugs of misuse in 12. SCRAs identified in more than 2 patients were 5F-ADB ($n = 14$), MDMB-CHMICA ($n = 8$), 5F-NPB-22 ($n = 8$), 5F-PB-22 ($n = 6$) 5F-ADB-PINACA ($n = 6$), 5F-AKB48 ($n = 5$), ADB-CHMINACA ($n = 3$), STS-135 ($n = 3$) and FUB-PB-22 ($n = 3$). The most common clinical features reported in the 25 patients with lone SCRA toxicity were reduced level of consciousness in 20 (80%), confusion in 17 (68%), acidosis in 14 (56%), tachycardia in 12 (48%), agitation in 11 (44%), paranoid ideation in 7 (28%), convulsions in 6 (24%) and increased creatine kinase, hallucinations or mydriasis, each in 5 (20%); 3 (12%) patients (exposed to (a) MDMB-CHMICA, (b) ADB-CHMINACA and (c) the combination of AB-CHMICA, BB22 and 5F-AKB48) required intubation and ventilation. All 25 survived to hospital discharge with mean length of stay 10 hours (range 3–77 hours). A higher proportion of patients recruited in 2016 than 2015 had samples positive for 5F-ADB (14/23 versus 0/19, $p < .0001$) and 5F-NPB 22 (7/23 versus 1/19, $p < .05$); the reverse was seen for MDMB-CHMICA (1/23 versus 7/19, $p < .01$).
Conclusion: This study has identified the SCRAs most commonly involved in episodes of severe toxicity presenting to participating English hospitals. The data suggest changes in patterns of SCRAs associated with severe toxicity in 2016 compared to 2015.

183. The migration of drugs of abuse from Europe to Denmark: analysis of pooled anonymous urine from urinals at Roskilde Festival 2016

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Objective: The spread of novel psychoactive substances (NPS) has expanded rapidly over the last decade with 570 new substances registered during the last 10 years [1]. New substances are developed to meet the demand for new variations in effect but also to bypass legislation. Traditional treatment guidelines are challenged due to the complexity of the effects of NPS. Thus, information on the emergence of new arrivals is of great value. Our knowledge on the actual range of drugs used and NPS available in Denmark is limited as identification is possible only when consumers become patients in the healthcare system or through police seizures [2]. We carried out a cross-sectional study of collected pooled anonymous urine, sampled from urinals at the biggest music festival during the year, Roskilde Festival, with the aim to detect classic recreational drugs and NPS. The aim of this study was to identify recreational drugs currently used and predict the emergence of NPS by comparing study data with seizure data from the previous year published by EMCDDA [1].
Methods: In total 44 urine samples were collected from three urinals at Roskilde Festival 2016. Two urinals were placed at music stages with late-night concerts and techno/electronic music, and one urinal was placed at a camp site. Samples were prepared using enzymatic hydrolysis and cationic and anionic solid phase extraction, and analysed using ultra-high performance liquid chromatography/high-resolution time-of-flight mass spectrometry (UHPLC-HR-TOFMS). Data was processed against an in-house library of 467 target substances, including legal and illegal drugs and metabolites.
Results: In total 77 drugs, including metabolites, were qualitatively identified in the 44 urine samples. The recreational drugs identified ($n =$ number of samples) were amphetamine ($n = 30$), cocaine ($n = 43$), MDMA ($n = 44$), 11-nor-9-carboxy-Δ9-tetrahydrocannnabinol (THCCOOH) ($n = 19$), and ketamine ($n = 17$).
Conclusion: Several classic recreational drugs were identified in pooled urine samples. While the widespread use of these drugs at the festival was confirmed, the prevalence of NPS was not as comprehensive as expected based on the EMCDDA report [1] and the Danish report on illegal drugs [2]. The limited use of NPS and the substantial dilution due to the pooled anonymous nature of the sampling scheme make it difficult to detect single intakes. Thus, the methods used did not allow predictions on the emergence of NPS in Denmark.

References

[1] European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2016: trends and developments. Luxembourg: Publications Office of the European Union; 2016.
[2] The Danish Health Authority. Illegal drugs in Denmark, 2015 [Danish].

184. The syndrome of inappropriate antidiuretic hormone secretion due to the 3-methyl-N-methylcathinone (3-MMC) intoxication

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Objective: 3-Methyl-N-methylcathinone (3-MMC) has had a significant impact on the illegal recreational drugs market in Slovenia in recent years [1]. The clinical characteristics of 3-MMC-related poisoning include sympathomimetic features, but can also result in profound hyponatremia [2]. Hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a long known adverse effect of many phenethylamines, but it has not been reported with 3-MMC. We present hyponatremia due to SIADH after 3-MMC exposure.
Case report: A 35-year-old man without previous medical history became somnolent and disoriented after snorting 3-MMC. On arrival at the Emergency Department 8 hours after exposure, he was agitated with tympanic temperature 36.5 °C, pulse 80/min, supine blood pressure 115/80 mmHg, and respiratory rate 18/min. Treatment with diazepam was started. The initial laboratory parameters included profound plasma hypoosmolality (236 mOsm/kg) proportional to hyponatremia (106 mmol/L) combined with inappropriately elevated urine osmolality (542 mOsm/kg) and high urine sodium concentration (42 mmol/L) indicating syndrome of inappropriate antidiuretic hormone secretion. A computerised tomography (CT) scan of the brain was found to be unremarkable and the thyroid and adrenal function were normal. A continuous infusion of 1 M sodium chloride was started. The intense psychomotor agitation and disorientation persisted despite several doses of diazepam (cumulative dose 35 mg), until the sodium serum concentration gradually improved to 125 mmol/L at a rate 0.6 mmol/h 36 hours after admission. A toxicological analysis of serum and urine taken 9 hours after exposure by liquid chromatography-tandem mass spectrometry (LC-MS/MS) revealed 3-MMC. No ethanol or other medications were found.
Conclusion: 3-MMC poisoning can result in symptomatic hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion. In patients exposed to 3-MMC presenting with reduced level of consciousness and agitation, which does not improve after treatment with benzodiazepines, a hyponatremic encephalopathy should be suspected.

References

[1] Sande M. Characteristics of the use of 3-MMC and other new psychoactive drugs in Slovenia, and the perceived problems experienced by users. Int J Drug Policy. 2016;27:65–73.
[2] Bäckberg M, Lindeman E, Beck O, et al. Characteristics of analytically confirmed 3-MMC-related intoxications from the Swedish STRIDA project. Clin Toxicol. 2015;53:46–53.

185. Use of technology to study bystander naloxone distribution

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Objective: Heroin overdose deaths continue to rise, prompting implementation of "bystander" naloxone programs in community and emergency department (ED) settings [1–4]. Rigorous data demonstrating the outcomes of naloxone rescue kits dispensed to heroin users are lacking. Advanced technology-based monitoring may help monitor efficacy of these programs [5]. We sought to determine heroin users' acceptance of bystander naloxone kits and attitudes toward use of advanced technology to study the kits' community penetrance and geographic distribution patterns.
Methods: A convenience sample of 11 adults in the ED with a complaint related to heroin use completed a survey regarding naloxone distribution programs and familiarity with advanced technology such as low-energy Bluetooth (BLE) tracking beacons. Participants were asked about duration of heroin use, other substances used (excluding alcohol/tobacco), familiarity with naloxone, and acceptability of dispensing BLE-tagged "smart naloxone kits" to characterize effectiveness of naloxone distribution programs.
Results: Participants were 64% male, median age 31 years, median heroin use duration 5 years. Overall 82% used other substances, including cocaine (64%), benzodiazepines (27%), marijuana (27%); 91% had previously overdosed on heroin and 73% knew someone who needed naloxone whilst 55% had needed to administer naloxone personally. In total 73% had used advanced technology (e.g., Global Positioning System [GPS], Bluetooth, smartphones) within the past month. Naloxone distribution programs were favorably received: 55% perfectly acceptable, 27% acceptable, 18% slightly acceptable. BLE technology was widely accepted and 18% felt they were more likely to carry BLE-tagged kits, while 82% felt BLE would not affect whether they carry the kits.
Conclusion: Our data demonstrate that heroin users are accepting of advanced technology deployment to study the efficacy of naloxone distribution programs. The readiness of individuals with substance use to accept BLE technology is important for the development of advanced monitoring devices to detect and respond to opioid overdose.

References

[1] Boyer EW. Management of opioid analgesic overdose. N Engl J Med. 2012;367:146–155.
[2] Doe-Simkins M, Walley AY, Epstein A, et al. Saved by the nose: bystander-administered intranasal naloxone hydrochloride for opioid overdose. Am J Public Health. 2009;99:788–791.
[3] Beletsky L, Rich JD, Walley AY. Prevention of fatal opioid overdose. JAMA. 2012;308:1863–1864.
[4] Rudd RA, Paulozzi LJ, Bauer MJ, et al. Increases in heroin overdose deaths – 28 States, 2010 to 2012. Morb Mortal Wkly Rep. 2014;63:849–854.
[5] Compton WM, Volkow ND, Throckmorton DC, et al. Expanded access to opioid overdose intervention: research, practice, and policy needs. Ann Intern Med. 2013;158:65–66.

186. Peyote use in the US, 2002–2013

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Objective: Peyote (*Lophophora williamsii*) is a small cactus native to Mexico and Texas that may be ingested or smoked for its psychedelic properties. Native American cultures have historically used peyote for ritualistic and spiritual purposes, while others have used it for its hallucinogenic experience. The objective of this study is to provide a descriptive analysis of peyote users and peyote use in the US as reported in the National Survey on Drug Use and Health (NSDUH).
Methods: Data from the NSDUH survey from 2002 to 2013 were obtained from the Substance Abuse and Mental Health Survey Administration. Data was queried for respondent answers to the question: "Have you ever, even once, used peyote?" Descriptive statistics were used to characterize respondents' age, gender, and race/ethnicity. A Spearman's rank-order correlation was run to assess the relationship between survey year and percent of the population who responded positively to peyote use.
Results: From 2002 to 2013, a total of 10,054 (1.5%) survey participants responded positively to having tried peyote. Peyote use was more common in males (70%) than females (30%). Persons aged 35–49 years (30.5%), 18–25 years (30.2%), and >50 years (20.5%) were most likely to have used peyote. Caucasians (75.3%), Native Americans/Alaskan Native (9%), Hispanics (8.4%) and persons of mixed race (4.5%) accounted for the majority of peyote exposures. However, of the 9627 Native American/Alaskan Natives who participated in the NSDUH survey, 901 (9.4%) of them reported having used peyote, whereas only 1.8% of all Caucasian respondents, 0.8% of Hispanic, and 2.3% of mixed race respondents reported having used peyote. A statistically significant negative monotonic trend existed between survey year and number of respondents who reported using peyote (rs [98] = −0.968, p <.0005). While this may represent a decline in peyote use, interpretation of this trend is limited by the cross-sectional nature of this survey data.
Conclusion: Peyote use is most common in males, Caucasians, and persons aged 35–49 and 18–25 years. However, as expected, a larger portion of the Native American/Alaskan Native population has tried peyote relative to other races. There was a strong negative correlation between peyote use and year, interpretation of which is limited by the cross sectional nature of this study. Other limitations include unknown frequency, quantity, and duration of peyote use, reason for peyote use, and age at the time of peyote use.

187. Cannabis smoke inhalation: an insidious cause of spontaneous pneumothorax in teenagers

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Objective: The association between cannabis smoke inhalation and spontaneous pneumothorax (SP) is showing a surprising increase in young adults [1]. The mechanism of lung damage is still not well known and several factors have been implicating in its etiology including the pattern of cannabis smoking, and the subsequent increased tar and chemical deposition within the alveoli, the development of giant upper zone bullae, and the possible contributing factors of a coexisting history of asthma and significant tobacco smoking history [2]. This link is not still well known in pediatric emergency departments (ED) representing an underestimated scenario for pediatricians. The aim of this study is to describe cases of SP in cannabis smokers during adolescence by drug abuse screening.
Methods: We conducted a retrospective study during the period from January 2013 to September 2016. We selected patients admitted at our tertiary ED with diagnosis of pneumothorax from GIPSE (software for admission at ED). Inclusion criteria were age over 12 years and no underlying conditions.
Results: Overall 28 patients reported pneumothorax and fifteen of them fulfilled the selection criteria. Most patients were male (93.3%). The leading clinical presentation was thorax pain (86.7%), followed by cough (33.3%) and respiratory distress (6.7%). Thorax drainage was needed in 25.7% of cases. No complications were described. During the hospital stay various diagnostic investigations were undertaken, including drug abuse screening in 4 suspicious cases. The screen was positive for cannabis in all 4 cases.
Conclusion: The prevalence of cannabis smoke inhalation in SP was 26% in our population but the phenomenon might be underestimated. The challenge for paediatricians in the ED is the early identification of SP due to an illicit drug inhalation. This requires a high index of suspicion when managing teenagers with spontaneous pneumothorax even when the history is not clearly suggestive of cannabis abuse. We concluded that all teenagers admitted at ED with SP should undergo drug abuse screening.

References

[1] Beshay M, Kaiser H, Niedhart D, et al. Emphysema and secondary pneumothorax in young adults smoking cannabis. Eur J Cardiothorac Surg. 2007;32:834–838.
[2] Fiorelli A, Accardo M, Vicidomini G, et al. Does cannabis smoking predispose to lung bulla formation? Asian Cardiovasc Thorac Ann. 2014;22:65–71.

188. Poisoning severity in intentional self-harm as a function of class of medication ingested

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Objective: Self-poisoning with one or more pharmaceutical agents is the leading cause of intentional self-harm in western, industrialized countries. A wide range of drugs are ingested in intentional self-harm, yet there is limited data on the severity of these events as a function of drug class.
Methods: This was a secondary analysis of cases treated at the bedside by the local toxicology consult service of a large US university medical center that participates in the multisite Toxicology Investigators Consortium Case Registry [1]. The current analyses examined local cases entered into the ToxIC Registry over a 4-plus year period (1 January 2011 to 27 July 2016), with a focus on intentional self-harm patients aged 13 to 65 who ingested one or more pharmaceutical agents ($n = 673$). Data were analyzed using a series of multivariate linear regression analyses. Poisoning Severity Score (PSS) [2] was the outcome in the analyses, presence versus absence (reference group) of a

drug in various classes (e.g., opioid) was the primary predictor, and age and sex were covariates.
Results: The ingestion of three pharmaceutical agents was associated with higher PSS score ($p < .001$): opioid, pulmonary medicine, sedative. These agents were commonly ingested in the intentional self-harm cases: opioid 10%, pulmonary medicine 9% and sedative 27%. The other agents examined (e.g., antidepressant) did not show an association with PSS score after statistical adjustment for age and sex ($p > 0.05$).
Conclusion: Opioids, pulmonary medicines, and sedatives are commonly ingested in intentional self-harm events that lead to medical attention and are associated with more severe poisoning. These results suggest that reducing access to these agents may be an important strategy in lowering the risk for severe poisonings resulting from intentional self-harm.

References

[1] Rhyee SH, Farrugia L, Campleman SL, et al. The Toxicology Investigators Consortium Case Registry – the 2014 Experience. J Med Toxicol. 2015;11:388–409.
[2] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.

189. A characterization of gabapentin abuse and misuse reported to US Poison Centers

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Objective: Anticonvulsant medications are commonly prescribed for several conditions including epilepsy, neuropathic pain, and mood disorders. Among them, gabapentin has been widely prescribed off-label for analgesia with the presumption that it has a very low abuse and misuse potential. Case reports of gabapentin abuse and misuse, however, have been increasing. Therefore, the purpose of this study was to characterize cases of intentional gabapentin abuse and misuse reported to US poison Centers using the National Poison Data System (NPDS).
Methods: All anticonvulsant exposures reported to the National Poison Data System specifically as intentional abuse or misuse between 1 January 2012 and 31 December 2015 were extracted from the National Poison Data System. System generic codes and product codes for gabapentin were used. Only single-agent cases as the major category were analyzed. Descriptive statistics were generated for demographic data, route of administration, clinical effects, treatments, and medical outcomes.
Results: During the 48-month study period, there were 4979 cases involving abuse and misuse of a single anticonvulsant; 1707 of these cases involved gabapentin (34.3%). Specifically for gabapentin, the mean age was 33.9 years (range 13–90). Cases had nearly equal gender representation (females $n = 880$; 51.6%). The most common routes of abuse and misuse were ingestion ($n = 1670$, 97.8%) and inhalational ($n = 34$, 2.0%). The most common clinical effects were drowsiness/lethargy ($n = 565$; 33.1%) and tachycardia ($n = 188$, 11%). Single seizure was reported in 72 patients (4.3%) and multiple seizures in 26 patients (1.5%). The majority of patients were treated and released ($n = 731$; 42.8%) and resulted in 525 minor (30.1%), 235 moderate (13.8%), and 25 major (1.5%) medical outcomes. Of these cases, 136 (8.0%) were admitted to a critical care unit, 17 (1.0%) had respiratory depression, 26 (1.5%) received naloxone, and 17 (1.0%) required intubation. The most common therapeutic intervention was intravenous fluids ($n = 334$; 19.6%). There were no deaths.
Conclusion: The cases were equal between men and women. Most exposures resulted in minor effects not requiring treatment, although a minority of exposures resulted in more severe effects, including seizures and respiratory depression requiring intubation. Gabapentin abuse and misuse is likely to become more frequent, and healthcare providers should be aware of the abuse of anticonvulsant medications as a relatively new and important trend.

190. A complicating factor: hidden salicylate poisoning in a septic patient

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Objective: Chronic salicylate poisoning (CSP) has been reported in the literature as being masked in patients presenting with a septic-like illness [1] and most commonly occurs in children and the elderly [2]. Urinary clearance of salicylate in CSP is known to be lengthy [3] with haemodialysis often being used in severe poisoning [4]. We aim to raise awareness of CSP by reporting a patient diagnosed with sepsis, acute kidney injury and acquired factor VII deficiency, but found to have an elevated serum salicylate concentration.
Case report: The UK National Poisons Information Service (NPIS) was contacted regarding a 47-year-old female who presented to the emergency department, incoherent with an unclear 48-hour history of malaise, confusion and agitation. She was hypoxic, hyperventilating and subsequently transferred to the intensive care unit (ICU) where sepsis was pursued as an initial diagnosis. She was intubated with a metabolic acidosis (venous pH 7.00, bicarbonate 12 mmol/L), raised C-reactive protein (CRP) (380 mg/L) and white cell count (24×10^9/L) and impaired renal function (urea 12 mmol/L, creatinine 130 µmol/L). Chest X-ray revealed left-sided pulmonary consolidation. Prothrombin time was grossly elevated at 200 s (INR 18.0) and acquired factor VII deficiency was considered locally as a potential diagnosis. A serum salicylate concentration sent 8 hours prior to the enquiry was 335 mg/L and at time of contact was 290 mg/L. Her family located empty aspirin packets supporting salicylate overdose. NPIS advice included urine alkalinisation with 8.4% sodium bicarbonate, review of computerised tomography (CT) head scan and aggressive anti-salicylate supportive management. Haemodialysis was considered but recommended only in the instances of pulmonary oedema or fluid overload. Repeat salicylate concentration at follow-up was recorded as 186 mg/L. Sodium bicarbonate was discontinued due to hypokalaemic concerns. She continued to improve on follow-up 5 days later, and was discharged 12 days post-admission.
Conclusion: The frequency of patients presenting with CSP is currently unknown. Serum salicylate concentrations should be considered in patients with an unclear history and features of sepsis, neurological impairment, metabolic acidosis, pulmonary oedema and renal dysfunction.

References

[1] Glisson JK, Vesa TS, Bowling MR. Current management of salicylate-induced pulmonary edema. South Med J. 2011;104:225–232.
[2] Proudfoot AT. Toxicity of salicylates. Am J Med. 1983;75:99–103.
[3] Wrathall G, Sinclair R, Moore A, et al. Three case reports of haemodiafiltration in the treatment of salicylate overdose. Hum Exp Toxicol. 2001;20:491–495.
[4] Fertel BS, Nelson LS, Goldfarb DS. The underutilization of hemodialysis in patients with salicylate poisoning. Kidney Int. 2009;75:1349–1353.

191. A rare but severe case of minoxidil poisoning in a child

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Objective: Minoxidil is a musculotropic vasodilator drug found in over-the-counter solutions for topical treatment for alopecia. Oral bioavailability of minoxidil is high. We present a case report regarding the ingestion of minoxidil by a child.
Case report: A 2-year-old, 12 kg child, grabbed a 60 mL bottle of Unipexil® (minoxidil 2%). The estimated ingested dose was 100 mg/kg. Thirty minutes later the child appeared drowsy and intoxicated. He was hospitalized and because of the development of low blood pressure, (minimum 67/35 mmHg at 1 hour), was given three administration of intravenous fluids (550 mL of sodium chloride at 1, 3 and 6.5 hours). An electrocardiogram (ECG) at 6.5 hours showed ST depression, repolarization disorders and a sinus tachycardia (200 bpm). The child also had metabolic acidosis (pH 7.24, CO_2 16.7 mmol/L bicarbonate 15.6 mmol/L). Blood pressure returned to normal at 27 hours, with a heart rate of 150 bpm. In blood samples taken at 1 hour the blood alcohol concentration was 0.13 g/L and the minoxidil concentration 5.45 mg/L. This case had a finally severity score of mild (PSS2) according to the Poison Severity Score.
Conclusion: Effects of an overdose of minoxidil observed in this child correspond to the expected effects considering the mechanism of action: selective relaxation of smooth muscle of peripheral arteries and increase in renin/angiotensin activity. ECG changes were similar to those reported in the literature. The toxicological assay was performed when blood pressure was lowest and at the peak plasma concentration of minoxidil. Although the duration of drug action is usually very long, this child recovered in 27 hours following appropriate treatment by vascular filling.

192. Acute tenofovir overdose causes benign symptoms: a case series

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Objective: The antiretroviral medication tenofovir is used alone in mono-infected hepatitis B patients or in combination therapy in patients with HIV. Hitherto, only a single case report of acute overdose has been published. That patient developed a reversible increase of the serum creatinine concentration as the only symptom [1]. We present four cases of acute tenofovir overdose.
Case series: Poison centre notes and hospital case records of four cases of acute suicidal tenofovir overdose were studied. The results are presented in Table 1. The poison centre recommended administration of IV fluids, close observation and monitoring of kidney and liver function in all cases. Three patients had overdosed on tablets that also contain other antiretroviral drugs. Upon arrival, one patient had a short period of central nervous system depression which was suspected to be functional. The patients were all discharged within two days after uneventful hospital courses with mild or no symptoms.
Conclusion: Tenofovir is a nucleotide analogue that has a favourable side effect profile compared to other nucleotide analogues. The most common adverse effects observed in clinical trials were gastrointestinal in nature [2]. There have been rare cases of Fanconi syndrome associated with tenofovir treatment [3], but none of the patients above showed signs of kidney impairment. These cases indicate a low toxicity of tenofovir even after acute overdose.

References

[1] Lee M, Eyer F, Felgenhauer N, et al. Overdose of dolutegravir in combination with tenofovir disaproxil fumarate/emtricitabine in suicide attempt in a 21-year old patient. AIDS Res Ther. 2015;12:18.
[2] Margolis AM, Heverling H, Pham PA, et al. A review of the toxicity of HIV medications. J Med Toxicol. 2014;10:26–39.
[3] Mathew G, Knaus SJ. Acquired Fanconi's syndrome associated with tenofovir therapy. J Gen Intern Med. 2016;21:C3–C5.

193. Acute valacyclovir overdose causing renal failure and neurotoxicity

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Objective: The antiviral agent valacyclovir is increasingly used in the treatment of herpesvirus infections. It is a prodrug that is rapidly converted to acyclovir and so it has similar toxic effects to acyclovir. Neurotoxicity and deterioration in renal function have been reported after ingestion of therapeutic doses for a few days administered in error to patients with impaired renal function [1], but reports of acute overdose in previously healthy persons are rare [2]. We present a case of acute valacyclovir overdose causing neuropsychiatric symptoms and renal failure, confirmed by high serum concentrations of acyclovir and its metabolite 9-carboxymethoxymethylguanine (CMMG).
Case report: A 73-year-old previously healthy man without regular medication was prescribed valacyclovir for herpes zoster. The day after prescription he overdosed on approximately 7 g (14 tablets) and subsequently developed diarrhea. The following day he fell and was brought to hospital. On arrival he was clearly confused and unable to follow instructions or express himself. A computerised tomography (CT) scan of the brain was normal. Laboratory results showed signs of acute renal failure (serum creatinine 535 µmol/L). Toxicological tests revealed a serum acyclovir

Table 1. Presentation of four cases of acute tenofovir overdose.

Gender, age	Ingested tablets	Tenofovir	Emitricitabine	Efavirenz	Atazanavir	Symptoms/signs	Treatment/outcome
Female, 28 years	30 Viread®	7.35 g	–	–	–	CNS depression (functional?).	Observation. Discharged after 36 h.
Male, 42 years	60 Atripla®	14.7 g	12 g	36 g	–	Tiredness.	Observation. Discharged after 36 h.
Male, 28 years	60 Truvada®, 30 Reyataz®, + ethanol (38 mmol/L)	14.7 g	12 g	–	9 g	Alcohol related symptoms only. Lactate 2.3 mmol/L.	Observation. Discharged after 18 h.
Male, 15 years	90 Atripla®	22 g	18 g	54 g		Tiredness, headache.	Activated charcoal, observation. Discharged after 18 h.

concentration of 56 µmol/L (reference <7 µmol/L) and a CMMG concentration of 61 µmol/L (reference 2–6 µmol/L). The patient was transferred to the intensive care unit for hemodialysis. Circulation and respiratory were stable but he was unresponsive. There was a pronounced improvement of his mental condition during the 4-hour dialysis. He became more responsive but was still confused and to some extent psychotic. One week after the overdose he was fully recovered and his neurological status was essentially normal. The patient was discharged 15 days after the overdose with good renal function (serum creatinine concentration was 81 µmol/L).

Conclusion: The correlation between symptoms and serum acyclovir concentrations is contradictory, but high concentrations of the metabolite CMMG are strongly associated with neuropsychiatric symptoms. Hemodialysis is effective for elimination of both agents and often indicated because of impaired renal function in some patients, as mentioned above. This case report indicates that an acute valacyclovir overdose may cause neurotoxicity and acute renal failure in a previously healthy person.

References

[1] Asahi T, Tsutsui M, Wakasugi D, et al. Valacyclovir neurotoxicity: clinical experience and review of the literature. Eur J Neurol. 2009;16:457–460.

[2] Roberts DM, Smith MWH, McMullan BJ, et al. Acute kidney injury due to crystalluria following acute valacyclovir overdose. Kidney Int. 2011;79:574.

194. Baclofen self-poisoning: is extrarenal epuration efficient in normorenal patients?

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Objective: Baclofen poisoning causes mainly neurological disorders such as coma, seizures, respiratory depression as well as cardiovascular issues. Nowadays, treatment of baclofen intoxication is symptomatic, with supportive care and mechanical ventilation if required. If the indication of renal replacement therapy for renal insufficiency seemed clear in severe poisoning, the indication for patients with preserved renal function is still debated. This study aimed to define the effectiveness of hemodialysis in the treatment of patients with severe baclofen poisoning without renal dysfunction on a cohort of patients.

Methods: We studied baclofen self-poisoning cases reported to the Angers Poison Control Center (PCC). We identified all cases of oral baclofen poisoning in patients without renal dysfunction, treated with or without hemodialysis. All cases with a known supposed ingested dose and at least one measurement of plasma baclofen were included. All the pharmacokinetic profiles were analysed using the non-parametric adaptive grip approach implemented in a R-package (Pmetrics version 1.5.0) [1]. The analysis was based on a 2-compartment open model. Baclofen half-lives were then compared between patients that did and did not receive renal replacement therapy. The duration of intubation was also reported to determine the clinical effectiveness of hemodialysis between the two groups.

Results: Pharmacokinetic profiles were analyzed from 24 patients, 7 underwent hemodialysis during their stay in intensive care and 18 were not hemodialysed. Average initial baclofen concentrations were 6.5 ± 3.6 mg/L and 2.4 ± 1.9 mg/L, respectively. Elimination half-lives of baclofen in these patients were 3.93 ± 2.45 hours and 4.09 ± 4.02 hours, respectively. The difference was not significant ($p = .763$). Mechanical ventilation was required for 20 patients. Among them, 15 were not hemodialysed and 5 received hemodialysis. The mean duration of intubation was not significantly different between each group (93.9 ± 56.5 and 80 ± 44.6 hours, respectively; $p = .530$).

Conclusion: It seems that renal replacement therapy is not indicated in baclofen overdose because it is of no biological and no clinical benefit. There are also risks and complications associated with renal replacement therapy to consider.

Reference

[1] Neely MN, van Guilder MG, Yamada WM, et al. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012;34:467–476.

195. Cardiovascular findings in acute poisoning with anticonvulsant drugs in children

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Objective: In Romania, anticonvulsant drugs are easily accessible to children, being prescribed to them or their kin both for epilepsy, as well as other neuropsychiatric disorders. Pharmacological effects of these drugs result in effects in organs other than those involved in epilepsy and toxic doses may impair the proper functioning of the cardiovascular system [1]. The aim of this study was to evaluate the cardiovascular findings in acute poisoning with anticonvulsant drugs in children.

Methods: We performed a 2-year prospective study in children admitted in our hospital for acute mono-drug poisoning with anticonvulsant drugs, who developed cardiovascular manifestations at admission or during hospitalization. In order to identify cardiotoxic effects, we performed clinical examination, cardiac monitoring and electrocardiographic recording in all cases. Combined drug poisoning was an exclusion criterion in our study.

Results: We identified 22 cases in children aged 2–17 years of acute mono-drug poisoning with anticonvulsant drugs that developed cardiovascular manifestations. The etiology was represented by carbamazepine (CBZ) in 17 cases, valproic acid (VPA) in 3 cases and oxcarbazepine (OCBZ) in 2 cases. Half of these cases were suicide attempts. The most frequent cardiovascular finding was tachycardia, present in 11 cases of CBZ poisoning, 2 cases of VPA ingestion and both cases of OCBZ ingestion. Bradycardia was rare in our study, and found in only 2 cases of CBZ poisoning. A short period of hypertension was found in 3 cases of CBZ poisoning, while hypotension was seen in 2 cases of CBZ and 1 case of VPA poisoning. In addition to narrow complex tachycardia and bradycardia, the electrocardiographic record identified other abnormalities: premature atrial beats (CBZ $n = 3$, OCBZ $n = 1$), premature ventricular beats (CBZ $n = 1$), sinusal pauses and sino-atrial block (CBZ $n = 1$), first degree atrioventricular block (CBZ $n = 3$), intraventricular conduction defects (CBZ $n = 9$, OCBZ $n = 1$), prolonged QTc interval (CBZ $n = 3$, OCBZ $n = 1$ case, VPL $n = 3$) and T wave inversion (VPL $n = 1$, OCBZ $n = 1$). Sodium bicarbonate was used as an antidote in 10 cases. The mean hospitalization duration was 2.86 ± 0.91 days. None of these cases had a fatal outcome.

Conclusion: In children, accidental or intentional ingestion of anticonvulsant drugs may affect the cardiovascular system in many ways, as shown in our study, with sinus tachycardia being the most frequent abnormality, followed by intraventricular conduction defects. In order to identify toxic effects, cardiac monitoring is essential in these cases.

Reference

[1] Shah RR. Cardiac effects of antiepileptic drugs. In: Panayiotopoulos CP, editor. Atlas of Epilepsies. London: Springer-Verlag; 2010, p. 1479–1486.

196. Clonidine exposures in children under 6 years: cases reported to Australia's largest poisons information centre

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Objective: Clonidine was developed in the 1960s as an antihypertensive. It is seldom used for this indication now, but is becoming increasingly popular as a treatment for children with behavioural disorders (e.g., attention deficit hyperactivity disorder [ADHD], autism). In Australia, the use of clonidine in children under 18 years is off-label. The Australian Medicines Handbook Children's Dosing Companion provides clonidine dosing advice for children 6–18 years, but use for those under 6 is not recommended. This study aims to describe clonidine exposures in children under 6 years of age.
Methods: A retrospective search of the New South Wales Poisons Information Centre (NSWPIC) database, January 2004 to June 2016. The NSWPIC is Australia's largest PIC, taking approximately 100,000 calls annually. Call records were searched for exposures to clonidine in children 0–5 years.
Results: There were 675 exposures to clonidine in children 0–5 years. Exposures have increased from 50 per year (2004–2006) to 67 per year (2013–2015); 80.4% ($n = 543$) were accidental exposures, 17.9% ($n = 121$) were therapeutic errors, 1.5% (=10) were intentional and one case was of undetermined intent. Most children were male ($n = 414$, 61.3%; females $n = 218$, 32.3%; gender not recorded in the remainder of cases. In total 26.7% of children (180) were documented to have had clonidine prescribed for them, 11.4% (77) ingested a sibling's medication and the source was not documented in the remainder. Median (IQR) dose taken and dose/kg was 150 µg (100–300 µg) and 8.3 µg/kg (5.3–15.2 µg/kg), respectively. At least 77.6% of children ($n = 524$) were hospitalised, with 6.5% ($n = 44$) of cases referred to consultant medical toxicologists. In 2015, clonidine was the most common substance requiring consultant referral for children under 6 at NSWPIC. Symptoms reported included drowsiness/central nervous system depression 43.6% ($n = 294$), bradycardia 11.3% ($n = 76$), hypotension 5.6% ($n = 38$), agitation/irritability 3.0% ($n = 20$), pallor 2.5% ($n = 17$), ataxia 1.9% ($n = 13$) and bradypnoea 1.6% ($n = 11$).
Conclusion: This study reveals a concerning increase in clonidine exposures in Australian children. This is likely to continue to rise as prescriptions increase. Clonidine exposures have a high hospital referral rate and high morbidity reflecting its narrow therapeutic index (therapeutic dosing for children 6 years and older is 2–4 µg/kg, the NSWPIC hospital referral threshold is 5 µg/kg for night-time exposures). Prescribers and parents should be aware that therapeutic errors with clonidine are potentially dangerous and to take precautions to prevent children accessing clonidine. Given the paucity of information regarding the efficacy and safety of clonidine use in this age group, therapeutic alternatives should be considered.

197. Delayed Ogilvie Syndrome induced by acute clozapine overdose

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Objective: Gastrointestinal hypomotility associated with clozapine may cause paralytic ileus, faecal impaction, aspiration of vomit, necrotizing colitis and/or intestinal perforation; fatalities provoked by these, often under-recognized, complications have been reported [1,2]. We report a patient with Ogilvie Syndrome and gastrointestinal bleeding as complications after reversal of typical clinical signs of acute clozapine overdose.
Case report: A previously healthy 31-year-old man was found unconscious with Glasgow Coma Score 6, non-reactive miotic pupils, hypersalivation and heart rate of 115 bpm. Toxicological analysis of the blood (high-performance liquid chromatography with photodiode array detector) identified the following drugs: clozapine (0.03 mg/L), N-desmethylclozapine (2.39 mg/L), diazepam (0.17 mg/L), haloperidol (0.04 mg/L) and biperiden (0.002 mg/L). The patient was referred to the intensive care unit of the toxicology ward for treatment. Clinical signs registered on admission, except for sinus tachycardia, were completely resolved by day 3 and the patient began to eat and had regular bowel movements. At day 7, the patient complained of abdominal fullness and nausea, followed by vomiting copious quantities of tea-colored fluid. Physical examination showed distended abdomen and decreased bowel sounds. High leucocyte count (10.6×10^9/L, 24.0×10^9/L, 20.0×10^9/L), with gradually falling concentrations of hemoglobin (100, 93, 80 g/L) and hematocrit (0.31, 0.27, 0.24 l/L) were detected. Non-obstructive dilatation of the stomach and intestine was confirmed on computed tomography (CT) scan. Multi-slice CT angiography of abdomen excluded occlusion of the mesenteric vessels. Conservative management with nasogastric suction, the usage of laxatives and neostigmine injections as well as colonic irrigation was performed with a good clinical response.
Conclusion: Clinicians should be aware of the potential of atypical antipsychotics to cause ileus, particularly in combination with other drugs with antimuscarinic properties, and be ready to rapidly detect and treat intestinal atony thus preventing life-threatening complications. Serum clozapine concentrations may not equate to clinical toxicity and the drug-näive patient may require more careful observation for complications in clozapine toxicity settings.

References

[1] Baptista T, Carrizo E, Fernandez E, et al. Colonic transit diagnostic test shows significant gastrointestinal hypomotility in clozapine-treated patients in comparison with subjects treated with other antipsychotics. Schizophr Res. 2015;166:207–211.
[2] Sarac H, Henigsberg N, Bagaric-Krakan L. Clozapine-induced paralytic ileus. Psychiatr Danub. 2015;2:283–284.

198. Dihydropyridine calcium channel blocker toxicity and the renin angiotensin axis

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Objective: Dihydropyridines have been perceived as having safer toxicology profiles than non-dihydropyridine calcium channel blockers (CCBs) such as verapamil and diltiazem. However, amlodipine was reported as a major cause of mortality amongst cardiovascular agents in poisoning [1]. We investigate the effects of dihydropyridine CCBs in overdose, alone or in combination with renin-angiotensin axis antagonists, that is, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB).
Methods: A prospective observational study of patients reported to the New South Wales, Queensland Poisons Information Centre and three toxicology units from September 2013 to September 2016. Patients with an overdose of dihydropyridine CCBs were recruited, excluding patients with co-ingestion of alpha or beta-blockers. The primary outcome was the proportion with hypotension; secondary outcomes were requirement for inotropic support and mortality.
Results: There were 30 patients. Median age was 55 years (range 28–75); 14 were males. Twenty-seven patients took amlodipine and 3 took lercanidipine with or without angiotensin antagonists (Table 1). Comparing the two groups, the median initial heart rate was similar but the systolic blood pressure was lower in the group that also co-ingested ACEI or ARB. Overall, inotropes were required in 11 patients (37%), all had ingested amlodipine and ACEI or ARB combinations. The 6 patients who took amlodipine or lercanidipine alone did not develop significant hypotension. The median number of vasopressor or inotropic agents used were 3 (range 1–4), including metaraminol, noradrenaline, adrenaline, vasopressin, high dose insulin dextrose therapy. There were no deaths.
Conclusion: On their own dihydropyridines, ACEI and ARBs are all usually benign in overdose. Amlodipine and lercanidipine commonly cause profound hypotension, when co-ingested with agents that impair homeostatic regulation through the renin angiotensin system.

Reference

[1] Mowry JB, Spyker DA, Brooks DE, et al. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol. 2015;53:962–1147.

199. Does serum procalcitonin predict the onset of toxic acute hepatitis in acetaminophen poisoning?

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Objective: Procalcitonin (PCT) is a pro-hormone mainly produced by thyroid C cells and routinely used as a diagnostic biomarker of bacterial infection. PCT synthesis has never been described in the liver, but its elevation has been suggested to occur in severe hepatocyte necrosis with inflammation [1]. To the best of our knowledge, no study has investigated the possible predictive value of PCT in acetaminophen poisoning. Our objectives were to report the distribution of serum PCT values in acetaminophen-poisoned patients according to the onset and severity of their toxic liver injury in order to assess any possible predictive value for this biomarker.
Methods: We conducted a retrospective single centre observational study including all acetaminophen-poisoned patients (either accidental or voluntary) admitted to the intensive care unit (ICU) from 2013 to 2016. Patients were treated with the 3-bag N-acetylcysteine protocol according to the international recommendations based on the interpretation (when possible) of the plasma acetaminophen concentration on the Rumack–Matthew nomogram (line to treat the patient starting at 150 mg/L at the 4th hour). Serum PCT was measured using an automated method (Elecsys® and Cobase® analyzers; range: 0.02–100 ng/mL) and plasma acetaminophen concentrations were determined using spectrophotometry. Comparisons were performed using chi-squared and Mann–Whitney tests. Receiver operating characteristic (ROC) curve and parameters of the predictive values of serum PCT were calculated with their 95%-confidence intervals.
Results: Seventy patients (50F/20M; age 34 years [21; 53] median [25; 75 percentiles]; poly-intoxications: 83%) were included in the study. The presumed ingested acetaminophen dose was 15.5 g [8.0; 29.0]. The delay between acetaminophen ingestion and N-acetylcysteine infusion was 4.5 hours [2.9; 9.0]. Serum PCT was markedly increased above the 1 µg/L threshold in the patients who already presented or further developed significant liver cytolysis defined by serum alanine aminotransferase (ALAT) $>$ 100 UI/L (twice normal) despite treatment with N-acetylcysteine and independently of the onset of any bacterial infection, with a specificity of 97.9% (88.9–89.6), sensitivity of 69.6% (49.1–84.4), positive predictive value of 94.1% (88.6–99.6) and negative predictive value of 86.8% (78.9–94.7).

Table 1. Demographics and clinical data on patients with overdose of dihydropyridine alone versus dihydropyridine with vasodilator agents.

Parameter	Amlodipine or lercanidipine only (n = 6)	Dihydropyridine with vasodilator agents (n = 24)
Median age (years)	61 (range 36–66)	55 (range 40–75)
Male (%)	3 (50%)	11 (46%)
Fixed dose combination product: dihydropyridine and ACEI or ARB	0	13 (54%)
Median initial heart rate per min	89 (range 75–120)	87 (range 57–120)
Median initial systolic blood pressure (mmHg)	120 (range 95–130)	90 (range 60–125)
Inotrope requirement (%)	0	11 (46%)
Fatality	0	0

Conclusion: Serum PCT measurement in acetaminophen-poisoned patients admitted to the ICU is helpful to identify patients who present significant acetaminophen-related liver toxicity already established or in progress on admission despite the administration of N-acetylcysteine according to international recommendations.

Reference

[1] Rule JA, Hynan LS, Attar N, et al. Procalcitonin identifies cell injury, not bacterial infection, in acute liver failure. PLoS One. 2015;10:e0138566.

200. Extended-release (XR) quetiapine overdose is associated with delayed development of peak toxicity and prolonged recovery when compared to immediate-release (IR) quetiapine overdose: a retrospective cohort study

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Objective: IR-quetiapine overdose is well characterised and this formulation has been available in Australia since 2008. There are no studies comparing toxicity after XR and IR quetiapine overdose. This study compares time course and severity of toxicity of XR and IR quetiapine overdose.
Methods: A retrospective analysis of toxicology consultations from July 2013 to April 2016 was performed. Information extracted included demographics, ingestion, type (IR, XR, mixed formulation, dose, tablet count, time to presentation, co-ingestants), lowest Glasgow Coma Scale (GCS), time to lowest GCS, fastest pulse, lowest systolic BP, time to recovery from sedation, frequency and intubation duration.
Results: There were 256 presentations in 210 patients comprising females 67% ($n = 141$), median age 31 years (IQR 23–43). Median quetiapine dose overall was 2 g (IQR 1–5). Sedating co-ingestants were ingested in 61%. Comparison of IR ($n = 43$) and XR ($n = 23$) overdoses without sedating co-ingestants revealed no significant difference in age or gender. Median ingested dose was greater for the XR formulation (5.7 g versus 1.75 g, $p = .004$), as was median tablet strength ingested (XR 200 mg versus IR 100 mg, $p < .001$). However, median ingested tablet count was similar (30). Median lowest GCS (XR 12.5 versus IR 13) and peak pulse (XR 122 bpm versus IR 118 bpm) were similar. Median time to lowest GCS was longer for XR (7 hours [IQR 4.9–11] versus 3.8 hours [IQR 2.4–5.7], $p < .001$). Median time to peak pulse was greater for XR (9 hours [IQR 3–12] versus 2.5 hours [IQR 1.5–5], $p = .01$). Median time to recovery from sedation was longer for XR (20 hours [IQR 12–39] versus 12 hours [IQR 5.5–22], $p < .05$). Median intubation duration was longer for XR, (47 hours versus 17 hours, $p = .04$). Inclusion of patients taking sedating co-ingestants resulted in loss of significant differences in time to peak sedation, recovery from sedation and the duration of intubation between groups.
Conclusion: XR quetiapine overdose without sedating co-ingestants was associated with a doubling of the time to peak sedation and pulse, and prolonged recovery from sedation. The effect was lost when patients also ingested other sedating drugs. Despite larger ingested doses for XR, the degree of sedation and tachycardia was similar to IR quetiapine overdose. Delayed absorption and reduced peak serum concentrations following XR ingestions may explain this. Prospective comparison of serum quetiapine concentrations following XR and IR overdose would help correlate toxicokinetics and clinical effects of the formulations. Finally, the absence of sedation or tachycardia 12 hours post-overdose of XR quetiapine seems a reasonable observation timeframe to rule out significant poisoning.

201. Favorable acute toxicity profile of morclofone in children

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Objective: Morclofone, a centrally acting non-narcotic antitussive, has been used in the treatment of non-productive cough in some European countries since the 1980s, mainly in children as a sucrose-containing syrup. The usual therapeutic single dose is 50 mg morclofone for children <3 years, and 150 mg for older children. Morclofone appears to have a favorable side effect profile [1], but modern approval studies are lacking. The aim of this study was to determine the acute toxicity profile of morclofone in overdose.
Methods: A retrospective review of acute morclofone monointoxications in children (<16 years), reported to our poisons centre between January 1997 and June 2016 with evidence of exposure and high causality. The severity of observed symptoms was graded according to the Poisoning Severity Score.
Results: Overall 29 patients, 10 (34.5%) females and 19 (65.5%) males with a mean age of 3 years (1.6–6 years) were included. Eight children remained asymptomatic, with minor symptoms in 21 cases. There were no moderate or severe cases, and no fatalities. In 21 cases the ingested dose was known, and ranged from 31 to 171 mg/kg (mean 64 mg/kg), corresponding to a 4- to 36-fold overdose of the therapeutic single dose (mean 9-fold). No symptoms occurred after ingestion of 31–82 mg/kg (mean 59 mg/kg), corresponding to a 6- to 30-fold overdose ($n = 6/21$), and mild symptoms were observed after ingestion of 33–171 mg/kg (mean 67 mg/kg), corresponding to a 4- to 36-fold overdose ($n = 15/21$). Observed signs were vomiting ($n = 15$), nausea ($n = 4$), abdominal pain ($n = 4$), drowsiness ($n = 4$), somnolence ($n = 2$), ataxia ($n = 1$), and tachycardia ($n = 1$). All symptoms were of short duration and resolved spontaneously. In 11 of the 29 cases the latency between ingestion and onset of symptoms was reported to be 30 to 120 minutes (mean 60 minutes), which is in accordance with the Tmax of 60–120 minutes. Gastrointestinal decontamination with a single dose of activated charcoal was performed in 9 patients; 2 remained asymptomatic, and 7 developed mild symptoms.
Conclusion: Morclofone has a favorable acute toxicity profile and significant overdoses up to 171 mg/kg were tolerated by children with only mild effects, which were predominantly gastrointestinal and neurological, consistent with the described adverse effects of this drug. Therefore, observation at home without gastrointestinal decontamination seems reasonable after ingestion of less than 171 mg/kg.

Reference

[1] Schenker H. [Efficacy of morclofon, a new synthetic antitussive agent, in geriatric patients. Results of a double-blind study]. Ther Umsch. 1983;40:358–361. German.

202. Fomepizole, dialysis and an increased dose of N-acetylcysteine in a case of massive paracetamol ingestion

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Objective: Large paracetamol overdose may cause early neurological symptoms and lactic acidosis through impairment of cellular respiration. A heavy body burden of paracetamol also increases the risk of severe hepatotoxicity which can occur despite timely treatment with standard doses of N-acetylcysteine (NAC). Non-standard treatment options in such cases include enhanced removal of paracetamol through extracorporeal elimination, increasing hepatic antioxidant capacity by increasing the NAC dosage and decreasing the formation of the toxic metabolite through administration of fomepizole, a potent inhibitor of CYP2E1. We present a case where all these treatment modalities were used.
Case report: A 21-year-old man ingested almost 100 g of paracetamol 2.5 hours before admission. Prior history included weight loss surgery 17 months previously, a possible risk factor for hepatotoxicity in paracetamol poisoning. On presentation he was awake but disoriented. Activated charcoal (50 g) was given, and treatment with NAC was started at 4 hours when the 2.5 hour paracetamol had been determined at 687 µg/mL (4547 µmol/L). Laboratory findings included lactate 11 mmol/L and glucose 21 mmol/L. The Swedish Poisons Information Centre was consulted and as the risk of complications was considered significant, treatment with fomepizole 15 mg/kg (from 5.5 hours) and dialysis was recommended. The second NAC dose was doubled (25 mg/kg/h) at 7 hours with initiation of continuous venovenous hemodiafiltration (CVVHDF) (effluent flow 48 mL/kg/h) to compensate for extracorporeal elimination of NAC. The third NAC dose was maintained on this level until 16 hours when it was lowered (12.5 mg/kg/h). Paracetamol concentrations (µg/mL) were 475 (6 hours); 101 (12.5 hours); 22 (18.5 hours); 7 (24.5 hours). Lactic acidosis resolved by 8 hours. Mental status was normal at 14 hours when sedation was reduced. NAC and CVVHDF were terminated at 40 hours. The ALT and INR were minimally elevated to 70 U/L (1.16 µkat/L) and 1.4, respectively at 8.5 hours, and were normal at 60 hours. Kidney function was unaffected.
Conclusion: This patient with massive paracetamol ingestion, altered mental status and early lactic acidosis made a rapid recovery and developed no liver damage. Non-standard therapy was used because of a perceived risk of inadequacy of standard therapy. Only the initial paracetamol concentration was available at the time of decision-making. NAC-dosing was increased and fomepizole and CVVHDF were administered. None of these treatments are of proven benefit and it is impossible to say if any of them contributed to the favourable outcome in this case.

203. High in-hospital death rate from calcium channel blocker and beta-blocker poisonings

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Objective: Mortality in poisoned patients who reach the hospital setting before irreversible organ damage has occurred is typically very low. Calcium channel blockers (CCBs) and beta-blockers (BBs) are among the remaining widely used substances feared for their ability to cause significant and intractable toxicity despite advanced medical care. The aim of this study was to quantify the in-hospital risk of death in patients with CCB and/or BB poisoning associated with significant hemodynamic symptoms that come to the attention of the Swedish Poison Center (PC).
Methods: Notes from consultations made to the PC are stored in a database and this was searched for cases with CCBs or BBs as the main intoxicant during the period January 2010 to August 2016. The search was filtered to include only calls made from hospitals and cases where a resident poison center clinical toxicologist was consulted by the pharmacist receiving the call. Pediatric ingestions and medical errors were excluded. The search result was examined to identify cases of serious hemodynamic toxicity and death. Cases where the PC records listed use of interventions for hemodynamic instability not limited to the administration of fluids and single doses of atropine (i.e., vasopressors or inotropes were used) were defined as serious. Cases where the PC records unambiguously stated that the patient had been pronounced dead were considered deaths.
Results: In total 350 cases of CCB and/or BB poisonings were identified using the defined search criteria. Of these 61 patients developed serious symptoms. Two deaths where the victims were in irreversible circulatory arrest on hospital arrival were excluded. The hospital mortality rate in the remaining 59 was 12% ($n = 7$). In a further 15% ($n = 9$) circulatory arrest occurred at some point during the course of treatment (cardiopulmonary resuscitation was administered in 7 patients, extracorporeal membrane oxygenation in 2 patients).
Conclusion: Patients with CCB and/or BB poisoning who develop symptoms that necessitate treatment with vasopressors or inotropes suffer a high risk of dying in hospital. Although selection bias may have artificially inflated the death rate in our material it is worth noting that several seemingly terminal cases in the data could not be included as deaths due to incompleteness and lack of follow up in the PC records. Our findings highlight the importance of continually re-examining treatment strategies for this at-risk patient population in order to optimize management.

204. Methotrexate therapeutic errors in non-oncology settings

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Objective: Methotrexate (MTX) originated as antineoplastic drug, but it is now also used in autoimmune/rheumatic diseases for its anti-inflammatory properties. Adverse reactions are described after therapeutic doses, especially in patients with risk factors (e.g., renal impairment, drug-drug interactions, predisposing genetic polymorphisms). Moreover, MTX use in outpatients may also increase the possibility of therapeutic error. High risk of toxicity is related to overdose. We evaluate the characteristics of cases of MTX overdose due to therapeutic error in non-oncology patients.
Methods: All cases of MTX overdose due to therapeutic error in non-oncology patients referred to our Poison Control Centre were retrospectively evaluated in an 8-year (June 2007 to June 2016) retrospective study. Data about patients, intoxication circumstances and clinical manifestations were analysed.
Results: Overall 35 cases were included (50% male), aged between 17 and 86 years. In 5 cases patients were nursing mothers (not in treatment) to which MTX was wrongly sold by the

pharmacist instead of methylergometrine. The remaining 30 cases involved patients who had been prescribed MTX for the first time for an autoimmune/rheumatic disease. In 27 cases the wrongly dose was prescribed, in 2 patients MTX was administrated in an incorrect way, and in 1 case was administered despite the presence of severe renal failure. In all the 28 patients with incorrect dosing, the weekly prescribed dose (range 2.5–12.5 mg/week) was taken daily (17.5–87.5 mg/week); this mistake was recognized after a period ranging from 2 to 21 days. Clinical manifestations were characterized by mucositis (14/35), myelosuppression (12/35), asthenia (6/35), acute renal failure (5/35), diarrhea (4/35), vomiting (4/35), headache (2/35) and hepatitis (2/35). All patients were treated with calcium levofolinate and forced alkaline diuresis. N-acetylcysteine was administered in 2 patients with hepatitis, and growth-factors in one. MTX plasma concentrations were available for 6 patients, and were within the therapeutic range. No lethal cases were registered. In the 5 nursing mothers breastfeeding was stopped for 4 days.
Conclusion: Medication errors are a cause of MTX toxicity. Most dosing errors are due to misunderstanding of medical prescriptions. Clear indications, possibly with electronic systems and clear explanation to patients are necessary in order to avoid these errors and consequent toxicity. MTX serum quantitative determination is useful during therapy and to administer the correct dose of antidote in acute overdose, but is not a good predictor of outcome in chronic overdose, due to the pharmacokinetic characteristics of the drug.

205. Nearly all cases of clioquinol intoxication result from medication errors

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Objective: The Dutch Poisons Information Center (DPIC) receives around 16,000 enquiries per year about human drug overdose. In 9% of cases overdose results from a medication error, but for some drugs this percentage is much higher. Clioquinol is an antiprotozoal drug which can cause serious neurotoxicity. It is orally administered with a pipette or syringe as a 100 mg/mL suspension. Our objective was to analyse the incidence and cause of medication errors with clioquinol, with the aim of preventing overdosage in the future.
Methods: Enquiries to the DPIC from 2011 to 2015 involving human exposure to clioquinol were selected from the database. Corresponding telephone calls were replayed, and data on patient characteristics, exposure circumstances, and symptoms were analysed.
Results: The DPIC received 51 enquiries about oral exposure to clioquinol (all mono-intoxications), involving 53 patients. For 50 patients (94%) overdosage was the result of a medication error. Most of these patients were 0–4 years old ($n = 25$); others were 5–12 years ($n = 17$) or adults ($n = 8$). Medication errors were caused by caretakers ($n = 32$), patients ($n = 7$), physicians ($n = 6$), pharmacists ($n = 4$), and once by a physician or pharmacist. Medication errors by caretakers and patients occurred during administration of clioquinol, when a tenfold dosing error was made in 18 out of 32 and 2 out of 7 cases, respectively. In the other cases overdosage was less than tenfold. Medication errors by physicians and pharmacists were the result of errors in prescription or on the label. In 4 out of 6 and 3 out of 4 cases a tenfold error occurred. In some cases medication errors resulted in a single overdose, while in others there was administration of multiple overdoses over several days. Seventeen patients had symptoms at the time the DPIC was contacted. Of these, 15 patients developed gastrointestinal effects, one showed skin rash and two developed fever. Seven patients developed neurotoxicity (e.g., dizziness, dysarthria). Of these, one child developed eye pain and photophobia, while two had ataxia/unstable gait.
Conclusion: Most cases of clioquinol overdose occur due to a medication error, which can result in neurotoxicity. Careful monitoring by pharmacists may prevent medication errors, by correcting and preventing errors in prescription and on the label. In addition, pharmacists can instruct the patient or caretaker on correct administration of clioquinol, and provide them with the smallest possible pipette or syringe. Marking the correct volume on the pipette or syringe may also help to prevent future medication errors.

206. Nicotinic acid overdose mimicking sepsis

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Objective: Nicotinic acid is purported to be useful as an aid to evade urine drug testing for illicit drugs, particularly marijuana metabolites. We describe a young male with a sepsis-like presentation following an overdose of nicotinic acid for the purpose of drug test evasion.
Case report: A healthy 21-year-old male presented to the Emergency Department with abdominal pain, nausea, vomiting, headache, photophobia and myalgias. He reported the ingestion of a large number of 500 mg nicotinic acid tablets over a 10 hour period. Vital signs were: blood pressure 112/47 mm/Hg, heart rate 114 beats/minute, respiratory rate 18 breaths/minute and temperature 36.4 °C. Physical examination was unremarkable. Laboratory evaluation was significant for an anion gap of 32, creatinine 132 µmol/L, lactic acid 16.2 mmol/L, serum glucose 3.4 mmol/L, AST 43 IU/L (normal 15–37), prothrombin time of 16.2 seconds and white blood cell count 39,400/µL. Blood cultures and spinal fluid were collected and the patient was started on broad spectrum antibiotics. The patient's symptoms improved over the next 16 hours with resolution of acidosis, creatinine 80 µmol/L and AST 26 IU/L. Prothrombin time increased to 21.9 seconds. Preliminary results of spinal fluid were normal and antibiotics were discontinued. The patient left on hospital day 1 and was lost to follow up. Blood and spinal fluid cultures remained negative.
Conclusion: This is the fourth reported case of high anion gap acidosis following nicotinic acid overdose [1,2]. Hypoglycemia, transaminitis and a prolonged prothrombin time were found in these other cases as well. Hypoglycemia is thought to occur due to the inhibition of lipolysis accompanied by fasting and vomiting. The pathogenesis of the metabolic acidosis, prothrombin time prolongation and profound leukocytosis is less well understood. The use of nicotinic acid to evade drug testing is common, despite its ineffectiveness. Rarely, severe toxicity occurs, including a high anion gap metabolic acidosis, profound leukocytosis and hypoglycemia. In a drug abusing population at risk for infectious diseases careful evaluation for an infectious etiology is indicated. Toxicologists should be aware of this dramatic complication of nicotinic acid overuse and abuse.

References

[1] Mittal Manoj K, Florin T, Perrone J, et al. Toxicity from the use of niacin to beat urine drug screening. Ann Emerg Med. 2007;50:587–590.
[2] Arcinegas-Rodriguez S, Gaspers MG, Lowe MC. Metabolic acidosis, hypoglycemia, and severe myalgias: an attempt to mask urine drug screen results. Ped Emerg Care. 2011;27:315–317.

207. Parenteral iron overdose: the experience of the UK National Poisons Information Service

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Objective: This study was performed to characterise the patterns of toxicity associated with overdose of parenteral pharmaceutical iron salt preparations.
Methods: The National Poisons Information Service (NPIS) national database (UKPID) was interrogated for enquiries involving parenteral administration of any type of pharmaceutical iron salt for the period 1 January 2009 to 1 September 2016.
Results: Of 4501 enquiries related to iron, 32 (0.71%) concerned parenteral exposure to a pharmaceutical iron preparation (involving 20 separate cases). All cases occurred in a healthcare setting, with the most common circumstance being therapeutic error ($n = 15$, 75%). Other circumstances included concern regarding serum iron concentrations ($n = 3$, 15%), 1 adverse drug reaction and a single extravasation error. Of the therapeutic errors, 8 cases concerned a single acute overdose, 5 cases where doses were administered too frequently and 2 formulation errors. Of the 20 cases, 12 (60%) had reported co-morbidities; as well as anaemia ($n = 6$) these included chronic kidney disease ($n = 5$), cardiac failure, liver failure, sepsis and Von Willebrand disease. At the time of the enquiry 14 patients (70%) were asymptomatic. Abnormal skin pigmentation was noted in two instances. Otherwise, no other clinical effect reported appeared more than once, with 8 of 11 effects observed occurring in a single patient. The maximum Poison Severity Score (PSS) [1] was available for 17 cases and was recorded as 0 (no effects) in 12 (70.5%), 1 (mild) in 2 cases (17.7%) and 2 (moderate) in 2 cases (11.7%). One patient had a maximum PSS of 4 (fatal), but there was substantial pre-existing co-morbidity (cardiac and renal failure and sepsis). Serum iron concentrations were reported for 7 cases (9 values in total). These ranged from 37.2 to 254.8 µmol/L (mean 151.32 µmol/L) and in seven cases the iron concentration was >90 µmol/L. Desferrioxamine was administered in two cases. Other than the single fatality described above, no other adverse outcomes were reported.
Conclusion: Parenteral iron overdose is rarely reported to the UK NPIS. From the limited information available, overdose is nearly always iatrogenic and patients often remain asymptomatic despite underlying co-morbidities and serum iron concentrations which would be associated with toxicity following oral iron overdose. However, significantly more case experience would be required to assess fully the risks from parenteral iron overdose.

Reference

[1] Persson H, Sjöberg G, Haines J, et al. Poisoning Severity Score: Grading of acute poisoning. Clin Toxicol. 1998;36:205–213.

208. Poisonings with modified or prolonged release paracetamol tablets in Denmark

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Objective: Overdosing on modified or prolonged release (MPR) paracetamol (PCM) tablets results in delayed and prolonged absorption of PCM [1]. Consequently patients may mistakenly be withheld treatment with N-acetylcysteine (NAC) due to plasma PCM concentrations below the treatment line on the risk nomogram. The risk nomogram is not used in Denmark; all patients admitted with a suspected PCM overdose are treated with NAC regardless of the initial plasma PCM concentration, and therefore the issue of poisoning with MPR-PCM may not be clinically relevant in Denmark, even though the sales of e.g., Panodil® 665 mg (P665) has doubled from 2010 to 2014 (5 to 11 million defined daily doses [DDD]). The purpose of the present study was to evaluate all enquiries to the Danish Poison Information Centre (DPIC) involving MPR-PCM.
Methods: All MPR-PCM enquiries from 2006 to August 2016 were analysed and the following data were extracted: type and dose of toxic agent, age and gender of the patient, cause of intake and the risk assessment score.
Results: Overall there were 113 MPR-PCM enquiries (mainly P665 with 100 enquiries). After 2012 the number of P665 enquiries increased markedly from 15 in 2013 to 31 in 2015. Compared to the total number of enquiries to the DPIC with PCM, the fraction of P665 enquiries increased from 1.3% in 2013 to 2.4% in 2015. Most patients were women (68%). The mean age was 45 years (range 2–97 years), and 48 of the enquiries came from physicians treating the patients. The mean P665 intake was 12 g (range 0.665–133 g). In 56 of the cases, NAC was recommended, and in 37 cases activated charcoal was recommended. The cause of intake was suicide attempts in 37 cases and medication errors in 32 cases (less severe cases). Using a hybrid of PSS (an untreated risk assessment score), 58 of the cases were categorised in the two most severe classes, and 37 in the two classes with less severe or no risk of poisoning.
Conclusion: MPR-PCM poisonings have increased within the last 4–5 years. In half of the patients, NAC was recommended, corresponding to the number of patients classified as being severely or moderately severely poisoned. The defensive Danish NAC guideline may ensure that patients poisoned with MPR-PCM are being treated with NAC.

Reference

[1] Graudins A, Chiew A, Chan B. Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol. Intern Med J. 2010;40:72–76.

209. Pregabalin abuse in Munich: an increasing problem

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Objective: Pregabalin is used in many countries for the treatment of neuropathic pain, epilepsy, anxiety disorder and fibromyalgia. During the last years, an increasing number of studies

have shown that pregabalin has a potential for abuse and addiction. The aim of our study was to show the trend of pregabalin abuse in Munich during the last few years and to describe typical clinical features of pregabalin users.
Methods: We performed a database analysis with the search term "Pregabalin" including all patients who were treated in the Department for Clinical Toxicology of the Technical University of Munich from 2008 to 2015. To evaluate pregabalin abuse in relation to other substances and to characterize pregabalin users, we analysed all patients who were admitted either with an acute drug overdose or who presented themselves for a course of detoxification over a one-year period (October 2013 to September 2014). Excluded from this analysis were patients with a singular ethanol intoxication or addiction.
Results: There were 263 cases involving pregabalin abuse from 2008 to 2015. The number of cases per year ranged between 0 and 5 from 2008 to 2011 and then substantially increased to 105 in 2015. From October 2013 to September 2014, 80 out of 370 patients (21.6%) with substance abuse had co-consumed pregabalin. It was the fifth most frequently misused substance in that time period besides opiates ($n = 239$), benzodiazepines ($n = 148$), tetrahydrocannabinol ($n = 118$) and ethanol ($n = 116$). Pregabalin users were predominantly male (65.0%) and on average 34 ± 8.4 years old; 27.5% had psychiatric and 52.5% somatic co-morbidities. On average, pregabalin users had consumed more substances than other patients (median 4 [1–6] versus 2 [1–6], $p < .001$*). They were also more often in an opioid substitution programme (41.2% versus 21.7%, $p < .001$*). The drugs most commonly used together with pregabalin were benzodiazepines (66.3%), methadone (48.8%), buprenorphine (32.5%) and heroin (22.5%).
Conclusion: Pregabalin abuse has dramatically increased over the past few years and now constitutes a significant abuse-related health issue. Patients with a history of substance abuse are particularly vulnerable to abuse pregabalin. Physicians should be aware of the addictive potential of pregabalin and reasonable care should be administered when prescribing it.

210. Prolonged toxicity from amphetamine and quetiapine following overdose in a patient also taking cobicistat

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Objective: We report a case of toxicity post-acute overdose where clinical signs persisted for longer than expected. We hypothesise that this was related to inhibition of the metabolism of quetiapine (sedation and tachycardia) by CYP3A4 inhibition by cobicistat rather than the persistent of amphetamines (tachycardia) which are substrates of CYP2D6.
Case report: A 29-year-old male was attended by paramedics 60 minutes after acute overdose of immediate release quetiapine 4.5 g and unknown amounts of intravenous methamphetamine, oral gammahydroxybutyrate (GHB) and lithium. Salient medical history included HIV positivity on Stribild (cobicistat, elvitegravir, emtricitabine, tenofovir). His Glasgow Coma Scale (GCS) was 4/15 which rapidly improved to 13/15 en route to hospital. On arrival, airway and breathing were stable, pulse 140/minute, BP 140/55 mmHg and GCS 14/15 with no focal neurology. Electrocardiogram (ECG) showed sinus tachycardia and blood tests were largely normal and serum lithium increased to 1.5 mmol/L. The patient remained mildly drowsy for 36 hours and tachycardic for 24 hours, followed by a full medical recovery. The initial marked sedation which rapidly resolved was attributed to GHB, but drowsiness and tachycardia persisted for longer than expected given the exposure reported. We hypothesised that this related to inhibition of the metabolism of quetiapine by cobicistat, so we measured amphetamine and quetiapine concentrations in serial blood samples collected during admission and calculated the elimination half-lives using a monophasic exponential decay formula. Methamphetamine, amphetamine and quetiapine were detected and the peak serum concentrations were methamphetamine 153 µg/L (admission), amphetamine 76 µg/L (admission) and quetiapine 1632 µg/L (13 hours post-admission). The elimination half-life was 36 hours for amphetamine which is prolonged in the absence of deliberate urinary alkalisation, and 16 hours for methamphetamine which is slightly longer than reported for therapeutic use. Quetiapine did not fit a one- or two-phase exponential decay to a concentration of zero, so the half-life could not be ascertained, but the maximum concentration exceeded that expected from the history and at 24 hours was 324 µg/L, which exceeds that noted in therapeutic doses (reference range 70–170 µg/L) and at 36 hours it was therapeutic at 127 µg/L.
Conclusion: Persistent tachycardia was likely due to ingestion of a larger amount of quetiapine than stated and the effect of cobicistat, and prolonged elimination of amphetamine, the reason for which is not apparent, but may relate to genetic variability in CYP2D6.

211. Recurrent seizures following a paroxetine overdose in an infant

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Objective: Paroxetine is a selective serotonin reuptake inhibitor (SSRI) prescribed for the treatment of depression and anxiety disorders. There is limited information concerning the clinical manifestations of paediatric paroxetine poisoning. Here we report a case of paroxetine poisoning in a child.
Case report: A one-month old infant was referred to a peripheral hospital because she had a one minute long, self-limiting episode of generalised tonic-clonic seizure, with dyspnea and cyanosis. Her mother reported that the first episode occurred 3 hour earlier, while being breast fed. Between these episodes the baby was drowsy and unresponsive to stimulation. Four hours after hospital admission she experienced three consecutive generalized clonic seizures more prominent over the right arm which required intramuscular administration of phenobarbital 80 mg. Due to her condition, the baby was transferred to the Neurology Unit of Meyer Children's Hospital, the regional reference centre for paediatric neurological diseases. During the admission, it was determined that she had accidentally been given a number of drops equivalent to 20 mg of paroxetine (approximately an adult dose) instead of the anti-foaming agent simethicone by her aunt. At the time of admission the baby was still drowsy but more responsive to stimuli. Clinical examination revealed mydriasis, clonus and sialorrhoea. Continuous electroencephalogram (EEG) monitoring showed frequent epileptiform dischargers with low amplitude spike-waves over the fronto-temporal regions. An electrocardiogram (ECG) performed during recovery was considered normal for her age. Qualitative blood plasma, performed after discharge through gas chromatography-mass spectrometry (GC-MS) analysis, was positive for paroxetine. Standard blood chemistries were normal. During recovery the child's condition slowly

improved without any new seizure episodes. After 8 days the baby was discharged with phenobarbital 6 mg twice daily gradually reducing the dosage during follow up control after 1 month.
Conclusion: Paroxetine is not approved for use in pediatric patients and safety and effectiveness in the pediatric population have not been established. Paroxetine overdose effects include sedation, constipation, CNS depression, serotonergic syndrome, sinus tachycardia, seizures, QRS complex prolongation and EEG alterations [1]. Major symptoms are likely to occur in poor metabolizer conditions such as immature liver. Due to these considerations, it is essential to pay greater attention when very young children are exposed to an SSRI.

Reference

[1] Fitzgerald KT, Bronstein AC. Selective serotonin reuptake inhibitor exposure. Top Companion Anim Med. 2013;28:13–17.

212. Severe and prolonged symptoms after intrathecal administration of gadobutrol (Gadovist®)

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Objective: Gadolinium-based magnetic resonance imaging (MRI) contrast agents are widely used for various diagnostic procedures and are approved for IV use only. A potential adverse effect is nephrogenic systemic fibrosis (NSF), whereas the risk of central nervous system toxicity is usually low [1]. In a patient with renal failure, gadolinium-induced encephalopathy developed after repeated IV doses of gadolinium over 7 days [2]. Encephalopathy after inadvertent entrance of gadolinium into the intrathecal compartment is a known complication and can cause a variety of neurologic symptoms [3]. We report on a case with severe and prolonged neurological symptoms following intrathecal misapplication of gadobutrol.
Case series: Between October 1996 and October 2016, a total of 11 exposures to gadolinium-based MRI contrast agents were reported to the Poisons Information Centre Erfurt. In 5 cases (45.5%), adverse reactions with therapeutic use were observed, in 3 cases (27.3%) the patient was administered the wrong dose, and in one case (9.1%) extravasation occurred. There was also one case (9.1%) of accidental exposure, when the agent splashed into the eye of a doctor. In the final case a 53-year-old female received 10 mL of Gadovist® (gadobutrol) intrathecally during a diagnostic procedure at the lumbar spine. She immediately developed severe pain and seizures, showing prolonged epileptic activity on an electroencephalogram (EEG). Contrary to the PIC's advice, cerebrospinal fluid lavage was not performed. The patient was sedated and treated with analgesics plus anticonvulsants. However, analgosedation could not suppress epileptic activity over 4 days. The patient´s condition gradually improved over the following two months, and she was transferred to a rehabilitation facility. As yet, long-term damage still cannot be ruled out completely.
Conclusion: Gadolinium-induced encephalopathy has been reported previously [2], however, gadolinium may not be the culprit in this case. The high volume (10 mL) and high osmolarity (1 mmol/mL) of the product could have induced a physicochemical imbalance of cerebral fluid, leading to irritation of the meninges resulting in the clinical signs described. Although cerebrospinal fluid lavage has not been evaluated for cases of gadolinium misapplication, it has successfully been applied for intrathecal vincristine poisoning, and may have been beneficial in this case, too.

References

[1] Product information Gadovist® [Internet]. [cited 2016 Oct 11]. Available from: http://www.bayerresources.com.au/resources/uploads/PI/file9345.pdf.
[2] Maramattom BV, Manno EM, Wijdicks EF, et al. Gadolinium encephalopathy in a patient with renal failure. Neurology. 2005;64:1276–1278.
[3] Kapoor R, Liu J, Devasenapathy A, et al. Gadolinium encephalopathy after intrathecal gadolinium injection. Pain Physician. 2010;13:E321–326.

213. Third degree heart block with accelerated junctional rhythm in verapamil overdose: a case series

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Objective: Bradydysrhythmias are common cardiac manifestations of verapamil poisoning. While atrioventricular (AV) junctional rhythm has been reported in human and animal models, third degree heart block with complete AV nodal disassociation is not widely described. We report two verapamil toxic patients with electrocardiograms (ECGs) consistent with complete AV node disassociation.
Case series: Case 1: An 18-year-old female presented to the emergency department (ED) after reportedly ingesting 1800 mg extended-release verapamil 12–18 hours prior to arrival. ECG at that time revealed a wide-complex escape rhythm of 40 beats per minute (bpm) with absence of P waves. She was transferred to an intensive care unit and endotracheal intubation, vasopressor infusion, calcium infusion, and high dose insulin (HDI) therapy (3 units/kg/h) were performed. She also received two boluses of 5 mg glucagon and three boluses of lipid emulsion (1.5 mL/kg). On hospital day 2, her rhythm morphed to a third degree heart block with an accelerated junctional rhythm between 70 and 90 ventricular bpm with an independent atrial rate in the 70s that persisted for 36 hours and eventually resolved. The patient subsequently had a complete recovery. Case 2: A 21-year-old female was transported to the ED following an intentional verapamil extended released ingestion with the following vital signs: pulse 42 bpm and a blood pressure of 70/42 mmHg. Her initial ECG demonstrated complete AV nodal disassociation with a ventricular rate of 47 bpm and an atrial rate of 83 bpm. She was started on HDI infusion (2 units/kg/h), calcium infusion, glucagon infusion, and norepinephrine infusion. She made a complete recovery three days later with return to normal sinus rhythm.
Conclusion: Non-dihydropyridine calcium channel antagonist (CCAs) toxicity can lead to decreased recovery of the SA and AV nodes, causing bradycardia with the potential for sinus arrest and AV nodal blockade. Additionally, the funny current of the sinoatrial node (SA) may be impaired, preventing atrial depolarization and subsequent loss of P waves on the ECG. These cases are unique due to complete AV nodal dissociation in the presence of P waves. Complete AV block without SA impairment has not been reported with CCAs. These cases also demonstrate the variability in rhythms manifesting in CCA poisoning. While it is unknown why this rhythm occurred in these cases, there may be

phenotypic variations in channel sensitivity to CCAs. Further research is required to better elucidate the pathophysiology of complete AV node blockade with verapamil poisoning.

214. Thyrotoxicosis and anorectic pills: a case report

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Objective: Iatrogenic thyrotoxicosis is a potentially fatal medical emergency. There are literature reports of life-threatening intoxications associated with anorectic pills containing variable, and often undisclosed, amounts of levothyroxine [1].
Case report: A 38-year-old woman presented to the Emergency Department referred by a neurologist. According to family members, she had developed spatial-temporal disorientation and headache in the previous days. On examination, psychomotor agitation, global aphasia, heart rate 170 beats/min, blood pressure 140/80 mmHg, temperature 36.5 °C and oxygen saturation 98% (room air), were present. gHead magnetic resonance imaging (MRI) and cerebrospinal fluid showed no abnormalities. Blood tests indicated hyperthyroidism: thyroid stimulating hormone (TSH) 0.01 µIU/mL, free T4 7.77 ng/dL, free T3 32.55 pg/mL. Medical history revealed she had been taking pharmacist-processed anorectic pills for months, containing levothyroxine 25 µg, spironolactone 30 mg, caffeine 180 mg and synephrine 20 mg. The patient was sedated with midazolam (5 mg IV), the electrocardiogram (ECG) monitored, and fluids given. Metoprolol produced only partial control of heart rate (160 beats/min) and propranolol (40 mg orally) and hydrocortisone (250 mg IV) were thus administered. On day 2, the patient was transferred to the intensive care unit, intubated and placed on a midazolam infusion. Treatment with propylthiouracil (400 mg/day) was initiated on day 3. Electroencephalogram (EEG) showed a generalized non-convulsive epileptic state, treated with phenytoin. On day 10 thyroid parameters normalized, and on day 13 propylthiouracil was discontinued. The development of a pneumonitic process required sedation and prolonged the hospital stay. She was discharged a month later with complete recovery.
Conclusion: This case underlines: i) the latency in onset of symptoms of intoxication due to the long half-life of levothyroxine (7 days); ii) the indication for propylthiouracil and corticosteroids in severe cases to decrease conversion of T4 to T3; [2] iii) the importance of suspecting thyrotoxicosis when evaluating malaise in patients taking dietary pills; iv) the risk of using pharmacist-processed anorectic preparations, taking into account dosage errors, presence of undisclosed active principles, and the possible interactions with other drugs [3].

References

[1] Ioos V, Das V, Maury E, et al. A thyrotoxicosis outbreak due to dietary pills in Paris. Ther Clin Risk Manag. 2008;4:1375–1379.
[2] Woeber KA. Update on the management of hyperthyroidism and hypothyroidism. Arch Intern Med. 2000;160:1067–1071.
[3] Di Lorenzo C, Ceschi A, Kupferschmidt H, et al. Adverse effects of plant food supplements and botanical preparations: a systemic review with critical evaluation of causality. Br J Clin Pharmacol. 2014;79:578–592.

215. Unintentional ingestion of apixaban in a toddler

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Objective: To report a case of unintentional ingestion of apixaban, an oral factor Xa inhibitor, in a child.
Case report: A previously healthy 2.5-year-old, 15 kg girl was brought to the emergency department 1.5 hours after a witnessed ingestion of 5 mg apixaban (0.33 mg/kg). Her vital signs were normal, and she had no overt bleeding. Two hours post-ingestion her PT and PTT were 11.8 and 29 seconds, respectively, INR 1.03, and hemoglobin 11.9 g/dL. At 17 and 40 hours post-ingestion, serum apixaban concentration was 30.3 ng/mL and undetectable, respectively. Coagulation profile and hemoglobin remained within normal limits during her entire admission, and she was discharged home asymptomatic.
Conclusion: We report a case of a toddler who ingested 0.33 mg/kg of apixaban, with a serum concentration of 30.3 ng/mL at 17 hours, normal coagulation profile, and without overt bleeding. This dose was high compared with the 0.05 mg/kg used in pediatric clinical trials [1]. The usual adult dose is 2.5–5 mg twice daily. A recent case-series reported no bleeding and normal INR in a pediatric sub-group of single ingestions of apixaban and rivaroxaban (another oral factor Xa inhibitor); dose and serum concentrations were not reported [2]. Up to 100 mg rivaroxaban ingestion in a toddler resulted in elevated INR (6.1) at 100 minutes post-ingestion, which resolved spontaneously. Serum concentrations were not reported [3]. In adults, single ingestion of 5 mg apixaban resulted in median Tmax and C_{max} of 3.3 hours and 105 ng/mL, respectively, and the adult 17 hour concentration was lower than the corresponding concentration found in our case [4]. Although unintentional single ingestion of oral factor Xa inhibitors seems to pose little risk in toddlers, more data are required to characterize the toxic dose, monitoring parameters, and observation period.

References

[1] von Vajna E, Alam R, So TY. Current clinical trials on the use of direct oral anticoagulants in the pediatric population. Cardiol Ther. 2016;5:19–41.
[2] Spiller HA, Mowry JB, Aleguas A Jr, et al. An observational study of the factor Xa inhibitors rivaroxaban and apixaban as reported to eight poison centers. Ann Emerg Med. 2016;67:189–195.
[3] Lynn A, Valento M, Chen BC. Laboratory abnormalities following an unintentional pediatric rivaroxaban ingestion. Clin Toxicol. 2015;53:748–749.
[4] Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol. 2013;75:476–487.

216. Validation analysis of Poisoning Severity Scores in intentional self-poisoning cases

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Objective: Poisoning Severity Score (PSS) [1] is a widely used assessment of the medical severity of poisoning events, yet validation data are limited overall and in specific populations. The current analyses examined the criterion validity of PSS scores in intentional self-poisoning cases by testing the hypothesis that PSS scores are associated with the deleterious effects of the poisoning events across a wide range of organ systems (pulmonary, etc.).
Methods: This was a secondary analysis of cases treated at the bedside by the local toxicology consult service of a large US university medical center that participates in the multisite Toxicology Investigators Consortium Case Registry [2]. The current analyses examined local cases entered into the ToxIC Registry over a 4-plus year period (1 January 2011 to 27 July 2016), with a focus on intentional self-harm patients aged 13 to 65 who ingested one or more pharmaceutical agents ($n = 673$). Data were analyzed using a series of multivariate linear regression analyses. The outcome in the analyses was Poisoning Severity Score. The predictor was a deleterious effect (presence or absence) of the act of self-poisoning on each of eight organ systems: vital signs, cardiovascular, pulmonary, nervous system, metabolic, gastrointestinal hepatic, hematological, and renal muscle. PSS scores were regressed on each organ system variable in a series of separate models, with statistical adjustment for age and sex.
Results: Higher PSS scores were associated with deleterious effect on each of the organ systems studied ($p < .001$).
Conclusion: The study hypothesis was confirmed. PSS scores represent a summary measure but, nonetheless, it is associated with deleterious effects in a wide range of specific organ systems in adolescents and adults with intentional self-poisoning, supporting validity.

References

[1] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.
[2] Rhyee SH, Farrugia L, Campleman SL, et al. The Toxicology Investigators Consortium Case Registry – the 2014 Experience. J Med Toxicol. 2015;11:388–409.

217. Zopiclone poisoning and methemoglobinemia: French poison control centers data, 1999 to 2016

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Objective: Between 1999 and 2016, the French Poison Control Centers (PCCs) registered 2.6 million medical records. Of these, 0.74% were related to zopiclone poisoning, and 65% of patients were symptomatic. Zopiclone is a cyclopyrrolone and is metabolized by the liver to two major metabolites, zopiclone-N-demethyl and zopiclone N-oxide, and eliminated primarily in the urine (80%). Its neurological toxicity is well known. However, in the literature, some cases of methemoglobinemia have been reported with zopiclone intoxication. Methemoglobinemia occurs when methemoglobin is formed by oxidation of hemoglobin ferrous iron (Fe 2+) to ferric iron (Fe 3+). The hemoglobin is unable to carry oxygen, and results in respiratory distress. With high doses, zopiclone induces methemoglobinemia via redox mechanisms involving metabolites. Methylene blue treatment for methemoglobinemia is specific and effective if administered quickly. Our objective was to describe cases of methemoglobinemia due to zopiclone from the cases reported in the French PCCs.
Methods: A retrospective study of zopiclone exposures with pathological methemoglobinemia, and recorded in the French PCCs from 1999 to 2016 was conducted.
Case series: In total 6 cases of non-zero drug causality were reported: 4 women (47, 84, 26 and 60 years), and two men (48 years). All were suicide attempts and 3 had a relevant medical history. The reported ingested doses ranged from 180 to 2250 mg. Four cases were poly-intoxications, 2 involved another toxic agent which could induce methemoglobinemia (dapsone and exhaust fumes). The methemoglobinemia concentration ranged from 19 to 43%. Cyanosis was present in all cases; 2 patients had hemolytic anemia, 2 patients presented a coma (Glasgow Coma Scale 3) and 1 had metabolic acidosis. Five patients received methylene blue and 4 required respiratory support. The Poisoning Severity Score of these patients were 3 ($n = 3$), 2 ($n = 2$) and 4 ($n = 1$, death). Five patients recovered without sequelae.
Conclusion: Methemoglobinemia is a rare and little known complication of zopiclone poisoning, and this effect should be included in the summary of product characteristics. Indeed, the clinical signs are not specific, and a delay in treatment could lead to death. In cases of poisoning by high doses of zopiclone, the methemoglobin concentration should be monitored.

218. Symptomatic elevation of antiepileptic drug concentrations after addition of hemp oil extract to a therapeutic regimen

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Objective: We describe a patient with symptomatic elevations of clobazam, valproic acid and lamotrigine concentrations following addition of hemp oil extract to her antiepileptic drug (AED) regimen.
Case report: A 7-year-old female with a past medical history of epilepsy, West Syndrome, ring chromosome 14, scoliosis, and constipation presented to the emergency department complaining of unsteady gait, sleepiness, and intermittent seizures over the past 2 weeks. Her medications included clobazam 15 mg oral twice daily, clonazepam 0.5 mg oral once daily, valproate 250 mg oral twice daily and lamotrigine 100 mg oral twice daily for seizures. One month prior to admission, the patient was started on hemp oil extract by her neurologist as an adjunctive treatment for seizures. On presentation, the vital signs were: temperature 36.9 °C, blood pressure 98/62 mmHg, oxygen saturation 100% (room air), heart rate 82 beats/minute, and respiratory rate 18/minute. On physical examination, she required assistance to stand from a seated position, had an unsteady gait, but was able to walk without assistance. The neurological examination revealed no focal findings. The toxicology service was consulted and discontinuation of the hemp oil extract was recommended due to the possibility of adverse interactions with her antiepileptic medication regimen. The patient remained seizure-free during her hospital stay with resolution of her unsteady gait and somnolence prior to discharge. Initial serum concentrations of the patient's AEDs were noted to be supratherapeutic with lamotrigine 37.8 µg/mL (normal range 2–20 µg/mL), valproate 122 µg/mL (normal range 50–100 µg/mL) from a previous

baseline of 66 µg/mL, and clobazam 367 ng/mL (normal range 30–300 ng/mL).
Conclusion: Cannabidiol contained in hemp oil extract inhibits CYP3A4 and CYP2C19, the primary isoenzymes involved in the metabolism of clobazam, and inhibits UDP-glucuronyl transferase, which is involved in the metabolism of lamotrigine and valproic acid. Symptomatic elevations in valproic acid and clobazam have been reported following the addition of cannabidiol to antiepileptic therapeutic regimens. Several studies have reported the efficacy of cannabidiol as an adjuvant therapy for refractory epilepsy, however evidence suggests that hemp extract may cause elevations of serum concentrations of various AEDs. Clinicians should be aware that the use of hemp extract in combination with AEDs requires caution and careful monitoring of serum AED concentrations.

219. Paracetamol-induced renal failure: an underestimated consequence of delayed managed overdoses

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Objective: Paracetamol poisoning is one of the most frequent drug intoxications with well-known risk of liver toxicity. However the direct renal toxicity of this painkiller is still mysterious and much less studied. In Southern France, paracetamol overdose is an everyday problem but observations with proven renal damage seem to be rare. In order to illustrate this notion, 9 cases of renal failure during paracetamol overdose managed in the Marseille Poison Centre are detailed.
Case series: Nine cases (6 suicide attempts, 3 self-medications) were studied, concerning 6 women and 3 men between 13 to 70 years old. In 7 cases there was acute poisoning after a massive quantity of paracetamol and 2 cases involved repeated high doses over 3 to 5 days. A classic hepatic cytolysis was observed in 7 cases but for 2 patients there was no liver impact. The acute kidney injury scores (Acute Kidney Impairment Network) were two grade I, two grade II and five grade III. Hemodialysis was required for 4 patients with grade III kidney impairment; all of them had delayed medical management. Oliguria/anuria was present for 3 to 14 days. For 2 patients a kidney biopsy was performed and showed a toxic acute tubular necrosis. All patients recovered.
Conclusion: Direct paracetamol toxicity on the kidneys seems to be a rare but serious event. This kind of toxicity is only reported when an oliguria or anuria is present; however in our everyday practice we do not evaluate the renal impact during a common paracetamol overdose. The kidney toxicity of paracetamol is certainly underestimated and should be studied more seriously. An important recent study [1] examined the correlation between the severity of the hepatic failure and the development of kidney disturbances, the possible efficient therapeutic activity of the acetylcysteine on the renal toxicity of the paracetamol, and the higher risk of renal failure when the medical management is delayed.

Reference

[1] Stollings JL, Wheeler AP, Rice TW. Incidence and characterization of acute kidney injury after acetaminophen overdose. J Crit Care. 2016;35:191–194.

220. Mechanistic biomarkers stratify patients after paracetamol overdose with high sensitivity and specificity

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Objective: Paracetamol (acetaminophen) overdose is the most common cause of liver toxicity in the Western world but patient stratification is sub-optimal. A number of new biomarkers that have improved hepatic expression (miR-122) or provide mechanistic insights (keratin-18 [K18], High Mobility Group Box-1 [HMGB1]), have been proposed to have higher specificity and sensitivity than currently used tests. The objective of this study was to prospectively explore the ability of these biomarkers to stratify patients by risk of subsequent liver injury in 2 paracetamol overdose patient cohorts that faithfully represented the spectrum of clinical presentations requiring treatment with acetylcysteine.
Methods: Patients who needed acetylcysteine treatment for paracetamol overdose were recruited. Independent derivation (Markers and Paracetamol Poisoning, 8 UK hospitals) and validation (Biomarkers of Paracetamol Hepatotoxicity, 10 UK hospitals) studies prospectively recruited 985 and 202 patients, respectively. Circulating biomarkers were measured at hospital presentation. The primary endpoint was acute liver injury (ALI), defined as peak alanine transaminase activity (ALT) >100 U/L. Secondary endpoints included ALT >1000 U/L and liver synthetic dysfunction (INR >1.5). Receiver Operator Characteristic Area Under the Curve (ROC-AUC) and Multivariate Net Reclassification Index (NRI) analyses were utilised to determine the ability of these novel biomarkers to stratify patients by liver injury risk.
Results: In the derivation and validation cohorts, ALI was predicted at presentation to hospital with high sensitivity and specificity by miR-122, HMGB1 and full length-K18 (FL-K18) (ROC-AUC values: 0.97 [0.95–0.98], 0.95 [0.93–0.98] and 0.95 [0.92–0.97], respectively). High predictive accuracy was maintained when the cohorts were censored by normal presentation ALT, time from overdose and overdose type (acute or staggered). For prediction of INR elevation, HMGB1 had the maximal prognostic ability in acute and staggered overdoses in both the derivation and validation cohorts (ROC-AUC: 0.94 [0.88–1.00]) compared with ALT (0.55 [0.39–0.72]).
Conclusion: In these two multi-centre prospective studies, we have demonstrated that a panel of mechanistic circulating biomarkers can predict subsequent liver injury and dysfunction with high accuracy despite treatment with acetylcysteine. Using these biomarkers, a precision medicine approach to patient stratification and management can be applied at hospital presentation. This study has directly contributed to the regulatory (Food and Drug Administration [FDA] and European Medicines Agency [EMEA]) letters of support for the further qualification of these biomarkers across the spectrum of drug-induced liver injury.

221. Ciguatoxin-induced chronic disease unmasks people carrying human leukocyte antigen (HLA) epitopes peculiar to celiac disease and rheumatoid arthritis

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Objective: Ciguatoxins (CTXs) are polyether marine neurotoxins in various reef fish, and are potent activators of voltage-gated sodium channels. After the acute phase (AC) of poisoning, some patients develop a chronic multisystem illness, chronic ciguatera (CC), that appears to be characterized by a dysregulation of the immune system. Here we present 10 Italian cases of CC and 1 of AC molecularly typed for HLA class I and II polymorphisms.
Methods: Genomic DNA was isolated from whole blood samples. Low-resolution genomic typing (HLA-A, B, C and DRB1 alleles) was performed in 106 ethnically matched controls (bone marrow donors from Pavia Registry). High-resolution typing (HLA-DQA1, DQB1 loci) was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP). HLA-A, B and C alleles were also considered as ligands of killer-cell immunoglobulin-like receptors (KIRs).
Results: Considering HLA class I molecules as ligands of KIR-receptors expressed on the NK cells, we observed that: 9/10 CC and 64/106 controls carried at least one HLA-A KIR ligand ($p = .06$, OR =5.91); 8/10 CC and 70/106 controls carried at least one HLA-B KIR ligand ($p = .36$, OR = 2.06); 7/10 CC and 37/106 controls carried one HLA-A and one HLA-B ligand ($p = .028$, OR =4.35); 3/10 CC and 27/106 controls were HLA-C KIR ligands C2/C2 ($p = .75$, OR =1.25); 2/10 CC and 39/106 controls were C1/C1 ($p = .28$, OR =0.43); 5/10 CC and 40/106 were C1/C2 ($p = .44$, OR =1.65). The only case of AC was lacking both HLA-A and HLA-B KIR ligands, a condition shared by only 9/106 controls, and was C2/C2 homozygous. Considering the HLA class II alleles, we observed a significantly increased frequency of the HLA-DRB1*04 ($p = .10$, OR =4.57), HLA-DQA1*03 ($p = .016$, OR =4.17) and HLA-DQB1*03:02 ($p = .0017$, OR =6.38) alleles. Interestingly, 8/10 chronic patients and 48/106 controls carried at least one HLA-DQ heterodimer of susceptibility to celiac disease ($p = .03$ OR =4.83) and 8/10 CC and 64/106 controls carried at least one HLA-DQ heterodimer of susceptibility to diabetes mellitus type 1 ($p = .22$, OR =2.63). In addition 6/10 CC patients and 36/106 controls carried at least one HLA-DRB1 arthritogenic epitope ($p = .10$ OR =2.92). The unique AC case was HLA-DRB1*10:01,*14:04; DQB1*05 positive and carried 2 HLA-DRB1 arthritogenic amino acid motifs, the distribution of HLA-DR shared epitope statistically deviated from the controls ($p = .002$).
Conclusion: CC seems to be conditioned by the presence of HLA class II profiles typical of autoimmune diseases, although no auto-antibodies were found, and by the presence of HLA-A or -B KIR ligands. The polyetheric structure of ciguatoxins could interfere indirectly with the peptide binding site of HLA class II molecules and induce immune dysfunction which is the hallmark of CC.

222. Imaging drug-drug interaction using positron emission tomography (PET) scans: investigating the impact of diazepam on buprenorphine-induced respiratory depression

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Objective: Buprenorphine (BUP) is a partial mu-opioid receptor (MOR) agonist with a "ceiling effect" that is supposed to prevent respiratory depression during pain management or opioid maintenance therapy. However, fatal respiratory depression with the typical opioid toxidrome has been reported, mainly when BUP has been co-ingested with benzodiazepines such as diazepam (DZP). In rats, we previously demonstrated that DZP (20 mg/kg subcutaneously) or BUP (30 mg/kg intraperitoneally) did not lead to respiratory depression while their combination resulted in severe respiratory depression. Based on *in vitro/ex vivo* experiments, we hypothesized benzodiazepine-induced alterations in MOR affinity/density, may provide a mechanistic explanation for the interaction between DZP and BUP *in vivo*.
Methods: The *in vivo* effects of acute DZP exposure on BUP brain kinetics and affinity were investigated using [11C]-BUP PET imaging (approximately 37 MBq, 90 minutes) in Sprague Dawley rats. Baseline brain [11C]-BUP kinetics (vehicle, $n = 4$) were compared to kinetics obtained i) after displacement with unlabeled pharmacological BUP dose (0.3 mg/kg) administered 20 minutes after [11C]-BUP ($n = 3$) and ii) pre-treatment with DZP (20 mg/kg subcutaneously) administered 15 minutes before PET ($n = 4$). Standardized uptake value (SUV) normalized [11C]-BUP PET images were co-registered in a template to generate time-activity curves (TACs) in several brain regions. [11C]-BUP binding potential (BPND) was estimated using the simplified reference-tissue model (SRTM) using the cerebellum as the reference region.
Results: Baseline [11C]-BUP brain kinetics in the cerebellum ($SUV90min = 0.29 \pm 0.07$) was influenced neither by the displacement ($SUV90min = 0.24 \pm 0.02$) nor by DZP pretreatment ($SUV90min = 0.38 \pm 0.05$) which makes it possible to use the cerebellum as reference tissue region. In the striatum, a MOR-rich region, baseline $SUV90min = 0.89 \pm 0.26$ was significantly decreased by displacement ($SUV90min = 0.51 \pm 0.10$; $p < .05$), showing the reversibility of [11C]-BUP binding, but not by DZP-pretreatment ($SUV90min = 0.90 \pm 0.13$). Kinetic modeling indicated that [11C]-BUP BPND was not influenced by DZP pretreatment in all tested regions including the striatum, frontal cortex, midbrain, pons, amygdala and medulla.
Conclusion: [11C]-BUP brain kinetics, reported for the first time in rodents, corresponds to the known distribution of MOR in the rat brain and can be described using SRTM. [11C]-BUP BPND was not influenced by DZP, indicating the absence of any measurable regulation of BUP affinity for MOR *in vivo*. Our results indicate that respiratory depression attributed to BUP/benzodiazepine combination observed in patients may result from the synergistic effects of these two drugs on respiratory function rather than from alteration of MOR availability or affinity for BUP.

223. Utility of QT interval corrected by the Rautaharju method to predict drug-induced torsades de pointes

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Objective: New QT correction formulae derived from large study populations are available, such as Rautaharju's [QTcRTH = QT* (120 + heart rate)/180]. This formula was derived from 57,595 cases and was recently shown not to contribute significant errors across a wide range of heart rates compared to others. Our objective were to determine the best cut-off value of QTcRTH as a predictor of torsades de pointes (TdP) and to compare the sensitivity and specificity using the cut-off value of QTcRTH with those of the QT nomogram, QTcFridericia (QTcF) and QTcBazett (QTcB).
Methods: Data were from two data sets. All patients were aged over 18 years with an exposure to QT prolonging drugs. In Group-1, all cases developed TdP and data were obtained from systematic review of reported cases from Medline since its establishment until 10 December 2015. Group-2 comprised those who overdosed on QT prolonging drugs, but did not develop TdP. This data set was previously extracted from a chart review of 3 medical centers from January 2008 to December 2010. Data from both groups were used to calculate QTcRTH. We then selected the cut-off value from QTcRTH that provided the best sensitivity and specificity to predict TdP. The same method was applied to find those values from QTcB, QTcF, and QT nomogram. The receiver operating characteristic curve (ROC) was applied where appropriate.
Results: In Group-1, there were 230 cases of drug-induced TdP. Group-2 (control group) which did not develop TdP, comprised 292 cases. After applying the Rautaharju formula to both groups, the QTcRTH cut-off that provided the highest accuracy (89.08%) with the highest sensitivity (91.30% [95% CI 86.89–94.61%]) and specificity (87.33% [95% CI 82.96–90.92%]) to predict TdP was 477 ms. The highest accuracy with the highest sensitivity and specificity was 86.97% with 88.26% (95% CI 83.38–92.12%) and 85.96% (95% CI 81.44–89.73%), respectively by the QTcB cut-off at 490 ms, and those were 88.89% with 89.13% (95% CI 84.37–92.84%) and 88.70% (95% CI 84.50–92.09%), respectively by the QTcF cut-off at 473 ms. We found a significant difference ($p = .0025$) between area under the ROC of the QTcRTH (0.9431) and QTcB (0.9230), but not QTcF (0.9333). The accuracy, sensitivity and specificity of the QT nomogram were 89.08%, 91.30% (95% CI 86.89–94.61%) and 87.33% (95% CI 82.96–90.92%), respectively, and they were all equal to those of QTcRTH.
Conclusion: The Rautaharju method not only produced minimal errors for QT interval correction, but also, at the QTcRTH 477 ms, could predict TdP as accurate as the QT nomogram and was better than the QTcB.

224. The role of expert identification of spiders in the correct management of spider bites: a pilot study from Pavia Poison Control Centre

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Objective: Spider bites are a frequent cause for concern due to myths that surround their toxic effects [1]. In most cases, clinical manifestations are not easily attributable to a spider bite because the patient has no information about the culprit. With the exception of *Latrodectus tredecimguttatus* and *Loxosceles rufescens*, most Italian spiders cause only short-term local manifestations. The aim of our study was to evaluate the role and the importance of an expert identification of the spider for the correct diagnosis and, consequently, clinical management.
Methods: We collected all bite cases over a 7-month period (March-September 2016). Inclusion criteria, as defined by medical literature [2], were: (i) the spider being caught at time of the bite, (ii) expert identification of the spider, and (iii) toxic effects at the time of the bite. Expert identification was performed via telemedicine (sharing photos with arachnologists). All cases were followed-up until clinical resolution.
Results: Twenty-one cases of spider bites (11 females; 1–85 years [mean 37 years]) met the inclusion criteria. *Cheiracanthium* species was involved in nine cases (43%), *Zoropsis spinimana* in four, *Loxosceles rufescens*, *Cteniza* species and *Segestria florentina* in two each, *Amblyocarenum nuragicus* and *Steatoda triangulosa* in one each. The most frequently bitten site was the hand (62%). At the time of Poison Control Centre consultation, 15 patients were in the emergency department (ED) and for seven (47%) an immediate discharge was proposed. Six people called our centre directly; for four the bite was considered non-toxic and medical evaluation was not necessary, for two a medical evaluation was suggested. In one case, the clinical manifestations (swelling, hyperemia and necrosis) were not related to the bite of the spider identified by the patient. Main clinical manifestations were local hyperemia (62%), pain (57%), swelling (38%), paresthesia (14%), itching (9%) and, in one case, necrosis. No systemic manifestation was recorded.
Conclusion: In 62% of the cases, expert identification was crucial for the correct management of the patient, particularly in allowing a rapid ED discharge (33%) or preventing hospitalization (14%). Urgent evaluation was suggested only in one case due to discrepancies between patient history and clinical manifestations. We conclude that the online consultation of experts in support of the specialized clinical evaluation is essential, especially in rapidly excluding potential toxic evolution.

References

[1] Isbister GK, Fan HW. Spider bite. Lancet. 2011;378:2039–2047.
[2] Vetter RS, Isbister GK. Medical aspects of spider bites. Ann Rev Entomol. 2008;53:409–429.

225. Spider bite: a rare case of cutaneous loxoscelism in the west of Iran

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Objective: Spider bites are quite frequent and often resolve quickly without sequelae. Only some species are capable of causing necrosis and systemic lesions in humans. These species are widespread in Latin America and the Mediterranean [1]. We describe this kind of spider bite in Iran.
Case report: A 40-year-old woman without any medical history came to the emergency department for a skin lesion that began 2 days before, after lifting a box of grapes. At first she had only pain and burning sensation but after 24 hours the erythema and pain increased and a central vesicle developed. In spite of antibiotics, the lesion increased, with a central blister and extensive inflammation and edema that affected the whole forearm. The patient was admitted to hospital and started on an intravenous antibiotic. The liver enzymes (AST and ALT) increased but resolved 3 days later. Within 48 hours the vesicle became hemorrhagic, necrotic lesions appeared in ecchymotic zones, and the erythema extended. The patient remembered that after lifting the box of grapes she saw a spider which was killed and that she had a picture of it. Symptomatic treatment was implemented and antibiotic treatment was continued for 14 days. The patient was reevaluated and the lesion had evolved into a necrotic ulcer in the middle of forearm. Erythema reduced and she was referred to a plastic surgeon. The spider appeared to be *Loxosceles rufescens* and the lesion was thought to be cutaneous loxoscelism.
Conclusion: Loxoscelism is caused by the bite of the brown recluse spider. This spider bite is usually painless but it later becomes an inflammatory, hemorrhagic and painful lesion [2]. Necrosis spreads a few days later and loxoscelism results in necrosis at the bite site. There are several reports of loxoscelism caused by *L. rufescens* in numerous part of the world but there are no confirmed reports of loxoscelism from Iran. This spider is found in Iran [3] and the necrosis in this case may be due to *L. rufescens*. Cutaneous loxoscelism should be considered in the differential diagnosis of dermonecrosis developing unfavorably with antibiotics, especially as the bite may be unnoticed by patient.

References

[1] Swanson DL, Vetter RS. Loxoscelism. Clin Dermatol. 2006;24:213–221.
[2] Tintinalli JE, Stapczynski JS, Ma OJ, et al. Tintinalli's emergency medicine: a comprehensive study guide. New York (NY): McGraw-Hill Medical; 2011.
[3] Zamani A, Rafinejad J. First record of the Mediterranean recluse spider *Loxosceles rufescens* (Araneae: Sicariidae) from Iran. J Arthropod Borne Dis. 2014;8:228–231.

226. A case of *Fallopia multiflora*-induced hepatotoxicity treated with acetylcysteine

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Objective: *Fallopia multiflora* (*Polygonum multiflora*) is a complementary medicine used frequently in the Chinese community for hair loss or as anti-aging tonic. We report a case of hepatotoxicity associated with chronic use and the potential utility of intravenous acetylcysteine.
Case report: A 51-year-old woman presented to the Emergency Department (ED) with a 1-week history of lethargy, nausea, abdominal discomfort and bilirubinuria. She had been taking a herbal supplement ("Hair Tonic") for her hair loss for the previous 4 weeks up until 3 days before her ED presentation. Product information listed that each tablet contained 1 g of *Fallopia multiflora*. She had been taking 4 g per day. She was referred by her general practitioner with acute jaundice and abnormal liver function tests (LFTs). She presented with icterus and marked hepatomegaly. Vital signs were otherwise within normal limits. LFTs were ALT 2412 IU/L, AST 1796 IU/L and bilirubinaemia of 95 µmol/L. Coagulation profile was normal (INR 1.1). ALT and AST improved post-administration of a 2 infusion course (20 hour) of intravenous acetylcysteine (ALT 2131, AST 1334, INR 1.2). Acetylcysteine was discontinued and LFTs improved. She was discharged on day 4 post-presentation. Paracetamol concentration and screening for other causes of acute liver injury including viral hepatitis was negative. Her LFTs 22 days after cessation of the herbal supplement had normalised (ALT 59 IU/L, AST 31 IU/L, bilirubin 15 µmol/L) and she remains well.
Conclusion: Previous analysis of *Fallopia multiflora* suggests that toxicity is associated with its anthraquinone constituent [1]. Anthraquinone is known to induce cell apoptosis and deplete intracellular glutathione. Use of acetylcysteine in *Fallopia multiflora* toxicity has not been reported. Acetylcysteine may have lessened further toxicity in our case by providing glutathione replacement and reducing oxidative free radical production. In one cases series average length of stay was 18 days compared to our case which was significantly less [2]. Chronic ingestion of *Fallopia multiflora* can result in hepatotoxicity and acetylcysteine may be useful in abating toxicity and decreasing length of stay.

References

[1] Lin L, Lin H, Zhang M, et al. A novel method to analyse hepatotoxic components in *Polygonum multiflorum* using ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. J Hazard Mat. 2015;299:249–259.
[2] Jung KA, Min HJ, Yoo SS, et al. Drug-induced liver injury: twenty five cases of acute hepatitis following ingestion of *Polygonum multiflorum* Thunb. Gut Liver. 2011;5:493–499.

227. Cardiotoxic hyperkalemia as a result of canary seed ingestion

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Objective: Canary seed (CD) (*Phalaris canariensis*), is a cereal grain, and a common component of bird feed [1]. It is also used as folk medicine to treat diabetes mellitus (DM) and hypertension (HTN) through purported weight loss properties [2]. Hairless canary seed has significantly more potassium per gram than wheat grain or bananas (385 mg/100 g, 355 mg, and 358 mg/100 g, respectively), and animal studies suggest that ingestion significantly increases creatinine and potassium concentrations [1,3,4]. We report the first case of a patient who presented with life-threatening hyperkalemia after CD ingestion.
Case report: A 76-year-old male with end-stage renal disease on hemodialysis (HD), with HTN, DM, coronary artery disease, and a permanent pacemaker presented to the emergency department reporting nausea, chest pain, and shortness of breath for one day. His last HD session was two days prior to presentation. On arrival, his vital signs were: blood pressure 66/36 mmHg, heart rate 72 bpm, respiration 20/min, oxygen saturation 100% (room air), and temperature 36.4 °C. Electrocardiogram (ECG) showed a paced, wide complex rhythm at 74 bpm with a QRS interval of 240 ms and absence of P waves. He was empirically treated for hyperkalemia with 3 g calcium gluconate, 3 amps of sodium bicarbonate, 10 units of regular insulin IV, and continuous nebulized albuterol. His QRS complex narrowed and his BP normalized. His initial potassium concentration was 7.1 mEq/L and decreased

to 4.1 mEq/L after urgent HD. Further history revealed that the patient had recently been ingesting "large" amounts of liquid CD in an effort to lose weight.
Conclusion: CD is known to have a high potassium content and use may be unsafe in populations vulnerable to hyperkalemia. Further study in humans is necessary to better establish the risks and benefits of ingestion.

References

[1] Magnuson B, Patterson C, Hucl P, et al. Safety assessment of consumption of glabrous canary seed (*Phalaris canariensis* L.) in rats. Food Chem Toxicol. 2014;63:91–103.
[2] Estradas-Salas P, Montero-Moran G, Martinez-Cuevas P, et al. Characterization of antidiabetic and antihypertensive properties of canary seed (*Phalaris canariensis* L.) peptides. J Agric Food Chem. 2014;62:427–433.
[3] Abder-Aal E, Hucl P, Miller S, et al. Microstructure and nutrient composition of hairless canary seed and its potential as a blending flour for food use. Food Chem 2011;125:410–416.
[4] US Department of Agriculture, Agriculture Research Service. USDA food composition databases. [Updated October 5, 2016] [cited 2016 Oct 16]. Available from: https://ndb.nal.usda.gov/ndb/nutrients/index

228. French health national survey on poisoning by mushrooms

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Objective: Picking mushrooms remains a traditional activity in France and is responsible for many poisonings each year. The National Institute for Public Health Surveillance and Grand Ouest Poison Center provide a national health monitoring of poisoning by mushrooms identified by all Centres Antipoison et de Toxicovigilance (CAPTV).
Methods: A descriptive study of cases of mushroom ingestion identified from 1 January to 31 December 2014. A case of exposure was determined by ingesting one or more fungi. For each case, severity (according to the Poisoning Severity Score [PSS]), causality and mycotoxic syndrome (defined by the combination of clinical and laboratory signs, determination of the species of fungus and offending/or specific mycotoxin content) were reassessed. A formal identification of species was carried out by referring mycologists (Mycoliste network) when a photograph of the offending mushrooms was available.
Results: In 2014, among 2325 cases of exposure, 2005 cases were included in the study. A mycotoxic syndrome was determined in 772 cases of the 1280 symptomatic cases (Table 1). The syndrome associated with gastrointestinal irritant-containing mushrooms was by far the most common and less severe, comprising 72% of the identified syndromes. With over 50% of high severity (23/39), the amatoxin syndrome remained the most morbid syndrome. For other symptomatic cases, a mycotoxin syndrome could not be assigned due to a lack of evidence or due to a non fungitoxic mechanism involved (bacterial contamination, excessive or raw consumption, individual sensitivity or unknown syndrome). In total 43% of asymptomatic cases (298 of 694) were accidental ingestions by children.
Conclusion: This is the first national series combining systematic syndromic analysis and mycological expertise. Mushroom poisoning remains a public health issue and this national monitoring enables real-time alerting to public authorities for a public information policy and identification of emerging syndromes.

229. Role of superoxide dismutase in severe mushroom poisoning: a case report

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Objective: Mushroom poisoning can occur after mistakes identifying the species. There are various toxins present in mushrooms but cyclopeptide toxins, such as amatoxins, are responsible for the severe hepatic pathogenicity of some species. Recent studies have highlighted correlation between alfa-amantine and lesions induced by oxygen reactive species. They induce a shift in oxidative status promoting oxidative stress. Superoxide dismutase (SOD) has a protective role on liver function and acts as an antioxidant. We present the case of a patient with severe liver toxicity after mushroom ingestion resulting in low SOD concentrations.
Case report: A 41-year-old female was admitted in the Critical Care Toxicology Unit 6 hours after mushroom ingestion exhibiting gastrointestinal manifestations. The mushroom was believed to be *Amanita phalloides*. On admission she presented an altered mental state, abdominal pain, somnolent, with visual hallucination. She had stable hemodynamic and respiratory function. Acute hepatic failure developed 3 days after ingestion. Laboratory data revealed severe hepatic cytolysis (peak aspartate

Table 1. Mycotoxic syndromes determined in cases of mushroom poisoning in France in 2014.

Mycotoxin syndromes	Total ($n = 772$)	PSS1 ($n = 631$)	PSS2 ($n = 105$)	PSS3 ($n = 31$)	PSS4 ($n = 5$)	Intended species	Offending species
Miscellaneous gastrointestinal irritants	557	511	44	2	0	Ceps	*Boletus*
Muscarine poisoning	81	57	20	2	2	Scotch bonnet	*Inocybe* species *Clitocybe* species
Ibotenic acid and muscimol poisoning	46	24	17	5	0	Caesar's mushrooms	*Amanita muscaria*
Psilocybin poisoning	14	3	11	0	0	*Psilocybe* species	
Coprine poisoning	1	0	1	0	0	Shaggy cap	
Amatoxins poisoning	39	12	6	18	3		*Amanita phalloides*
Orellanine poisoning	7	0	3	4	0	Girolles (Chanterelle), false girolles	*Cortinarius* species
Morels neurotoxic syndrome	23	20	3	0	0	*Morchella* species	
Flagellate dermatitis	4	4	0	0	0	*Lentinula edodes*	

aminotransferase (AST) 11,600 U/L; peak alanine aminotransferase (ALT) 8700 U/L), electrolyte imbalance, cholestasis, hyperammonemia and coagulopathy. The superoxide dismutase (SOD) blood concentration on admission was 2800 U/g hemoglobin and daily values were obtained showing a decrease in the 3rd day (1630 U/g hemoglobin). This change was a marker of a decrease in antioxidant defense mechanisms. Management included volemic and electrolytic replacement, gastroprotectants, antiemetics, digestive decontamination, vitamins and diuretics. We also administered antioxidant therapy with SOD capsules 6000 units McCord/Fridovich. Patient evolution was favorable with normalization of clinical and laboratory parameters at 10 days after admission, including the SOD concentration (over 1800 U/g hemoglobin).
Conclusion: Some mushrooms contain toxins which can induce a liver pro-oxidative status with progressive consumption of antioxidant enzymes and a higher vulnerability of liver cells. Supplementary therapy with SOD may help improve the hepatocyte defense mechanisms following toxic injury.

230. QT prolongation in opioid poisoning is mostly due to methadone

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Objective: Drug overdose remains a common cause of death in Australasia. Emergency department (ED) attendance for opioid self-poisoning (deliberate and recreational) has increased considerably over the last decade. This has mirrored increased medical awareness of prolonged QT interval in self-poisoning patients presenting to ED. The QT nomogram is used to risk stratify based on QT interval and heart rate (HR) pair [1]. This study aims to describe the relationship between opioids and QT interval in patients presenting with opioid poisoning. The main outcome was the proportion of opioid overdoses with QT/HR pair above the nomogram line on the electrocardiograph (ECG) at ED presentation.
Methods: Retrospective review of all opioid-poisoned patients presenting to Western Sydney tertiary-referral hospitals from January 2010 to September 2014. ED presentations were identified from the toxicology databases of both hospitals. Baseline QT intervals were measured manually in the 12-lead ECG in multiple leads (i.e., three leads and median QT calculated). The QT intervals were then plotted on the QT nomogram against the heart rate recorded on the ECG.
Results: A total of 117 cases of opioid poisoning were identified, of which 51 involved methadone overdose. In 5 cases, there was a clear breach of the QT nomogram line with methadone featuring in each one of them. Median dose was found to be 100 mg (range 55–180 mg). This group included one case of torsades de pointes (TdP). In another 5 cases, the median QT interval lay exactly on the nomogram line. Once again, methadone featured in 3 cases, median dose of 130 mg (range 50–360 mg) and oxycodone in 2 cases (300 mg and 1100 mg).
Conclusion: In this series, opioids were found to prolong the QT interval in 10 out of 117 cases (9%). This finding was mostly seen in patients who presented with methadone overdose [2]. However, the incidence of developing a life-threatening TdP is rare.

References

[1] Chan A, Isbister GK, Kirkpatrick CM, et al. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM. 2007;100:609–615.
[2] Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. Am J Health Syst Pharm. 2009;66:825–833.

231. Comparison of self-reported recreational substance use with immunoassay and liquid chromatography mass spectrometry findings in cases with acute recreational drug toxicity

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Objective: In cases of acute recreational drug toxicity immunoassay (IA) can be very helpful in providing information about the substance(s) used, especially if no information is available from the patient. Unfortunately these assays, although quick and easy to use, can give false positive/negative results due to the unspecificity of the antibodies used. Novel psychoactive substances cannot be detected in most cases, typically because of missing cross reactivities, and other additional methods such as liquid chromatography mass spectrometry (LC-MS/MS) have to be used to detect these compounds. The aim of this study was to compare self-reported substances to those detected with IA and LC-MS/MS in the same patient.
Methods: The study was conducted at the University Hospital of Basel, Switzerland, between October 2013 and July 2016 and within the Euro-DEN project. All cases presenting with acute recreational drug toxicity where IA and LC-MS/MS data were available were included.
Results: During the study period there were 141,605 emergency department attendances of which 611 were directly related to acute drugs of abuse toxicity. Analytical confirmation with IA and LC-MS/MS was available in 248 cases. Among the cases with the most commonly self-reported substances (cocaine $n = 89$; cannabis $n = 46$; amphetamines $n = 45$; benzodiazepines $n = 30$; heroin $n = 27$), agreement between IA and LC-MS was high for cocaine, methadone and heroin (97.8%, 90.9%, and 88.9%, respectively). The lowest agreement was seen for amphetamine-like substances (77.8%), where LC-MS/MS detection was positive in 8 cases and IAs in 2 cases. In cases with self-report of an unknown substance ($n = 29$) the most commonly detected substances were amphetamines (both IA and LC-MS/MS positive in 8 cases, LC-MS/MS only in 4 cases). In cases without self-reported substances (e.g., in unconscious or uncooperative patients, $n = 27$), the most commonly detected substance was cocaine (both methods positive in 17 cases, LC-MS/MS only positive in 1 case). In cases with a positive IA for amphetamines ($n = 48$) further identification of the exact substance(s) used was possible with LC-MS/MS: amphetamine $n = 22$; methamphetamine $n = 4$; MDMA $n = 30$. The use of more than one substance was demonstrated in some cases. Furthermore, the LC-MS/MS result was positive in 22 cases with a negative IA for amphetamines (amphetamine $n = 15$; methamphetamine $n = 4$; MDMA $n = 6$; MDA $n = 1$; 2C-B $n = 1$).

Conclusion: While IAs were accurate for testing for substances such as cocaine and opioids, LC-MS/MS analysis demonstrated advantages regarding novel substances and the detection and differentiation of amphetamine-related substances.

232. Prognostic utility of initial lactate for Emergency Department (ED) drug overdose fatality: a validation cohort

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Objective: We aimed to externally validate our previous findings [1] that the initial ED lactate has prognostic utility for in-hospital mortality from acute drug poisoning.
Methods: This was an observational, prospective, cohort study over 5 years at two urban teaching hospitals. Subjects were consecutive adult (>18 years) ED acute drug overdose patients; we excluded children, prehospital cardiac arrest, alternative diagnoses, non-drug overdose, and missing data. Demographics, history, vitals, and drug exposures were obtained from medical records using standardized data abstraction. Initial lactate was drawn as part of clinical care by ED clinicians, and used for receiver operating characteristics (ROC) to determine optimal lactate cut points. The primary outcome was inpatient fatality, and the secondary outcome was occurrence of shock (vasopressor requirement).
Results: Out of 3739 patients screened, 2333 met exclusion criteria (1,487 missing lactate, 376 children, 278 missing outcomes, 141 alternate diagnoses, 37 non-drugs, 14 prehospital arrests), leaving 1406 patients for analysis (56% female, mean age 43.1 years). Of these 54 patients had shock (3.9%), and 24 died (1.7%). Mean initial lactate (mmol/L) was 8.1 ± 5.6 for fatalities and 2.4 ± 6.7 for survivors ($p < .001$). The ROC area under the curve for prediction of fatality was 0.85 (CI 0.73–0.95). The optimal lactate cut point for fatality was 5.0 mmol/L (OR 34.2, CI 13.7–84.2) and the occurrence of either shock or death was 2.7 mmol/L (OR 7.9, CI 4.5–13.9). Initial lactate under 2.0 mmol/L had 99.5% negative predictive value (CI 98.8–99.9). Optimal prognostic lactate cut points for common drug classes are outlined in the Table 1.
Conclusion: Lactate should be used as a biomarker for early decision-making in ED patients with acute drug overdose; the highest prognostic utility was for salicylates, sympathomimetics, and paracetamol.

Table 1. Initial ED lactate prognostic utility for overdose fatality according to selected drug classes.

Drug class	AUC[a]	Optimal cut point[b]	Sensitivity/specificity of cut point
All classes combined	0.85	5.0 mmol/L	70.8%/93.3%
Salicylates	0.98	6.0	100/96.7
Sympathomimetics	0.98	7.8	100/96.3
Paracetamol	0.98	10.0	100/95.3
Opioids	0.97	3.1	100/86.5
Digoxin	0.92	2.4	100/86.7
Anticonvulsants	0.91	3.0	100/80.4
Antipsychotics	0.83	3.0	100/83.2
Antidepressants	0.79	3.0	75/80.9
Benzodiazepines	0.78	8.7	62.5/98.5
Beta-/Calcium channel blocker	0.73	7.1	57.1/94.2
Diuretics	0.55	1.1	100/40.0
ACE Inhibitor or ARB	0.16	0.9	100/12.0

AUC: area under the curve; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker.
[a]Based on ROC analysis.
[b]Defined as the point that maximizes the sum of sensitivity plus specificity.

Reference

[1] Manini AF, Kumar A, Olsen D, et al. Utility of serum lactate to predict drug-overdose fatality. Clin Toxicol. 2010;48:730–736.

233. Does targeted temperature management improve hospital survival for presumed drug overdose-related cardiac arrest?

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Objective: Drug overdose is the leading cause of non-traumatic out-of-hospital cardiac arrest (OHCA) among young adults [1] but there is limited data regarding the efficacy of targeted temperature management (TTM) among this population. Theoretically, TTM may worsen overdose-related survival through slowed drug metabolism. This study investigates the effect of TTM among presumed overdose-related cases of cardiac arrest.
Methods: We performed a retrospective chart review of all cardiac arrests that presented to the emergency department (ED) at an urban tertiary care hospital from January 2011 to September 2015. Patients aged ≤50 years were eligible, and primary traumatic, respiratory or cardiac etiology (e.g., ST segment elevation myocardial infarction [STEMI])) arrests were excluded, resulting in presumed overdose-related cardiac arrests. Variables explored included demographic data, ED versus OHCA cardiac arrest, initial arrest rhythm, use of 20% fat emulsion therapy, and ED mortality. The primary outcome was in-hospital survival, and the secondary outcome was in-hospital duration of survival (DOS) in days. TTM was carried out with a combination of the Arctic Sun device, refrigerated crystalloid and antipyretics for a goal temperature of 33 °C, maintained for 24 hours. In April 2014 the goal temperature was set to 36 °C. The decision to start TTM was made by the primary clinical caretakers of each patient.
Results: In total 923 cardiac arrests were eligible; there were 195 patients ≤50 years old, of which 24 respiratory, 32 traumatic, and 5 cardiac etiologies were excluded, leaving 134 patients with presumed drug overdose-related cardiac arrest (14.5%). Most arrests were OHCAs (89%), median age was 41 years, 73.9% were male, and the most common rhythm was asystole (53.7%). Overall 39 (29.1%) patients survived their ED course; 35/39 survivors (89.7%) received TTM. Among all presumed overdose-related arrests the average DOS was 6.04 days (23.0 DOS among survivors); 14 patients (35.9% of survivors) survived to hospital discharge. TTM conferred an almost 10-fold increased odds of survival among the entire cohort (OR 9.5, 95% CI 2.8–32.8, $p < .001$) and had a clinically but not statistically significant improvement in mean DOS (12.9 versus 3.6 days, $p = .14$). OHCA had a 77% decreased odds of hospital survival compared to in-hospital arrest (OR 0.23, 95% CI 0.06–0.86, $p = .019$). There was no survival among any patient that received lipid resuscitation ($p = .49$); these patients also had significantly shorter mean DOS (0 versus 6.23 days, $p = .033$).
Conclusion: Among presumed drug-overdose related cardiac arrests, TTM was associated with a significantly higher chance of in-hospital survival and clinically significant increase in mean in-hospital DOS.

Reference

[1] Deasy C, Bray JE, Smith K, et al. Out-of-hospital cardiac arrests in young adults in Melbourne, Australia. Resuscitation. 2011;82:830–834.

234. Pharmacokinetics and pharmacodynamics of two doses of oral LSD in healthy subjects

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Objective: Lysergic acid diethylamide (LSD) is used recreationally and in clinical research. The aim of the present study was to characterize the pharmacokinetics and exposure-response relationship of representative oral doses of LSD.
Methods: We conducted two placebo-controlled, double-blind, cross-over studies using oral administration of 100 and 200 µg LSD in 24 and 16 subjects, respectively. Plasma concentrations of LSD, subjective effects and vital signs were repeatedly assessed. Pharmacokinetic parameters were determined using compartmental modeling. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling.
Results: Geometric mean (95% confidence interval) C_{max} values of 1.3 (1.2–1.9) and 3.1 (2.6–4.0) ng/mL were reached 1.4 and 1.5 hours after administration of 100 and 200 µg LSD, respectively. The plasma half-life was 2.6 hours (2.2–3.4). The subjective effects lasted (mean ± SD) 8.2 ± 2.1 and 11.6 ± 1.7 hours for the 100 and 200 µg LSD doses, respectively. Subjective peak effects were reached 2.8 and 2.5 hours after administration of 100 and 200 µg LSD, respectively. A close relationship was observed between the LSD concentration and subjective response within-subjects, with moderate counter clockwise hysteresis. The half maximal effective concentration EC_{50} values were in the range of 1 ng/mL. No correlations were found between plasma LSD concentrations and its effects across subjects.
Conclusion: The present pharmacokinetic data are important for the interpretation of LSD intoxication. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination up to 12 hours. The effects of LSD were related to changes in plasma concentrations over time, with no evidence of acute tolerance.

235. Relationship between poison center opioid exposure data and mortality rates and National Vital Statistics System mortality rates

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Objective: Over the past 25 years, increased therapeutic use of prescription opioids has led to an epidemic of opioid abuse, diversion, and overdose throughout the USA [1]. Much of the data surrounding deaths due to opioid overdose is provided by the Centers for Disease Control and Prevention (CDC) National Vital Statistics System (NVSS) [2]. However, this data is often delayed and may not be able to discriminate between licit and illicit forms of opioids. Data from poison centers (PCs) are reported in real-time and have more detailed information regarding substances involved. Our objective was to compare opioid exposure and mortality rates between PC and NVSS data.
Methods: Trends over time were evaluated for the Research, Abuse, Diversion and Addiction Related Surveillance (RADARS®) system PC Program exposures and direct deaths and the NVSS multiple cause-of-death mortality files for natural and semisynthetic opioids, synthetic opioids, and methadone from 2003 through 2015. Rates were calculated per population, and Pearson correlation coefficients were calculated comparing PC with NVSS rates.
Results: PC exposure and mortality rates peaked for natural and semisynthetic opioids in 2010 (15.58 and 0.68 per 100,000, respectively), synthetic opioids in 2010 (1.66, 0.01), and methadone in 2007 (1.46, 0.02). NVSS mortality rates peaked for natural and semisynthetic opioids in 2014 (3.81 per 100,000), synthetic opioids in 2014 (1.74), and methadone in 2007 (1.83). PC opioid exposure and mortality rates correlated with NVSS mortality rates for natural and semisynthetic opioids ($r = 0.83$, $r = 0.67$) and methadone ($r = 0.83$, $r = 0.47$). These rates also correlated well for synthetic opioids through 2014 ($r = 0.83$, $r = 0.61$) but diverged from 2012 to 2014 ($r = 0.64$, $r = 0.14$).
Conclusion: Trends in PC opioid exposure and mortality rates track well with trends in NVSS mortality rates, however PC data may be more timely and better able to discriminate between specific types of opioids and specific products. The time frame where the synthetic opioid mortality rates diverged drastically from 2012 through 2014 coincides with the marked increase in illicit fentanyl abuse. NVSS data is unable to differentiate between illicit fentanyl and prescription fentanyl, and likely overestimates the mortality rate associated with prescription synthetic opioids compared to PC data.

References

[1] The DAWN Report: Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. SAMHSA, 2014. [cited 2016 Oct 20]. Available from: http://archive.samhsa.gov/data/2k13/DAWN127/sr127-DAWN-highlights.htm
[2] Rudd RA, Aleshire N, Zibbell JE, et al. Increases in drug and opioid overdose deaths – US, 2000–2014. Morb Mortal Wkly Rep. 2016;64:1378–1382.

236. Tramadol poisoning in the intensive care unit: clinical presentation and prognostic value of plasma tramadol concentration on admission

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Objective: Tramadol poisonings are increasing significantly due to the increase in prescriptions since dextropropoxyphene was withdrawn from the European market in 2011. Tramadol-related analgesic effects are mediated by its antagonist activity on the norepinephrine and serotonin transporters in addition to the

agonist activity of its major active metabolite M1 on the mu-opioid receptors. Thus, tramadol overdose may result in various toxic effects including central nervous system depression, seizures and serotonin syndrome. The relative prevalence of each of these complications is debated. We aimed to describe the clinical features in tramadol-poisoned patients and to study the prognostic value of the plasma concentration of tramadol and its metabolites on intensive care unit (ICU) admission.

Methods: We conducted a prospective single centre observational study including all tramadol-poisoned patients admitted to the ICU from 2012 to 2016. The plasma concentrations of tramadol and its metabolites were determined using high-performance liquid chromatography coupled to mass spectrometry. Subgroup comparisons were performed using chi-squared and Mann–Whitney tests.

Results: Forty-two tramadol-poisoned patients were included. The demographics included age 41 years [26; 55], median [25; 75 percentiles] with 30 females and 12 males. Most cases (90%) involved poly-intoxications. The presumed ingested dose of tramadol was 2000 mg [1,000; 4,000] and the plasma tramadol concentration on admission was 1.48 mg/L (1.17; 2.34). The patients presented consciousness impairment (Glasgow Coma Scale 13 [6; 15]), opioid syndrome (48%), serotonin syndrome (36%) and seizures (24%). Life-threatening complications occurred including prehospital cardiac arrest (10%), cardiovascular failure (31%), aspiration pneumonia (34%), disseminated intravascular coagulation (5%) and fatality (7%). There was a significant relationship between plasma tramadol concentration measured on admission and the risk of seizure onset ($p < .05$). Patients presenting opioid syndrome on admission had significantly lower plasma tramadol concentrations on admission than patients presenting with serotonin syndrome ($p < .03$).

Conclusion: Tramadol poisoning may result in significant morbidities requiring invasive ICU management. Onset of seizures is not related to serotonin syndrome. Measurement of the concentrations of tramadol and its metabolites on ICU admission seems helpful to predict the kind of toxic syndromes presented and the nature of further complications.

237. Pack size restriction of mild analgesics sold as over-the-counter drugs in pharmacies in Denmark: preliminary register findings

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Objective: Mild analgesics are sold in all European countries, and some countries have observed increased contact with emergency departments due to overdose by these agents, especially paracetamol [1]. There is significant evidence that restricting access to means is an effective suicide prevention strategy [2], and moreover controlling availability of analgesics has proven to be effective [3]. The aim of the study was to investigate changes in numbers and rates of overdose before and after the pack size restriction on mild analgesics sold over-the-counter (OTC) in pharmacies in Denmark implemented in September 2013, and secondly to investigate potential substitution of self-harming agents.

Methods: A national register study in a pre-post design. The study population consisted of all Danish citizens registered with an overdose from 2011 to 2015 (ICD-10 codes T39, X60, X64 and T43). This abstract is focused on the 27 months pre- and 27 months post-legislative changes.

Results: We found a significant decrease in the rate of hospital contacts for T39 overdoses; the rate was 42.2 (95% CI 41.1–43.4) per 100,000 person-years during the period prior to the legislative change and 17.1 (95% CI 16.4–17.8) per 100,000 after. Similar findings were observed for the X60 and X64 codes with rates of 3.5 (95% CI 3.2–3.8) per 100,000 prior to the intervention decreasing to 2.0 (95% CI 1.9–2.3) per 100,000 and 2.0 (95% CI 1.7–2.2) to 1.0 (9% CI 0.8–1.2) per 100,000, respectively after implementation. Rates of the diagnosis involving T43 (psychotropic medication) significantly decreased. The rate of overdose by T43 was 35.7 (95% CI 34.6–36.7) per 100,000 before the restriction compared to 25.2 (95% CI 24.3–26.0) after, indicating that the decrease in non-opioid analgesics rates was not replaced by psychotropic medication.

Conclusion: Our study supports pack size restriction as an effective method in relation to accidental as well as intentional overdoses by non-opioid analgesics. In addition we demonstrated a significant decrease in poisonings with psychotropics in the study period, indicating that these agents are not used as replacement.

References

[1] Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: worldwide patterns of use and misuse. Suicide Life Threat Behav. 2000;30:313–326.

[2] Yip PS, Caine E, Yousuf S, et al. Means restriction for suicide prevention. Lancet. 2012;379:2393–2399.

[3] Zalsman G, Hawton K, Wasserman D, et al. Suicide prevention strategies revisited: 10-year systematic review. Lancet Psychiatry. 2016;3:646–659.

238. Seasonality in intentional drug intake by adolescents

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Objective: Suicides and suicide attempts have been reported to occur more often during spring and autumn. Analyses of the US National Poison Database System suggest that suicide attempts are more common on certain days of the week or year. Moreover, psychiatrists have hypothesized that stress related to school might influence suicidal behaviour among adolescents.

Methods: All drug intakes reported to the Dutch Poisons Information Center (DPIC) between 2006 and 2015 were retrospectively analysed, using mixed models for repeated data. The "intentional" nature of drug ingestions has only been registered in our system since 2013, hence we performed two analyses: intentional drug ingestions between 2013 and 2015, and moderate and severe cases of intoxications with ibuprofen or paracetamol between 2006 and 2015. Ibuprofen and paracetamol cases were chosen as a "proxy" for intentional intoxication, as they represented 28% of the suicide attempts between 2013 and 2015.

Results: From 2013 to 2015, no seasonality was observed regarding all intentional cases. However when considering the subgroup of 13–17-year-old patients, significantly less intentional intakes occurred in July and August compared to other months. Similarly, between 2006 and 2015, significantly less moderate and severe intoxications with ibuprofen and paracetamol occurred amongst adolescents in July and August. The number of non-school days and the number of moderate and severe ibuprofen and paracetamol intoxications in this age group were significantly and inversely related. Moderate and severe ibuprofen and paracetamol intoxications occurred most often on Tuesdays and Wednesdays and less often on Saturdays and Sundays amongst adolescents. Amongst adults (18–65 years), they occurred most often on Monday, Tuesday and Wednesday and less often on Saturday and Sunday, although differences were less pronounced than in adolescents.
Conclusion: In the Netherlands, the number of intentional ingestions by adolescents (13–17 years) is lowest during July and August. In this period, most adolescents are on holiday for 6 weeks, which might suggest school to be one of the environmental factors influencing the occurrence of intentional intoxications. This is further underpinned by the inverse relationship between non-school days and self-intoxications, and the observation that self-intoxications occur less often during the weekends. Our data support the hypothesis by some psychiatrists that stress related to school might influence suicidal behaviour among adolescents.

239. Caustic ingestion in children: experience of a Pediatric Emergency Department in Rome

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Objective: The ingestion of corrosive and irritant substances among children mostly occurs accidentally. The aim of this study is to describe the pediatric population treated according to internal validated guidelines for caustic ingestion, and to evaluate the relationship between symptoms and lesions found during esophagogastroduodenoscopy (EGD).
Methods: Pediatric patients admitted to the Emergency Department for suspected or confirmed ingestion of caustics (including laundry pods [LP]) were retrospectively evaluated during an 11-year period (2005–2016). All hospitalized cases were assessed for age, product, symptoms, treatment and outcome and scored according to Zargar's grading [1]. Grade 2 patients on EGD received a proton pump inhibitor (PPI), grade 3 received PPI, dexamethasone and antibiotic therapy.
Results: A total of 282 patients (mean age 3.2 years, range 3 months to 17 years; 54% male) were evaluated. An alkaline product was ingested in 176 cases (63%), an acid in 55 (19%), a LP in 45 (16%) and was unknown in 6 cases (2%). On admission 45% of cases were asymptomatic. Gastrointestinal signs were present in 55% with vomiting (41.6%), excessive salivation (22.4%), retrosternal pain (6.4%), dysphagia (3.8%) and oral cavity lesions (71%). EGD was performed on 134 patients (47.5%) between 12 and 24 hours after ingestion in both asymptomatic and symptomatic children. Of these 37.5% were positive for lesions. In the alkali group ($n = 88$), 37 (42%) patients had lesions: 12 grade 1, 13 grade 2 and 12 grade 3. In the acid group ($n = 27$), nine (33.3%) patients had lesions: 4 grade 1, 3 grade 2 and 2 grade 3. In the LP group ($n = 16$) only 2 patients had lesions: one grade 1 and one grade 2, of which one needed intubation for respiratory distress. In the unknown product group, one patient presented with grade 2 lesions. A follow-up EGD at four weeks was performed in all 32 cases presenting grade 2 or 3. In symptomatic patients 8 presented with stenosis and 3 with esophagitis, while asymptomatic patients had no late complications.
Conclusion: Alkaline substances are more harmful than acid products and exposure occurs more frequently. In our experience LPs rarely cause injuries and do not result in severe long-term complications. Also, in pediatrics the lack of symptoms does not always correspond to the absence of lesions in the gastrointestinal tract.

Reference

[1] Zargar SA, Kochhar R, Mehta S, et al. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. Gastrointest Endosc. 1991;37:165–169.

240. Drug-facilitated crimes (DFC): four years of admission in a French emergency medico-legal center specializing in victims of assaults

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Objective: To determine the characteristics of victims of drug-facilitated crimes (DFCs) reported in a French emergency medico-legal center specializing in victims of assaults (CAUVA) in Bordeaux University Hospital.
Methods: Epidemiological, observational, retrospective and monocentric study, based on the victim's medico-legal records. Inclusion criteria: victims of violence suspected of DFC admitted to CAUVA between 1 January 2011 and 31 December 2014 in whom toxicology samples (blood, urine, hair) were taken. Variables: victim demographics, circumstances of the aggression, consultation in CAUVA (delay between aggression and consultation, complaints, clinical examination), and toxicology tests (cannabis, alcohol, psychoactive drugs, gammahydroxybutyrate [GHB] and derivatives). Each case was classified as plausible DFC (documented aggression + psychoactive substance confirmed + consistent chronology), possible DFC (suspected assault or insufficient clinical data or negative toxicology result) or "chemical vulnerability" (voluntary use of substances which weakened the victim, making her vulnerable to aggression) according to the definitions of the French National Agency for Medicines and Health Products Safety (ANSM).
Results: Overall 305 patients (259 female, 46 males, mean age 27 years) met the inclusion criteria. Blood, urine and hair samples were analyzed on demand by magistrates ($n = 56$, 18.4%). The 249 remaining samples were not considered useful for the investigations. The typical victim of DFC was a woman (85%) aged 18–44 years (63%), sexually assaulted during a weekend party (52%). She did not know her assaulter, and after the assault she went first to the police (59%) before being sent to the CAUVA. Main clinical data were anterograde amnesia and fainting, and more injuries following resistance to the aggressor were noted rather than sexual wounds. Median delay between drug intake

and sampling was 23 hours. Toxic drugs were used alone ($n = 24$, 42.8%), mainly alcohol (27%) or a benzodiazepine (9%) or in association ($n = 25$, 44%) with mainly alcohol plus cannabis (44%) or alcohol plus a benzodiazepine (20%). In 7 victims toxicological analyses were negative. Ten cases of plausible DFCs were identified (17.9%) with alcohol and benzodiazepines as main psychotropic substances, 17 possible cases (30.9%) were isolated and associated with a majority of negatives toxicological analyses, and 29 chemical vulnerabilities (51.8%) associated with alcohol intoxication alone or alcohol plus cannabis.
Conclusion: DFCs occurred in people who make themselves vulnerable by absorbing drugs during parties. There is a major role for educating potential victims on the risks of such behaviour.

241. Severe poisonings and their outcomes reported to the National Poisons Information Service (NPIS), 2008–2015

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Objective: To analyse patient-related exposures reported to the National Poisons Information Service (NPIS) by telephone from 2008 to 2015 using the Poisons Severity Score (PSS) as a measure of severity. Of particular interest was whether there has been any change in the occurrence of enquiries concerning severe poisonings over this time.
Methods: A retrospective analysis of patient-related poisoning events reported to NPIS and recorded on the UK Poisons Information Database (UKPID) between 2008 and 2015. PSS is an ordinal severity scale which scores clinical features as none (0), minor (1), moderate (2) or severe (3) [1]. PSS was assigned at the time of each enquiry. The NPIS performs follow up of severe cases as part of its operational protocol. Chi square tests were used to compare proportions; p values less than .05 were considered significant.
Results: The proportion of "severe," PSS3, enquiries received each year remained fairly steady. However, there has been an increase in the number and proportion of enquiries concerning severe cases which have a fatal outcome ($p < .001$), despite falling call numbers. The increasing proportion of fatal outcomes shows an approximately linear trend ($R^2 = 0.77$).
Conclusion: The NPIS receives approximately 800 enquiries relating to severely poisoned patients per year and also provides information via its online service Toxbase®. Although enquiries about patients with severe features have remained relatively constant both in absolute numbers and as a proportion of the yearly total enquiries, the numbers of severe cases with a fatal outcome has increased. This suggests that there has been a qualitative change in the type of telephone enquiry received by the NPIS in recent years.

Reference

[1] Persson HE, Sjöberg JK, Haines JA et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.

242. Emergency Department presentations with illicit drugs associated with problematic drug use (iPDU) toxicity are not commonly associated with co-use of new psychoactive substances (NPS)

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Objective: There has been increasing interest in the use of new psychoactive substances (NPS) together with illicit drugs potentially associated with problematic drug use (iPDU); the aim of this study was to investigate the prevalence of use of NPS in patients presenting to the ED with acute iPDU toxicity.
Methods: The Euro-DEN Plus project collects longitudinal data from 16 sentinel centres in 10 European countries on ED presentations with acute recreational drug toxicity. The Euro-DEN Plus database was searched October 2013–September 2015 for presentations involving an iPDU (buprenorphine, crack cocaine, fentanyl, heroin or methadone) with and without an NPS.
Results: Over the 2 years, there were 10,956 Euro-DEN Plus presentations; 30.0% involved the use of an iPDU and 10.7% involved the use of an NPS. Of the 3288 presentations involving an iPDU, co-use of an NPS occurred in only 67 (2.0%). These iPDU/NPS presentations occurred most commonly in Munich ($n = 35$, 52.2%) and Dublin ($n = 22$, 32.8%). The most common iPDUs in the iPDU/NPS presentations were heroin ($n = 28$, 41.2%) and methadone ($n = 27$, 40.3%); the most common NPS were mephedrone ($n = 25$, 37.3%) and MDPV (3,4-methylenedioxypyrovalerone; $n = 16$, 23.9%). The NPS used in iPDU presentations were centre specific: Munich, predominately cathinones ($n = 28$, 80.0%); Dublin, only mephedrone ($n = 22$,100%); London STH,

Table 1. Severe poisonings and their outcomes reported to the National Poisons Information Service (NPIS), 2008 to 2015.

Year	Number of enquiries classified as PSS3	Total number of patient-related enquiries	Proportion of enquiries classified as PSS3	Number of enquiries classified PSS3 with a fatal outcome	Proportion of enquiries classified PSS3 with a fatal outcome
2008	803	53704	0.01495	45	0.000838
2009	755	53852	0.01402	48	0.000891
2010	810	50349	0.01609	43	0.000854
2011	828	47064	0.01759	71	0.001509
2012	801	48793	0.01642	65	0.001332
2013	819	51593	0.01587	72	0.001396
2014	809	47447	0.01705	66	0.001391
2015	741	47011	0.01576	87	0.001851

predominately synthetic cannabinoid receptor agonists (SCRAs: 5, 62.5%). There were 10 centres in which there were no iPDU presentations associated with the co-use of NPS; in two of these centres, NPS were involved in a significant proportion of all presentations (London KCH [14.9% NPS across all presentations] and York [30.1% NPS presentations]). The median (IQR, range) age in the iPDU/NPS presentations was 33 (28–36, 21–46) years and 58.2% were male. The median (IQR, range) age for the lone iPDU presentations was 43 (29–43, 15–69) years and 78.5% were male. The median (IQR) length of stay in iPDU/NPS presentations was 5 hours 24 minutes (3 h 8 min–9 h 42 min); in the lone iPDU presentations it was 13.5 hours (3 h 56 min–37 h 41 min).
Conclusion: The co-use of NPS in acute iPDU toxicity ED presentations was uncommon in this study and was very centre specific, this is despite there being a high prevalence of both iPDU and NPS presentations overall in the Euro-DEN Plus project. Where co-use does occur, the pattern of co-used NPS varies across Europe and therefore harm reduction strategies need to be tailored based on local presentation patterns.

243. Impact of online toxicology training on health professionals: the Global Educational Toxicology Uniting Project (GETUP)

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Objective: The Global Educational Toxicology Uniting Project (GETUP), supported by the American College of Medical Toxicology, links countries with and without toxicology services via distance education with the aim to improve education [1]. Due to the lack of toxicology services in some countries there is a knowledge gap in the management of poisonings. We describe our experience with the worldwide delivery of an online introductory toxicology curriculum to emergency doctors and other health professionals treating poisoned patients.
Methods: We delivered a 15-module introductory Internet-based toxicology curriculum to emergency doctors and health professionals. We describe preliminary data collected from August to September 2016. This Internet-based curriculum was adapted from one used to teach emergency residents toxicology in the USA. The curriculum was supplemented with regionally-relevant topics (organophosphate and paraquat) adapted from Wikitox. Modules covered themes such as pharmaceutical ($n = 8$), toxidromes ($n = 2$) and agrochemical ($n = 5$) poisoning. Participants completed 80 pretest and 80 post-test multiple choice questions (MCQ) before and after completing the online module, respectively, throughout the course. We collected information on participant demographics, education and training, and perception of relevance of the curriculum.
Results: One hundred and ninety-seven health professionals from 37 countries participated in the course: 159 emergency doctors/medical officers, 30 physicians, three pharmacists, two toxicologists, two medical students and one nurse. Median age of participants was 33 years. Median number of years postgraduate was six. Seventy-five (38%) of participants were currently enrolled in a postgraduate degree course. One hundred and seventy (85%) had access to either a poisons information centre over the telephone or toxicologist and thirty (15%) did not. All participants expected the course to help improve their knowledge. From the preliminary results, median pre-module MCQ scores for the first eight modules were 60% (95% CI 40,78%) compared to median post-module MCQ scores of 89% (95% CI 75,100%) ($p < .0001$).
Conclusion: Our participants demonstrated an increase in medical knowledge based on performance on MCQs. An online toxicology curriculum is an effective way to deliver education to health professionals treating poisoned patients and can help bridge the knowledge gap in developed and developing countries.

Reference

[1] Wong A, Vohra R, Ruha AM, et al. The Global Educational Toxicology Uniting Project (GETUP): an analysis of the first year of a novel toxicology education project. J Med Toxicol. 2015;11:295–300.

244. Sliding drugs: a co-production by a Poison Centre and School of Cinema for preventing NPS use by teenagers

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Objective: The abuse of new psychoactive substances (NPS) (e.g., synthetic cannabinoids and cathinones, phenethylamines, ketamine analogues) has increased in the last 10 years, especially among young people. Despite the widespread use, adolescents are poorly and mistakenly informed regarding NPS and their acute and chronic severe toxic effects. Our objective was to improve a NPS preventive/informative action targeted at adolescents (15–18 years) with an appropriate and effective language: the modality of film-documentary.
Methods: In an 11 month period (October 2015 to September 2016), a collaboration between the Pavia Poison Control Centre (PPCC) and the Milan School of Cinema was undertaken. The film-documentary was intended for a teenage (15–18 years) public. Scientific items identified by the PPCC were: some of the classes of NPS (synthetic cannabinoids, synthetic cathinones, phenethylamines, ketamine analogues), the mechanisms of action, and the main acute and chronic toxic effects. Artistic and technical aspects related to the production and managed by the School of Cinema were: screenplay, language, setting and editing. A close collaboration (training, meetings) between the PPCC and the School of Cinema allowed us to achieve the scientific goal with a proper and effective language.
Results: The final product was a 20 minute film-documentary titled "Sliding drugs", telling a journey of a boy across subway wagons representing the NPS-world. Scientific items were adapted to the targeted public to simplify the message. We chose narrative language not just to inform, but to show NPS effects.
Conclusion: Alternative means of disseminating knowledge is needed to reach the target population with these messages on the toxic effects and risks of NPS use. This final product is an easy to use prevention tool.

245. Can duration of hemodialysis be estimated based on the on-arrival laboratory tests and clinical manifestations in methanol-poisoned patients?

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Objective: We aimed to evaluate the efficacy of the Lachance formula [1] and more readily available clinical or laboratory factors (other than serum methanol concentration) in the prediction of the time required for hemodialysis (HD) in methanol-poisoned patients.
Methods: In a retrospective cross-sectional study, all patients who were referred to us between March 2008 and March 2016, hospitalized with diagnosis of methanol toxicity and had undergone hemodialysis were enrolled. A questionnaire collected information on: demographic characteristics, time elapsed between ingestion and hospital presentation, signs and symptoms on presentation, on-arrival vital signs, biochemistry and venous blood gas analysis, number of the dialysis episodes and total duration of dialysis, place the dialysis was performed, cause of repetition of dialysis (persistent acidosis, persistent visual disturbances, and methanol concentration greater than 20 mg/dL after the first session of HD), methanol concentration on presentation, time estimated for hemodialysis based on the Lachance formula, hospitalization period, and patients' final outcome (death versus survival). The patients were assigned one of two groups: those who were dialyzed adequately based on the formula estimation and those who were over- or underestimated based on the formula. Total duration of dialysis (in one or two sessions of HD) was also calculated. The patients were then evaluated to see if the formula could reliably predict duration of dialysis. In the next phase, we searched for other factors that could prognosticate the duration of HD.
Results: Of 72 patients enrolled, 54 underwent hemodialysis once (group 1) and 18 needed more than one session of hemodialysis (group 2). All were treated with ethanol, bicarbonate and leucovorin (folinic acid). The Lachance formula overestimated the patients with higher methanol concentrations and underestimated those with lower methanol concentrations. It properly predicted the time required for hemodialysis when the methanol concentration was between 15 and 25 mg/dL. After performance of logistic regression analysis, creatinine was the only factor that significantly predicted the time needed for HD ($p = .02$). Median creatinine concentrations were 1.3 [1, 6, 0.8–2.7) and 1.4 [1.35, 2.1, 0.8–6.5) in the patients who were dialyzed once and twice, respectively.
Conclusion: Creatinine is possibly a readily available test that can predict the appropriate time required for hemodialysis in methanol-poisoned patients.

Reference

[1] Lachance P, Mac-Way F, Desmeules S, et al. Prediction and validation of hemodialysis duration in acute methanol poisoning. Kidney Int. 2015;88:1170–1177.

246. Emergency anesthetic management of dapsone-induced methemoglobinemia: a case report

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Objective: Dapsone represents a therapeutic alternative for patients diagnosed with panniculitis. Methemoglobinemia (MetHb) is a potentially serious adverse reaction in dapsone-treated patients. A MetHb concentration exceeding 40% is associated with coma and 70% or more can be lethal. The diagnosis and early treatment of MetHb is essential for proper anesthetic management.
Case report: We report a case of a 38-year-old female who was transferred from a Rheumatology Department into our Intensive Care Unit. She had been diagnosed with Weber-Christian's disease (idiopathic lobular panniculitis) over 14 years previously, which had required dapsone 100 mg daily for one month. On hospital admission, the patient presented severe dyspnea, marked fatigue, peripheral cyanosis and significant metrorrhagia. The initial examination showed an altered clinical state, tachypnea with orthopnea, vesicular murmur at pulmonary auscultation, decreased oxygen saturation, tachycardia and normal urinary output. Laboratory investigations revealed a MetHb concentration of 38% and normocytic normochromic anemia with a hemoglobin of 4.8 g/dL. Based on both clinical and biological investigations, we could rule out acute myocardial infarction, acute cardiac insufficiency or a thromboembolic event. Our medical team initiated electrolyte rebalancing, oxygen therapy, erythrocyte mass transfusion, gastric protection, diuretic agents, corticotherapy, vitamin supplementation and targeted therapy, including methylene blue (2 g per day), N-acetylcysteine (900 mg per day) and high dose of ascorbic acid (2 g per day), with rapid favorable evolution regarding MetHb concentration and respiratory function. A hysterectomy under general anesthesia was performed. Due to the long half-life of dapsone (up to 72 hours) and the possibility of rebound methemoglobinemia we decided to maintain mechanical ventilation. Indeed, the patient experienced a high concentration of MetHb 6 hour post-intervention despite continuous methylene blue infusion but she had recovered at 48 hours, enabling extubating and she was discharged on the 8th day.
Conclusion: As methemoglobinemia can occur with standard dapsone dosage, regular monitoring is required. The present case report emphasizes the importance of diagnosis and aggressive treatment of methemoglobinemia, particularly when a subsequent surgical intervention is necessary, in order to wisely choose the time window when the patient may survive an anesthetic procedure. Maintenance of mechanical ventilation and antidote administration may need to be continued after surgery because of MetHb rebound and respiratory failure.

247. Fetal deaths as reported to the USA National Poison Data System, 2011–2015

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Objective: There is a scarcity of literature reporting toxicologic exposures in pregnancy resulting in fetal death. Our objective

was to provide a descriptive analysis of cases resulting in fetal death as reported to the US National Poison Data System (NPDS).
Methods: A retrospective analysis was performed on all cases involving fetal death recorded in the US NPDS database from 2011 to 2015. Data points collected included maternal age, fetal gestational age, chronicity of exposure, substance of exposure, presence of co-ingestants, reason for exposure (e.g., intentional), use of gastrointestinal (GI) decontamination techniques, use of enhanced elimination techniques, and corresponding maternal outcome.
Results: There were 25 fetal deaths reported to US NPDS from 2011 to 2015. Of those, 10 (40%) were directly related, and 11 (44%) were potentially related to the toxicologic exposure. Four (16%) fetal deaths were deemed not related to maternal exposure and were excluded from analysis. Among included cases, maternal age ranged from 15 to 43 years old, and the majority of fetal deaths occurred in mothers who were 19–25 years (42.6%). Most fetal deaths occurred in the first (38.1%) or second (28.6%) trimesters, and were due to acute exposures ($n = 14$, 66.7%). The reason for exposure was intentional in 17 cases (81.0%) cases, with 8 (38.1%) of those cases being suspected suicide attempts. Most cases ($n = 18$, 85.7%) were single-substance exposures, two cases (9.5%) involved exposure to two substances, and one case (4.8%) involved exposure to five substances. Acetaminophen and acetaminophen-containing products were the only substances reported in more than one NPDS case, and were present in 38.1% of cases. GI decontamination techniques were not used in any case. Six patients (28.6%) required intubation, four patients (19%) required vasopressors, and five patients (23.8%) underwent hemodialysis. Maternal clinical outcomes were described as minor in one case (4.8%), moderate in three cases (14.3%), and major in 15 (71.5%) cases. In two cases (9.5%) maternal death accompanied fetal death.
Conclusion: Fetal poisoning deaths, as reported in the US NPDS, are relatively uncommon. Most fetal deaths occurred as a result of exposures in early pregnancy, among mothers 19–25 years, as part of an intentional single substance exposure. Acetaminophen and acetaminophen-containing products were the most commonly encountered substances of exposure.

248. Role of a poison centre in the management of suspected rabies infections

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Objective: Post-exposure prophylaxis (PEP) in suspected rabies human exposures must be applied according to international guidelines and requires prompt administration of vaccine alone or combined with human rabies immunoglobulin (HRIG). Without PEP rabies has a 100% fatality rate. Over the last few years, Pavia Poison Control Centre (Pavia-PCC) registered an increase in specialist advice requests for the clinical management of potentially rabies-infected patients and/or for vaccine/HRIG supplies. Even though Italy was declared free from urban rabies in 1973, sporadic cases of infected animals (in the North East) as well as human rabies imported with fatal outcome have been identified. We evaluated the cases for which the Pavia-PCC provided advice for rabies.
Methods: All human cases of suspected rabies (animal bite or scratch from suspected rabid animal) were retrospectively analysed (2007–2015) to evaluate in a real emergency (i) the applicability of the routinely adopted risk criteria, (ii) the adherence to national/international guidelines, and (iii) the role of a National Reference Centre. Risk assessment was performed considering type of animal, geographic area and grade of cutaneous lesion.
Results: Overall 161 patients were included, mean age 31 ± 23.3 years (4 months-85 years; 48.5% male). Sixteen cases (10%) regarded travellers bitten in endemic areas (Asia 43%; dogs in 57%) or patients bitten in Italy by an imported suspected animal. According to the adopted risk assessment criteria, patients were divided in four groups, for which the treatment has been assessed. Group-A (risk only for lesion, $n = 87$): treated 5% (vaccine 3 cases, vaccine + HRIG 1 case); Group-B (risk for lesion + geographical area, $n = 6$): treated 33% (vaccine 1 case, vaccine + HRIG 1 case); Group-C (risk for lesion + geographical area + animal, $n = 16$): treated 81% (vaccine 3 cases, vaccine + HRIG 13 cases); group-D (risk only for lesion + animal, $n = 43$): treated 32% (vaccine 7 cases, vaccine + HRIG 7 cases). No acute adverse reaction to vaccine or HRIG administration were reported. No cases of full blown human rabies were diagnosed.
Conclusion: Data evidenced important differences in clinical approach and management of rabies in the emergency setting. In particular, cases at risk only for the characteristic lesion/wound were overtreated in 4.6% of cases. In contrast, cases at high risk for rabies (Group-C) were undertreated in about 20% of cases. International and national guidelines should be updated, taking into consideration the surveillance of veterinarians, and applied/discussed in every suspected case. A critical revision of procedures for the emergency treatment of patients potentially exposed to rabies presenting to hospital is required.

249. Reductions in emergency department referrals from primary care after use of the UK National Poisons Information Service

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Objective: Suspected poisoning is a common reason for referral to hospital emergency departments (ED), general practitioners (GP) or pharmacies, but many referrals could be avoided by consultation with a poisons centre. In the UK advice is available to health professionals from the National Poisons Information Service (NPIS) via its online database TOXBASE® and the specialist telephone advice service. This study was performed to establish the proportion of primary care telephone enquiries or TOXBASE® accesses where further referral was avoided by use of these NPIS resources.
Methods: A prospective survey was conducted of National Health Service (NHS) primary healthcare providers using the telephone advice service or TOXBASE®. Enquirers were asked to choose their planned course of management (a) prior to and (b) after advice and information had been received. Referral options were to (1) ED (2) GP (3) Pharmacy or (4) Home care. Cost calculations were based on minimum 2014/15 National Health Service reference costs (e.g., £156.64 per ED attendance).

Results: Between 4 January and 19 February 2016, about 2028 primary care telephone enquirers completed the survey. The number of cases considered to need referral was reduced from 1178 before to 819 after NPIS advice (absolute reduction 17.7%, 95% CI 14.6–20.7). Extrapolated across the year this would account for almost 6000 avoided ED visits and an estimated saving of £0.94M annually. Absolute reductions were also seen in GP (15.3%, 95% CI 12.9, 17.6) and pharmacy (2.6%, 95% CI 1.8, 3.5) referrals. Between 9 May and 14 June 2016, 31,151 TOXBASE® page loads from primary care users were recorded, with 851 responses completed (2.7%). Cases considered to need ED referral reduced from 410 to 341, an absolute reduction of 8.1% (95% CI 3.3, 12.9), following access to TOXBASE®. This extrapolates to approximately 25,000 avoided ED attendances and an estimated cost saving of £3.9M annually. TOXBASE® access did not significantly affect GP (absolute reduction 1.8%, 95% CI −2.1, 5.6) or pharmacy (0.7%, 95% CI −0.7, 2.2) referrals.
Conclusion: Use of NPIS services significantly reduces ED referrals from primary care and the resulting savings are greater than the total NPIS budget (currently £3.5M). Further studies are needed to evaluate other benefits, such as improvements in quality of care, reductions in morbidity, mortality or hospital inpatient stay, avoidance of referral to other health services and avoidance of productivity loss related to unnecessary healthcare.

250. Venlafaxine poisoning in the intensive care unit: clinical presentation and role of the cytochrome P450 2D6 phenotype in the onset of cardiovascular complications

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Objective: Venlafaxine, an antidepressant drug with properties of serotonin and norepinephrine reuptake inhibition, may be responsible for life-threatening cardiovascular complications in overdose. Venlafaxine toxicity additionally includes a possible interaction at elevated concentrations with membrane sodium channels resulting in membrane stabilizing effects. To date, vulnerability factors to develop such cardiovascular complications are unknown. Based on a limited number of reported cases, poor cytochrome P450 (CYP) 2D6 metabolizers have been suggested to develop increased cardiovascular toxicity. This liver enzyme metabolizes venlafaxine to O-desmethyl-venlafaxine (or norvenlafaxine) and an altered norvenlafaxine-to-venlafaxine metabolic ratio was suggested to support cardiotoxicity onset. We aimed to describe venlafaxine-related toxicity in patients admitted to the intensive care unit (ICU) and test the proposed hypothesis of vulnerability.
Methods: We conducted a prospective single centre observational study including all venlafaxine-poisoned patients admitted to the ICU from 2010 to 2016. Plasma venlafaxine and norvenlafaxine concentrations were determined using gas chromatography coupled to nitrogen-phosphorus detector (GC-NPD) after initial detection using high-performance liquid chromatography coupled to diode array detector and mass spectrometry (LC-DAD/MS). CYP2D6 genotyping was performed with the patient's consent, to classifying the patients into poor, rapid, and ultra-rapid CYP2D6 metabolizers.
Results: Fifty-two patients (60% F/40% M; age 44 years [32; 52], median [25; 75 percentiles]) exposed to venlafaxine (presumed ingested dose 1.9 g [1.0; 3.0]; plasma venlafaxine concentration on admission 0.8 mg/L [0.3; 2.0] and at the peak 0.9 mg/L [0.4; 2.7]; 98% poly-intoxications) were included. Clinical features included consciousness impairment (Glasgow Coma Scale 8 [4; 14]) and seizure onset (14%), requiring mechanical ventilation (56%). Nineteen patients (37%) presented cardiovascular complications and three patients (6%) died in the ICU. CYP2D6 phenotype distribution among these patients was as follows: slow metabolizers ($n = 4$), rapid metabolizers ($n = 46$) and ultra-rapid metabolizers ($n = 2$). Based on an univariate analysis, onset of cardiovascular toxicity was significantly associated with deeper coma ($p = .04$), reduced PaO_2/FiO_2 ratio ($p = .004$), onset of acute renal failure ($p = .02$), requirement of mechanical ventilation ($p = .02$) and fatality ($p = .04$). No statistical relationships were found between cardiovascular toxicity and plasma venlafaxine concentration and norvenlafaxine-to-venlafaxine ratio on admission and at their respective peaks. When focusing on the patients with cardiovascular manifestations strictly attributed to venlafaxine toxicity, no statistical link was found with CYP2D6 phenotype.
Conclusion: Venlafaxine poisoning may result in severe complications including cardiovascular toxicity and even fatality. Cardiac toxicity is responsible for increased morbi-mortality but is not related to CYP2D6 phenotype. However, inclusion of additional patients is still warranted in our possibly underpowered study before any definitive conclusions can be made.

251. Baclofen poisoning in the intensive care unit: clinical features and investigation of the relationships between toxic encephalopathy and the plasma baclofen concentration

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Objective: Baclofen, a GABA-B receptor agonist with muscle relaxant properties used since 1974, has been recently used at elevated doses to treat ethanol dependence. The number of prescriptions has exponentially increased without an exact evaluation of its toxicity. We aimed to describe acute baclofen poisoning requiring intensive care unit (ICU) admission and study the relationships between toxic encephalopathy and plasma baclofen concentrations.
Methods: We conducted a single-centre retrospective study including all baclofen-poisoned patients admitted to the ICU in 2013–2016. When requested by the clinical situation, repeated electroencephalograms (EEG) and measurements of the plasma baclofen concentrations were performed. Toxic EEG encephalopathy on a scale of 0 to 5 was graded according to the international rating system [1]. Plasma baclofen concentration was determined using liquid chromatography coupled to mass spectrometry in tandem developed with a Quantum Ultra apparatus (Thermo Fisher Scientific) and electrospray source ionization in positive mode (limit of quantification: 5 ng/mL). Linear regression and chi-squared or Mann–Whitney tests were used as requested for subgroup comparisons. Baclofen pharmacokinetics and the relationship between the toxic encephalopathy and the plasma

concentration were modeled using WinNonlin software v.5.3 (Pharsight Corporation, CA).
Results: Twenty-eight patients (17 males, 11 females; age 41 years [32; 49] (median [25th; 75th percentiles]) were included. Poisoning was mainly multidrug ingestion (92%) by suicide attempt (63%) occurring in chronic alcoholic patients (71%). The presumed ingested dose of baclofen was 210 mg [109; 460] and the initial plasma concentration 1425 ng/mL [206; 2298]. Poisoning features included coma (Glasgow coma score 3 [3; 11]) with hypotonia (46%), seizures (39%), abnormal pupil diameter (75%), sinus bradycardia (39%), aspiration pneumonia (21%) and EEG disturbances (43%) including the presence of burst suppressions, spikes, spike-waves, background slowing and even prolonged isoelectric trace in one severely poisoned patient. Management was supportive including mechanical ventilation (54%); the duration was related to the plasma concentration of baclofen ($r2 = 0.67$). One patient was dialyzed. No patient died. Baclofen half-lives of elimination (7 hours [4; 9]) were close to the observed values reported at therapeutic doses. The relationship between baclofen-induced encephalopathy as a function of the baclofen concentration was described using a sigmoidal Emax model.
Conclusion: Baclofen poisoning may be life-threatening. Toxic encephalopathy is well-described with EEG observations and its grade correlated to the baclofen concentration. Prescribers should be aware of the dangers of baclofen, particularly as the benefits to treat alcohol dependence are still lacking.

Reference

[1] Markland ON. Electroencephalography in diffuse encephalopathies. J Clin Neurophysiol. 1984;1:357–407.

252. Myanmar Snakebite Project: analysis of the first 627 prospective cases

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Objective: To analyse characteristics of snakebite patients in Mandalay Division, Myanmar to inform strategy development to improve care as part of a project funded by the Australian Department of Foreign Affairs and Trade.
Methods: Snakebite patients presenting acutely at Mandalay General Hospital (MGH) and giving informed consent for study participation were prospectively enrolled and data collected using a standard form and entered into a database.
Results: In total 648 patients were enrolled from January to October 2016 (data were available for 627 cases). Snake identification was uncertain in some cases ($n = 106$). Russell's viper (RV; *Daboia siamensis*; 437/521 cases where snake identity known) caused most bites, with few cases by cobras (*Naja kaouthia* or *N. mandalayensis*; 14/521), two krait cases (*Bungarus* sp.) and 38 cases by "green snakes" (*Trimeresurus* spp.; GPVS). RV bite is the dominant cause of acute kidney injury (AKI) in this region (MGH has the regional renal dialysis unit). Of the 437 RV bites, 68.2% developed coagulopathy as detected by the 20-minute whole blood clotting test (20 WBCT), 33.5% developed AKI requiring dialysis, 15.8% died (some deaths occurred before dialysis could be started). In total 97.7% received antivenom but in 59.4% the initial dose was suboptimal. Of fatal cases 78% died despite receiving antivenom within the first 6 hours (suboptimal initial dose in 69%). The common features of RV envenoming included renal injury 69.5%, thrombocytopenia 44.3 and shock 10.3%. GPVS bites were associated with coagulopathy (25% of cases), shock (8%), necrosis (5%) and AKI (one case), indicating potential diagnostic confusion with RV bites if the biting snake was not witnessed. No antivenom is available for GPVS bites.
Conclusion: In the Mandalay region of central Myanmar snakebite is common and Russell's viper dominates as a cause of bites, AKI and fatalities. However, green pit viper bites are more common than previously recognised and require further study.

253. Mushroom poisonings in the Slovak Republic: a 20-year retrospective analysis

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Objective: In Slovakia, mushrooms enjoy a very high popularity both among hobby mycologists and gourmets. Some people consider wild mushrooms as particularly healthy and digestible. During a 20-year period the National Toxicological Information Centre (NTIC) has received 57,268 inquiries from all over Slovakia. Mushroom exposures represent about 4.5% of all cases collected by the NTIC. Enquiries concerning mushrooms are among the most severe cases of poisoning and we sought to analyse these cases.
Methods: To obtain more information we performed a retrospective analysis of all telephone calls involving mushrooms to the NTIC from 1996 to 2015.
Results: During the 20-year period 2609 mushroom intoxications were reported to the NTIC. Adults made up 80.5% and children 19.5% of all the reported cases. Gastrointestinal syndrome was noted in 84.5% of the cases. The second most frequent syndrome was cyclopeptide syndrome (6.9%); 36 cases resulted in death (24 adults and 12 children) as a result of *Amanita phalloides* ingestion. Based on the figures collected in the first 10-year period, mortality was 24.6% (29 deaths) while in the second 10-year period it was 10.4% (7 deaths). The clinical symptoms of ingestion such as vomiting, abdominal pain and diarrhea appeared 6–24 hours (mean 11.2 hours) post-ingestion. Administration of the antidote silibinin was recommended. The clinical symptoms of ingestion of the muscarinic syndrome represented 3.4%, pantherine syndrome 3.4%, psilocybe 1.3% and orellanine syndrome 0.2%. In 650 cases, spores in biological material (vomit, gastric lavage, remainder of food, fresh, dried, frozen mushroom material) were analyzed in our centre by 2014. Since 2004 an early diagnosis of amanitin intoxications for all healthcare facilities has been provided in a specialized biochemistry laboratory based in central Slovakia.
Conclusion: Slovakia is rich in wild poisonous mushrooms that can easily be mistaken for edible ones. *Amanita* poisoning was mostly confused with *Macrolepiota*, *Russula* and *Agaricus* species. This analysis also highlights that people tend to underestimate mushroom ingestion because of late onset of gastrointestinal symptoms. This results in late hospitalization and treatment.

Due to intensive education among the lay public, the number of cyclopeptide intoxications and deaths has decreased in the last ten years. The method of early determination of amanitin in biological material has significantly contributed to more efficient management of mushroom poisonings in Slovakia.

254. Molecular and toxicological study of Italian Viper venom neurotoxicity

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Objective: Snakebites represent a neglected growing public health problem causing thousands of deaths worldwide, especially in developing countries inhabited by the most poisonous snake species. In Europe, all the medically-relevant snakes are members of the genus *Vipera* which can induce severe envenomation and death. Neurotoxicity, which is in general one of the most relevant and dangerous systemic effect of snake venoms, has been reported for Viperidae, but it seems to be associated only with some viper subspecies. Changes in venom composition could become a relevant problem even in cases of human envenomation. Here we studied *V. aspis* and *V. berus* venoms, two of the most common European vipers, to investigate their neurotoxic properties and evaluated whether antivenoms used in clinical practice neutralize the neurotoxic components.
Methods: We evaluated the neurotoxicity and the neutralization capability of the two venoms *in vitro*, by biochemistry and neuronal culture models, and *in vivo*, by electrophysiology and tissue immunohistochemistry.
Results: Both venoms contain an active phospholipases A2 (PLA2) component, which is one of the most common neurotoxic components in snake venoms. However, when tested in neuronal cultures, only *V. aspis* venom generates "neuronal bulges", a typical hallmark of PLA2-neurotoxin activity in cultured neurons. By injecting sub-lethal amounts of venoms intramuscularly in the mouse hind limb *in vivo*, we found that the venom from *V. aspis* causes paralysis, as assessed by the lack of soleus muscle contraction and by quantifying the nerve-muscle neurotransmission through electrophysiology. At variance, the venom of *V. berus* induced a huge hemorrhagic effect, but no evident effects on neurotransmission. Consistently, by immunohistochemistry, we found that only *V. aspis*, but not *V. berus*, venom induces (reversible) motor axon terminals degeneration. Importantly, some antivenoms, clearly prevent the hemorrhagic effect caused by *V. berus* venom, but display very little neutralization capacity against *V. aspis* venom neurotoxicity, as evaluated by electrophysiology and immunohistochemistry.
Conclusion: *V. aspis*, but not *V. berus*, venom has a powerful neurotoxic component, which, very likely, is responsible for the neurological symptoms reported in humans. Together with previous reports, our results suggest that viper venoms display high inter/intraspecies heterogeneity in terms of composition, biochemical properties and toxicological effects. Such variability is particularly relevant considering that antisera are generally obtained using one specific venom, thus possibly providing limited interspecies cross reactivity, as we found in the case of *V. aspis* neurotoxicity.

255. A case of voluntary exposure to the venom of the giant leaf frog *(Phyllomedusa bicolor)*

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Objective: To describe an uncommon case of toxicity related to a ritual with the venom of the giant leaf frog *(Phyllomedusa bicolor)*.
Case report: A 28-year-old woman presented herself to the emergency department because she felt unwell, was suffering from pronounced vomiting, epigastric and right fossa pain. She had participated in an Amazonian shamanic ritual called Kambo or Sapo with application of dried secretions of the giant leaf frog *Phyllomedusa bicolor* on provoked burn wounds to the right leg. The secretions contain toxins such as phyllocaeruleine, phyllomedusine, phyllokinine, dermorphine and deltorphine [1]. As part of the "purification" ritual she had to drink 3 L of water. Consciousness and vital parameters were normal. Abdominal examination revealed a positive McBurney's sign. Blood results showed a hyponatremia of 132 mEq/L (normal 135–144 mEq/L) and a hypokalemia of 3.4 mEq/L (normal 3.6–4.8 mEq/L). Abdominal ultrasonography revealed no abnormalities. The treatment was symptomatic with an analgesic, anti-emetic and fluid restriction. During observation in the emergency department the gastrointestinal complaints disappeared, and she was discharged after 24 hours with normal serum electrolytes concentrations.
Conclusion: This is the first case of its kind reported to the Belgian Poison Control Centre. Only one similar case has been described with a patient developing more severe symptoms which were ascribed to phyllomedusine toxin-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) [2]. Emergency physicians must be aware of unusual voluntary intoxications with the venom of the giant leaf frog during Kambo or Sapo rituals. Toxicity may be due to the toxic substances, but also due to water intoxication as these rituals are often combined with an excessive water intake resulting in hyponatremia.

References

[1] Erspamer V, Erspamer G, Severini C, et al. Pharmacological studies of 'sapo' from the frog *Phyllomedusa bicolor* skin: a drug used by the Peruvian Matses Indians in shamanic hunting practices. Toxicon. 1993;31:1099–1111.
[2] Leban V, Kozelj G, Brvar M. The syndrome of inappropriate antidiuretic hormone secretion after giant leaf frog (*Phyllomedusa bicolor*) venom exposure. Toxicon. 2016;120:107–109.

256. A study of verified spider bites in Slovenia

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Objective: Spiders in Slovenia are mostly not harmful to humans, since *Latrodectus* species is not present in the Slovenian part of Istrian peninsula. Spider bites generally have a benign clinical course with minor effects and a rapid, complete recovery [1].

The aim of this study was to evaluate telephone enquiries as well as admissions due to spider bites in Ljubljana.
Methods: A retrospective study of all verified spider bites reported to the clinical toxicology consulting service and patients admitted to the toxicology department at the University Medical Centre, Ljubljana between 2000 and 2016. Spider bites were classified as "verified spider bite" when the spider bite was observed, the spider was caught or photographed immediately after the bite and sent to us for identification, and when the presented case matched the clinical course of a spider bite.
Results: A total of only 5 cases of verified spider bite enquiries occurred involving *Cheiracanthium punctorium* ($n = 3$), *Steatoda bipunctata* ($n = 1$) and *Hogna radiata* ($n = 1$). In patients bitten by *Cheiracanthium* or *Steatoda* spiders, an immediate severe pain, comparable to a wasp or bee sting, was reported. Locally, a major swelling with erythema developed. In the patient bitten by *Hogna radiata*, the pain was moderate, with barely noticeable redness and swelling of the bite site. The proposed outpatient treatment for all 5 patients was conservative, including wound cleansing, cool compresses and analgesics. No hospital admission due to the consequences of a verified spider bite was necessary.
Conclusion: The overall incidence of verified spider bites in Slovenia is estimated to be around 0.01% of all calls to the toxicology consulting service. Bites of Slovene spiders result in only mild local symptoms. Despite a high abundance of species and the frequency of spiders in our environment, spider bites do not constitute a toxicological threat in Slovenia.

Reference

[1] Nentwig W, Gnädinger M, Fuchs J, et al. A two year study of verified spider bites in Switzerland and a review of the European spider bite literature. Toxicon. 2013;73:104–110.

257. Antidote treatment in viper envenomation in Italy: a comparison of two antivenoms

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Objective: EU marketed viper antivenoms differ in their pharmaceutical characteristics, equine/ovine origin, *Vipera* species neutralizing activity, dosage and registered route of administration. In Italy, hospital availability of 5 different antivenoms influences their use. The aim of this study was to evaluate the clinical response in envenomed patients treated with the two antivenoms (Zagreb and Biomed) mainly used in the last 4 years. There are no differences for host animal and fragment type [$F(ab')_2$]; regarding the specific activity, Zagreb is declared active against *Vipera aspis,* V. *ammodytes, V. berus, V. labetina* and *V. xanthine*, Biomed only against *Vipera berus.*
Methods: All viper bitten patients treated with one of these antivenoms (administered according to the manufacturer's recommended dose) from 2013 to September 2016 were retrospectively assessed for sex/age, site of bite, time elapsed between bite and admission/antivenom administration, antivenom administered and effects. Grading Severity Score (GSS) was applied at admission, at antivenom administrations, and after 6 hours. Improvement was defined as amelioration/no evolution of local effects and/or no appearance of systemic effects (including neurological symptoms). Patients were followed until discharge.
Results: Overall 66 patients (age 44.3 ± 27.2 years; male 70%) were included; 16 were paediatric (1–15 years). *Vipera aspis* the most common species involved. Upper and lower limbs were involved in 88% and 12% of cases, respectively. Average time between bite and admission was 4 hours (0.25–23 hours); an average 9 hours (40 minutes to 26 hours) elapsed between bite and antivenom administration in patients with GSS 2 or 3. Both antivenoms were administered intravenously: Zagreb in 31/66 (47%) and Biomed in 35/66 (53%) cases. Clinical improvement was registered in 94% (29/31) and 57% (20/35) of patients treated respectively with Zagreb and Biomed ($p = .0007$). Considering two subgroups (≤15 [$n = 16$] or >15 [$n = 50$] years), Zagreb increases the probability of clinical improvement in both with more evidence in the paediatric group (Zagreb 85.71% versus Biomed 22.2%, OR = 16, $p = .041$). Acute adverse reactions occurred after Zagreb (3 cases, angioedema, pruritus, bradycardia) and Biomed administration (1 case, vasovagal syncope). Serum sickness (3 weeks later) occurred in 1 case (Biomed).
Conclusion: Biomed appears to be less efficacious, both considering all patients and the paediatric sub-group, but these results should be cautiously evaluated because of the small paediatric population. Intravenous administration is usually safe (even if off-label as used for Biomed). It remains difficult to ascertain which species of viper is responsible of the envenomation, and Biomed performance is probably influenced by being only active against *V. berus*.

258. Local envenoming from Western hognose snake bites

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Objective: Bites from Western hognose snakes (*Heterodon nasicus*) are infrequently reported to the UK National Poisons Information Service (NPIS) and commonly involve bites from snakes kept as pets or in zoos. The Western hognose snake is considered to be non-venomous, with bites resulting in low severity symptoms including local pain and inflammation. Our objective was to analyse the severity of symptoms seen following bites from the Western hognose snake.
Methods: We retrospectively analysed all enquiries to the UK NPIS involving bites from Western hognose snakes between September 2007 and August 2016. Calls were analysed with respect to poisoning severity, symptoms experienced and investigations or treatments recommended.
Results: The UK NPIS received 36 telephone enquiries regarding bites from the Western hognose snake during the 9-year study period. Poisoning Severity Score (PSS) [1] was recorded as 0 (none) or 1 (mild) for 83.2% of the calls and 2 (moderate) for 11.1%. No calls were graded as PSS 3 (severe). One call was for information only (no management advice was required). Symptoms reported included oedema (61.1%), pain (11.1%), paraesthesia (8.3%) and inflammation (5.6%). Other symptoms included dizziness, fever, pruritus, vomiting and blurred vision (all 2.8%). Recommended investigations included blood tests (16.7%),

electrocardiogram 5.6%, and X-ray of the affected area (8.3%). Of the four cases graded as moderate severity (PSS2), all developed features consistent with envenoming, including bruising and swelling of the affected limb beyond the adjacent joint. One patient developed pain, tachycardia and hypertension. There is no specific antivenom for Western hognose bites and treatment is symptomatic and supportive.
Conclusion: The UK NPIS received 36 enquiries concerning bites from Western hognose snakes over a 9-year period. Although 11.1% of cases developed symptoms consistent with local envenoming, the majority of cases were of no or low severity and recovered completely with symptomatic treatment only.

Reference

[1] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998; 36:205–213.

259. Pain management in erucism: outcome in 286 cases from the Campinas Poison Control Center

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Objective: To assess the pain profile of patients with erucism (injuries due to moth caterpillars) and the outcomes of pain management at admission.
Methods: A cohort study of consecutive patients held in-site by Campinas Poison Control Center (CCI Campinas), Brazil from January 2010 to April 2016. On admission, anamnesis was performed and pain was assessed by a 10-point pain scale, repeated at 5, 15, 30 and 60 minutes. Pain control included oral or intravenous analgesics (dipyrone, paracetamol, codeine + paracetamol, tramadol) or anesthetic blockade (lidocaine injection at site of contact plus analgesics). We grouped patients in (1) no intervention, (2) analgesics and (3) anesthetic blockade. Differences between groups were analyzed by two repeated measures strategies: ANOVA and mixed model via restricted maximum likelihood adjusted by sex and age. Sensitivity analysis by bootstrap (reanalysis with 50 random subsamples was performed to assess the robustness). We used STATA 14 to perform all calculations.
Results: In total 286 patients were included (56% men; mean age 38 ± 22 years), in 260 the caterpillar was seen and the genus was identified in 134 cases (78% were *Podalia* species). Most accidents happened in urban areas (91%), at home (61%) or work (18%). Most exposures occurred on the hands (59%) and arms (25%). Baseline mean pain score was 2.30 ± 2.88 in the no intervention patients ($n = 27$); 6.67 ± 5.06 in the analgesic group ($n = 101$) and 8.81 ± 1.43 in the blockade group ($n = 108$) (missing pain scale at baseline $n = 50$). Mean decrease after 60 minutes was −1.38 ± 2.00 (group 1, $n = 8$), −4.27 ± 2.33 (group 2, $n = 51$), and −5.49 ± 3.17 ($n = 74$, group 3) (missing pain scale at 60 minutes $n = 153$). The difference in effect of no intervention, analgesics and blockade on pain reduction across times was statistically significant ($p < .001$). The mean reduction in pain compared to no intervention was −1.11 at 5 minutes ($p = .086$), −1.99 at 15 minutes ($p = .002$), −2.59 at 30 minutes and −3.51 at 60 minutes ($p < .001$) for analgesics and −5.26 at 5 minutes, −5.68 at 15 minutes, −4.95 at 30 minutes and −4.83 at 60 minutes ($p < .001$) for blockade. Results remained significant after sensitivity analysis.
Conclusion: Patients with more severe pain were treated with analgesics or anesthetic blockade. Analgesics significantly reduced pain after 30 and 60 minutes. Blockade was effective from 5 minutes, despite the higher pain of these patients. Results are limited by missing data during follow up and not taking into account previous or further pain control.

260. Safety of non-steroidal anti-inflammatory drugs in copperhead snakebite patients

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Objective: Guidelines for management of pit viper envenomations recommend against using non-steroidal anti-inflammatory drugs (NSAIDs) for pain and inflammation in snakebite patients due to concern for platelet dysfunction and coagulopathy despite low-quality evidence [1,2]. Copperhead (*Agkistrodon contortrix*) bites, which are the most frequent venomous snakebites in the US, do not appear to cause coagulopathy [3]. We propose that there is no difference in clinically apparent bleeding or laboratory measures of abnormal coagulation between copperhead snakebite patients who received NSAIDs and those who did not.
Methods: A retrospective chart review of snakebite patients who presented to St. Louis Children's Hospital (SLCH) or Barnes-Jewish Hospital (BJH) between January 1998 and December 2012. The primary inclusion criterion was a presumptive or positive copperhead snakebite.
Results: There were 63 presumptive and 50 positive copperhead snakebite patients. Most patients were male (71.7%) with a mean age of 19.4 years. Treatment included NSAIDs in 49 patients (43.4%), did not include NSAIDs in 52 patients (46.0%), and was unknown regarding NSAIDs in 12 patients (10.6%). There was no significant difference in most abnormal International Normalized Ratio (INR), partial thromboplastin time (PTT), fibrinogen, platelet count, serum creatinine, and hematocrit values (p values .07380, 0.4074, 0.8869, 0.2118, 0.3663, and 0.02556) between copperhead snakebite patients who received NSAIDs and those who did not. Only 2 patients (1.8%) had any clinically apparent bleeding. Both had epistaxis reported at the referring hospitals but not present on arrival at our hospital; both later received NSAIDs without adverse effect. The remaining 111 patients (98.2%) did not exhibit bleeding. There was no significant association between treatment with NSAIDs and bleeding in copperhead snakebite patients ($p = .2329$).
Conclusion: There are no adverse outcomes attributable to NSAID usage among copperhead snakebite patients who received NSAIDs compared to those who did not. The use of NSAIDs in managing pain and inflammation in copperhead snakebite patients is safe.

References

[1] Kanaan NC, Ray J, Stewart M, et al. Wilderness Medical Society practice guidelines for the treatment of pitviper envenomations in the US and Canada. Wilderness Environ Med. 2015;26:472–487.
[2] Lavonas EJ, Ruha AM, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the US: results of an evidence-informed consensus workshop. BMC Emerg Med. 2011;11:2.
[3] Ali AJ, Horwitz DA, Mullins ME. Lack of coagulopathy after copperhead snakebites. Ann Emerg Med. 2015;65:404–409.

261. Severe and fatal envenomation by wandering spiders (genus *Phoneutria*) in Brazil: a review of literature reports

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Objective: Wandering spiders of the genus *Phoneutria* are found in southern Central America (Costa Rica) and throughout South America, east of the Andes into northern Argentina. Most of the bites by this genus are reported in Brazil (approximately 4000 cases/year; 2 cases/100,000 inhabitants). Despite the large number of bites by *Phoneutria* species, few detailed clinical reports have been published. We reviewed reports of severe and fatal bites by *Phoneutria* in Brazil from 1925 to 2016.
Methods: Electronic bibliographic databases, standard textbooks on toxicology/toxinology, and conference proceedings abstracts were searched for reports of severe/fatal envenomation by *Phoneutria*. Only reports with clinical descriptions of envenomation were included. The variables recorded included identification of the offending spider, patient age and sex, bite site, clinical manifestations, treatment, including use of antivenom, and clinical evolution of the cases.
Results: Nine reports (four papers, two abstracts, one personal communication, and two reports from Brazilian Poison Control Centers) were identified and involved 12 patients (median age 19 years; range 9 months to 74 years) with severe envenomation (two fatalities). Most patients were male ($n = 8$). In 11 cases the bite occurred on the hands ($n = 4$), feet ($n = 3$), neck ($n = 3$) and wrist ($n = 1$); the offending spider was brought for identification in eight cases (*P. nigriventer* $n = 6$; *Phoneutria* species $n = 2$). The main clinical features described were local pain ($n = 12$), tachycardia ($n = 12$), diaphoresis ($n = 10$), blurred vision ($n = 6$), prostration ($n = 6$), vomiting ($n = 6$), tremors ($n = 6$), poor peripheral perfusion ($n = 6$), cyanosis ($n = 6$), agitation ($n = 5$), arrhythmic pulse ($n = 5$), dyspnea ($n = 5$), pulmonary edema ($n = 5$), sialorrhea ($n = 4$) and priapism ($n = 4$). Laboratory results obtained in seven cases revealed leukocytosis ($n = 6$), hyperglycemia ($n = 5$), metabolic acidosis ($n = 4$) and hypoxemia ($n = 2$). Therapeutic procedures included use of antivenom ($n = 10$), mechanical ventilation ($n = 2$), and inotropic/vasopressor drugs plus electric cardioversion ($n = 1$). Two deaths with a confirmed causal nexus were identified, both in children (3 and 4 years old) who developed pulmonary edema.
Conclusion: Life-threatening and fatal envenomation by *Phoneutria* species is very uncommon. The clinical and laboratory features described in severe/fatal envenomation are possibly related to increased sympathetic activity, nitric oxide release and a systemic inflammatory response [1,2].

References

[1] Yonamine CM, Troncone LR, Camillo MA. Blockade of neuronal nitric oxide synthase abolishes the toxic effects of Tx2–5, a lethal *Phoneutria nigriventer* spider toxin. Toxicon. 2004;44:169–172.
[2] Bucaretchi F, Mello SM, Viera RJ, et al. Systemic envenomation caused by the wandering spider *Phoneutria nigriventer*, with quantification of circulating venom. Clin Toxicol. 2008;46:885–889.

262. Successful treatment of persistent ciguatera with intravenous mannitol

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Objective: We report a case of successful use of mannitol to treat persistent ciguatera symptoms.
Case report: An active 60-year-old woman in good health became ill during a sailing holiday in the British Virgin Islands. She had eaten various fish in local restaurants during the trip. After one fish lunch she developed nausea, diarrhea, dizziness, headache and, light-headedness. In the days following, she suffered "intense itching" in the ears, dizziness, malaise, "fluttering feeling" throughout the body, genito-urinary sensitivity, and "rhythmic buzzing sensation near the rectum". These symptoms persisted, and she saw her primary physician one month later. He ordered laboratory tests including complete blood count, erythrocyte sedimentation rate, Lyme antibodies, Ehrlichia and Anaplasma antibodies, rheumatoid factor, vitamin B2212, thyroid stimulating hormone, and antinuclear antibodies. All tests were negative. She noticed that eating fish or drinking alcohol worsened her symptoms. She continued to have symptoms for another three months when she consulted the Toxicology Service. The toxicologists agreed that her symptoms and circumstances were consistent with ciguatera fish poisoning and agreed to treat with mannitol 100 g IV infusion. During the infusion, she reported rapid symptom relief but developed nasal congestion and sneezing that responded to diphenhydramine. Following the mannitol infusion, she reported feeling "much better". At follow-up 10 days after treatment, she remained improved and reported "more energy".
Conclusion: Mannitol appears to be most successful when given early in the course of ciguatera fish poisoning [1,2]. In one large case series, the longest interval from symptom onset to successful treatment was 70 days, although the majority of patients with satisfactory results received mannitol in the first few days [1]. Our patient experienced rapid relief with IV mannitol given 140 days from her onset of symptoms.

References

[1] Blythe DG, Fleming LE, Ayyar DR, et al. Mannitol therapy for acute and chronic ciguatera fish poisoning. Mem Queensl Mus 1994;34:465–470.
[2] Schwarz ES, Mullins ME, Brooks CB. Delayed mannitol in ciguatera poisoning. Ann Emerg Med. 2008;52:476–477.

263. The EVEIT model as a means of improving the understanding of venom ophthalmia

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Objective: Snakes belonging to the genus *Naja* (Elapid family), also known as "spitting cobras", can spit venom towards the eyes of a predator as a defensive strategy, causing potentially blinding ocular envenoming. Venom ophthalmia is characterized by pain, hyperemia, blepharitis, blepharospasm and corneal erosions. Delay or lack of treatment may result in corneal opacity, hypopyon and/or blindness [1]. Although the clinical features and management of envenoming following bites are well described, Elapid venom ophthalmia is not well documented and no management guidelines exist. Furthermore, accidental ejection of venom by non-spitting vipers, such as *Bothrops*, also occurs. Recent important progress in the knowledge of chemical ocular burns has been made using the *Ex vivo* Eye Irritation Test model (EVEIT) developed by ACTO (Aachen Center for Technology transfer in Ophthalmology) [2]. Considering the lack of an experimental animal model to study the mechanisms of venom ophthalmia, we adapted the EVEIT to envenomation.
Methods: *Ex vivo* rabbit eyes were exposed for 30 minutes to the venom of *Naja naja*, *Naja mossambica*, *Naja nigricollis*, *Bothrops jararaca* and *Bothrops lanceolatus*. After 20 hours of incubation at 30 °C, corneal thickness was assessed using high resolution optical coherence tomography (HR-OCT) imaging and the eyes were fixed for histological analysis.
Results: In the conditions of the assay, *Bothrops* venoms did not induce any significant edema, but they caused disorganization of the collagen structure and damaged the epithelium. *B. jararaca* venom caused endothelial detachment and more severe damage than *B. lanceolatus* venom. All *Naja* venoms induced a significant corneal edema, collagen structure disorganization and epithelial necrosis. The corneas envenomed with *N. mossambica* and *N. nigricollis* venoms were completely opaque, whereas those exposed to *N. naja* displayed endothelial detachment.
Conclusion: We successfully adapted the EVEIT model to set a new experimental *ex vivo* animal model of snake venom-induced ophthalmia. The present data highlight the deep and irreversible corneal damage that *Naja* and *Bothrops* snake venoms potentially cause in the absence of treatment. Those preliminary results enable a better understanding of the mechanisms of venom ophthalmia.

References

[1] Chu ER, Weinstein SA, White J, et al. Venom ophthalmia caused by venoms of spitting elapid and other snakes: Report of ten cases with review of epidemiology, clinical features, pathophysiology and management. Toxicon. 2010;56:259–272.
[2] Spöler F, Först M, Kurz H, et al. Dynamic analysis of chemical eye burns using high-resolution optical coherence tomography. J Biomed Opt. 2007;12:041203.

264. The need of a second antivenom dose after snake bites by *Vipera berus*

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Objective: To estimate how often a single dose of antivenom is insufficient to permanently reduce local and general symptoms after a Common European Adder bite.
Methods: All hospital cases reported to the Swedish Poisons Information Centre (PC) during 2016, up to the end of September, concerning *Vipera berus* snake bites were screened. Cases initially treated with the antivenom ViperaTAb™ (specific ovine Fab fragments) were retrospectively analyzed for recurrence of symptoms.
Results: In total 81 cases (aged 5–94 years) were identified where the local reaction and/or generalized symptoms had a severity grave enough to meet the criteria for antivenom treatment. As a standard, 200 mg of ViperaTAb™ was given intravenously during 30 minutes. Due to significant recurrence of symptoms a second antivenom dose was given on 16 occasions (20%). Six of these cases received this dose within seven hours after the first. Ten patients received the second dose at a later stage, >13 hours after the first. In these patients local symptoms had often progressed substantially at the time of the call to the PC.
Conclusion: The half-life of the antivenom is shorter than the half-life of the snake venom; hence, it is foreseeable that many patients will show recurrence. In an earlier study at our PC a second dose was needed in 15% of the cases [1], why this number now has increased to 20% is unclear. In the present study, surgical fasciotomy was performed in 3 patients that might instead have benefitted from antivenom (one case) and an early second dose (two cases). In some of the 81 cases, the PC was consulted at such a late stage that a second dose of antivenom was judged to be of little value. If the PC had been contacted earlier the frequency of second antivenom doses would have gone up even further. In *Vipera berus* snake bites, recurring symptoms after treatment with ViperaTAb™ are common. Repeated treatment is indicated in at least 20% of the cases. The second dose should be given when the first signs of exacerbation occur to prevent expanding extensive local reactions.

Reference

[1] Karlson-Stiber C, Salmonson H, Persson H. Antivenom treatment in *Vipera berus* bites – repeated administration in 66 cases treated during the period 1995 to 2008. Clin Toxicol. 2009;47:436–510.

265. Thromboelastography in suspected *Crotalus horridus horridus* envenomation

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Objective: Thromboelastography (TEG) is an evolving technology to better describe whole blood coagulopathy and direct treatment. Its use has not been widely reported in pit viper (*Crotalinea*) envenomation. We describe the use of a TEG to guide treatment of coagulopathy resulting from pit viper envenomation.
Case report: A 61-year-old male with a history of coronary artery disease presented to the emergency department with severe right foot pain after being bitten by a "brown" snake in the South Eastern US. One hour post-envenomation, the patient's platelet count was 132.9×10^3/μL (reference $150–450 \times 10^3$/μL), International Normalized Ratio (INR) 0.98 (reference 0.9–1.2), and fibrinogen 351 mg/dL (reference 150–400 mg/dL). Immediately prior to treatment, a TEG was drawn that demonstrated a decreased alpha angle (62.1 degrees, reference 65.4–74.8 degrees) consistent with delayed fibrin cross-linking and dampened mean amplitude (47.2 mm, reference 50–70 mm) consistent with inadequate clot strength and decreased platelet function. His curve demonstrated rapid degradation of the amplitude, indicating rapidly diminishing clot strength. He was empirically treated with 6 vials of crotalinae Fab antivenom 4 hours following envenomation for rapid, severe swelling. Six hours following antivenom treatment, a repeat TEG demonstrated

complete normalization of all clotting parameters including amplitude degradation. Platelets continued to decline to a nadir of 80.2×10^3/μL at 22 hours post-envenomation before improving while the patient's fibrinogen and INR remained within normal limits. Pain and swelling improved following the initial antivenom dose. The patient never suffered any clinically significant hemorrhage. A diagnosis of suspected *Crotalus horridus horridus* envenomation was made based on the severity of clinical symptoms and thrombocytopenia.

Conclusion: This case is remarkable for a TEG consistent with delayed clot formation and rapid clot degradation despite mild thrombocytopenia in a patient following suspected *Crotalus horridus* envenomation. In addition, his TEG normalized following antivenom treatment, while his platelets continued to decrease. Following treatment, even as more pronounced thrombocytopenia manifested, the platelet activity improved leading to increased clot strength. These findings may represent the importance of platelet function over concentration. Further evaluation of pit viper envenomation with TEG may help better define the mechanism of pit viper-induced coagulopathy and thrombocytopenia, improving the cost-effectiveness and clinical outcomes of treatment.

266. Venom-induced recurrent coagulopathy and hemorrhage in pregnancy

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Objective: North American rattlesnake envenomation (RSE) may produce coagulopathy, which results primarily from the action of thrombin-like enzymes on fibrinogen. Treatment with Crotalidae Polyvalent Immune Fab (CroFab) antivenom usually reverses coagulopathy but recurrent hypofibrinogenemia may occur up to two weeks following treatment. In the absence of thrombocytopenia or other risk factors for bleeding, patients with recurrent venom-induced coagulopathy are monitored as outpatients [1]. Coagulopathic recurrence following treatment of RSE has not been described during pregnancy. Few published US data regarding RSE in pregnancy exist. Two poison center reviews include 15 cases of RSE without data on pregnancy outcomes or development of coagulopathic recurrence [2,3].

Case report: We report a case of recurrent coagulopathy and hemorrhage in a 33-year-old, 5w4d pregnant woman. The patient was bitten on her right great toe by an unknown species of rattlesnake. She received a total of 14 vials of CroFab antivenom in the 13 hours following the bite. Swelling and pain improved, and she was discharged on hospital day 3 with normal coagulation studies. Three days later routine follow-up coagulation studies were significant for prothrombin time >200 sec, fibrinogen <35 mg/dL and platelet count 199 K/mm^3. The patient reported vaginal spotting and pelvic cramping and was referred to the emergency department, where she developed severe vaginal hemorrhage. She was given 6 vials of CroFab and intravenous fluid boluses. Transvaginal ultrasound demonstrated an intrauterine gestational sac that passed into the vagina during the examination without evidence of retained products of conception. She continued hemorrhaging and hemoglobin dropped from 12.4 g/dL to 6.6 g/dL. She ultimately received methylergonovine, 6 units of packed red blood cells and 20 vials of CroFab prior to resolution of bleeding and coagulopathy. On outpatient follow-up she did not have further bleeding or coagulopathy.

Conclusion: Rattlesnake envenomation during pregnancy with recurrent venom-induced coagulopathy, first trimester spontaneous abortion, and life-threatening hemorrhage has not been previously described in the medical literature. Clinicians caring for pregnant women with rattlesnake bites should carefully monitor for onset of coagulopathy following treatment of RSE with CroFab.

References

[1] Ruha AM, Curry SC, Albrecht C, et al. Late hematologic toxicity following treatment of rattlesnake envenomation with crotalidae polyvalent immune Fab antivenom. Toxicon. 2011;57:53–59.

[2] Seifert SA, Boyer LV, Benson BE, et al. AAPCC database characterization of native U.S. venomous snake exposures, 2001–2005. Clin Toxicol. 2009; 47:327–335.

[3] Seifert SA, Rayburn WF. Rattlesnake bites in pregnant women. J Reprod Med. 2010;55:520–522.

267. Viperidae snakebites and antivenoms in central and southeastern European and neighbouring countries of Asia and Middle East

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Objective: In Europe, snakebites affect 4–11 people per million population per year [1]. In central and south eastern parts of Europe and neighboring countries of Asia and the Middle East *Vipera berus*, *V. aspis*, *V. ammodytes*, *V. ursinii*, *Macrovipera lebetina*, *Montivipera xanthina* Viperidae can be found. The aim was to evaluate the epidemiology of Viperide snakebites and antivenom availably in central and southeastern Europe and neighboring countries between 1 April and 30 September 2016.
Methods: This was a multicentre web survey about Viperidae family snakebites and the availability of antivenoms in poison control centres and toxicology departments in Estonia, Latvia, Lithuania, Poland, Czech Republic, Slovakia, Hungary, Slovenia, Croatia, Serbia, Montenegro, Macedonia, Bulgaria, Romania, Belarus, Russia, Turkey, Armenia, Georgia, Azerbaijan, Kazakhstan, Moldova, and Iran. Data collected included human population, Viperidae species in their service area, the number of confirmed snakebites, treatment and outcomes.
Results: The survey was completed by 24 poison control centres and toxicology departments in 19 countries (79%), covering a population of 95.8 million. The incidence of Viperidae snakebites is estimated at 6.2/million and antivenom was used in approximately 40% of cases. The incidence of symptomatic bites and antivenom treatment for the different Viperidae species are presented in Table 1. *Macrovipera lebetina* snakebites were reported only in Azerbaijan and Iran. There were no recorded snakebites of *Vipera ursinii* and *Montivipera xanthina* species. Snakebites by unidentified snakes represented 13% of all reported Viperidae bites; 56% were treated with antivenom. Lethal outcome was recorded in 2 patients bitten by *Macrovipera lebetina*.
Conclusion: The incidence of Viperidae snakebites in central and southeastern Europe and neighboring countries of Asia and the Middle East is estimated at 6.2/million population. Eleven different anti-Viperidae antivenoms are used, 4 in countries of the European Union and 7 in neighboring countries; none are European Medicines Agency (EMEA)-approved.

Reference

[1] Chippaux JP. Epidemiology of snakebites in Europe: a systematic review of the literature. Toxicon. 2012;59:86–99.

268. Two cases of tetrodotoxin poisoning from pufferfish consumption in Taiwan

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Objective: Pufferfish are well recognised as poisonous fish and are commonly found in Asia and the Indo-Pacific. Pufferfish contain tetrodotoxin, a potent neurotoxin affecting skeletal muscle, autonomic motor and sensory nerves, central and peripheral nervous systems [1,2]. Tetrodotoxin poisoning occurs sporadically in Taiwan. We report two patients experiencing acute tetrodotoxin poisoning after consumption of pufferfish.
Case report: Two fishermen were transported to the emergency department with a history of consuming an unknown quantity of pufferfish captured at sea. One was a 35-year-old man who complained of vomiting and muscle weakness in both limbs shortly after consumption. Clinical examination revealed normal findings except decreased muscle power of grade 4 in both limbs. He was transferred to the intensive care unit. During hospitalization, he presented with perioral and limb paraesthesia. After conservative treatment, his symptoms gradually resolved and he was discharged without any sequelae. The other patient was a 59-year-old man who developed vomiting and loss of consciousness immediately after consumption. On arrival at the emergency department, he had a cardiac arrest. After resuscitation including tracheal intubation and inotropic support, he had return of spontaneous circulation. He was then transferred to the intensive care unit. Despite intensive supporting measures, he remained in a deep coma with complete paralysis and lack of pupil reactions. He expired 26 days after admission.
Conclusion: Tetrodotoxin poisoning can induce symptoms ranging from mild gastrointestinal effects and paraesthesia to widespread paralysis, hypotension, respiratory depression and death [1–3]. To date, no effective antidote is available for treating tetrodotoxin poisoning and the mainstay of treatment remains supportive including mechanical ventilation or inotropic support in severe or life-threatening cases [4]. These two cases demonstrated a constellation of symptoms and signs caused by tetrodotoxin poisoning from pufferfish consumption. Clinical physicians should be aware of such medical emergencies and acquire adequate knowledge for appropriate management.

References

[1] Lago J, Rodríguez LP, Blanco L, et al. Tetrodotoxin, an extremely potent marine neurotoxin: distribution, toxicity, origin and therapeutical uses. Mar Drugs. 2015;13:6384–6406.
[2] Ahasan HA, Mamun AA, Karim SR, et al. Paralytic complications of puffer fish (tetrodotoxin) poisoning. Singapore Med J. 2004;45:73–4.

Table 1. Incidence of poisonous snakebites and snakebites treated with antivenom between 1 April and 30 September 2016 in the service area of participating PCCs of the EAPCCT Central European and Accession Countries Working group members.

Species of poisonous snake	Incidence of all symptomatic snakebite (per million inhabitants)[a]	Incidence of snakebites treated with antivenom (per million inhabitants)[a]	Incidence of all symptomatic snakebite (per million inhabitants in service areas within distribution areal of snake species)	Number of inhabitants living in service areas within distribution area of snake species (in millions)
Vipera berus	4.00	0.79	5.01	76.4
Vipera ammodytes	0.20	0.11	0.84	23.8
Vipera aspis	0.01	0.00	0.11	8.9
Macrovipera lebetina	1.16	1.16	6.17	18.0
Unidentified	0.80	0.45	1.28	60.0
Total	**6.27**	**2.52**	/	/

[a]Total population is approximately 95.8 million inhabitants.

[3] Field J. Puffer fish poisoning. J Accid Emerg Med. 1998;15:334–336.
[4] Yong YS, Quek LS, Lim EK, et al. A case report of puffer fish poisoning in Singapore. Case Rep Med. 2013;2013:206971.

269. Accidental exposure to chemical compounds in Danish schools: a report from the Danish Poison Information Center

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Objective: In Denmark about one fifth of accidents involving children aged 6 to 14 years leading to hospital contact occur at school. Around 0.11% of these are due to chemical exposure [1]. The aim of this study was to investigate the nature and distribution of enquiries to the Danish Poison Information Center (DPIC) due to accidental exposure to chemical compounds in Danish schools.
Methods: We performed a retrospective search of all enquiries to the DPIC between January 2006 and October 2016 identifying cases where the place of accidental exposure was registered as being at a school. Information on chemical agent, age, gender and risk assessment was also retrieved. Enquiries involving drugs, medication, plants, mushrooms and animals were excluded.
Results: A total of 1380 enquiries were retrieved, revealing an average of two enquiries per week. The majority of patients (75%) were of school age (6–18 years) with a median age of 14 years (range 6–48 years). The most frequent accidents involved exposure to copper sulphate (8.9%), acids (6.3%), gases (3.5%), compounds of sodium (3.3%), sulphur (3.2%), potassium (2.9%), ammonium (2.7%), chlorine compounds (2.6%) and ethanol (2.4%). Other exposures included silver (1.8%), bromide compounds (1.5%), cleaning products (1.7%), calcium compounds (1.5%), petroleum (1.3%), mercury (1.2%), glue (1.2%), organic solvents (1.2%) and lead (0.4%). The remaining 52.4% consisted of cases involving a vast variety of different chemical agents where the cases of each agent accounted for n <10. Risk assessment was distributed as followed: no risk (34.3%), minor (31.2%), moderate (19.6%) and life-threatening risk (0.3%). The cases assessed as life-threatening risk ($n = 4$) involved ingestion of ammoniac ($n = 2$), quinine ($n = 1$) and copper sulphate ($n = 1$). In many cases the contact to DPIC was made by the student him/herself several hours after the accidental exposure.
Conclusion: We hope this report will draw attention from authorities and schools to the need for improving the safety of activities with chemical compounds in Danish schools. Teachers and other school staff must be trained in preventing and managing accidental exposures more efficiently. It is important to keep in mind that only the cases leading to contact to the DPIC were included in this report. The total number of accidental chemical exposure in Danish schools is believed to be higher.

Reference

[1] Laursen B, Nielsen LT, Christensen PH, et al. Børneulykker i Danmark. En registerbaseret analyse. [Child accidents in Denmark. A register-based analysis]. Statens Institut for Folkesundhed, September 2006. Danish.

270. Acute phenobarbital poisoning: Moroccan Poison Control and Pharmacovigilance Centre data (2008–2014)

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Objective: The use of barbiturates in the West has declined rapidly with the advent of benzodiazepines and newer antiepileptic drugs. Despite the decline in barbiturate use, cases of acute poisoning with severe toxicity are still noted at staggering rates in developing countries, where resource limitations and the affordability of barbiturates lend to their increased use as anticonvulsants. The purpose of this study was to investigate the epidemiological data of acute phenobarbital poisoning in Morocco.
Methods: A retrospective study of all medical records of the Moroccan Poison Control and Pharmacovigilance Centre (CAPM), received from 2008 to 2014 concerning acute phenobarbital poisoning, was conducted. The data included circumstances of poisoning, sex, age distribution, symptomatology and outcome. The age classification used was the International Programme on Chemical Safety classification.
Results: In total 97 enquiries involving acute phenobarbital poisoning were received at CAPM over the study period. The sex-ratio was 0.4 (69 females, 27 males). The average age was 19.1 ± 12 years; 45.4% of cases were adults and 27.8% were adolescents. Suicidal attempts corresponded to 55.7% of cases and 25.7% of exposures were unintentional. Therapeutic errors accounted for 6.2%. Drug abuse was detected in one case. Nervous system disorders occurred in 25 cases. Multiple doses of activated charcoal were used in three patients. The mortality rate was 2.1%.
Conclusion: Phenobarbital poisoning remains a health problem in Morocco. The availability of this drug at the home could be responsible for the increase in accidental poisoning cases. A study of the relationship between the use of this drug and the suicide attempts rate would be interesting.

272. Energy drink consumption patterns and knowledge of adverse effects amongst medical students, pharmacy students, pharmacists and residents in Québec, Canada

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Objective: The primary goal was to determine energy drink (ED) consumption patterns amongst Québec's medical/pharmacy students and McGill University Health Center (MUHC) pharmacists and residents. We also sought to discover potentially underreported risks associated with ED consumption, examine the awareness of the study participants of these risks and explore the experience of the respondents with patients presenting with signs of ED toxicity.

Methods: A 20 question online survey was sent from 1 October to 16 October to 3368 medical and pharmacy students, 84 pharmacists and all residents of the MUHC. The study was approved by McGill Faculty of Medicine Institutional Review Board.
Results: The survey was sent to 4000 different email addresses via different intermediaries. In 2 weeks, 432 out of 501 respondents completed the entire questionnaire. The response rate varied between groups of respondents; 23.1% of respondents answered to have consumed at least one ED. Of these, 50% use ED to study and 67.3% mixed at least once ED with alcohol. Most of these participants consumed 1 can or less on a daily average, but 8.8% consumed 3 or more in a single day at least once. Adverse effects were reported in 47.1% of these respondents, with palpitations (33.3%) and anxiety (20%) being the most common. The consumption of coffee (72%) or tea (70%) was frequent among the study population, with 51% and 25% of participants using at least one cup of coffee or tea per day, respectively. Only 58% of ED consumers knew of the recommended daily caffeine limit of 400 mg of Health Canada. Lastly, less than 5.4% of the pharmacists and residents surveyed routinely ask their patients about use of energy drinks.
Conclusion: The difference in response rate highlighted unforeseen issues in the survey distribution with one group not receiving the full survey invitation. Despite the low overall response rate obtained in these two weeks, results indicate that energy drinks are used in the medical community but that less than half of participants know of important aspects concerning their safety profile. Furthermore, the caffeine content of energy drinks added to other caffeine rich beverages (coffee, tea) could possibly exceed the daily recommended limit and lead to side effects. With the tremendous growth of the energy drinks market in the last decade, medical and pharmacy students could benefit from education on the toxicity risks posed by these beverages for themselves and their patients.

273. Epidemiology of poisonings by psychoactive substances in Russia

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Objective: Poisoning by psychoactive substances occurs in Russia as well as in other countries. We studied the prevalence and types of psychoactive substances for drug intoxication.
Methods: We analysed data for the period 2013–2016 from toxicological centers in 5 regions of Russia: Moscow and St Petersburg (European region), Ekaterinburg (Ural), Omsk and Krasnoyarsk (both in Siberia) and Khabarovsk (Far East).
Results: Overall 4 territories in the study showed a particularly marked increase in cases of poisoning involving narcotics and other psychoactive substances (PASs): Ekaterinburg from 171 to 408, Omsk 538 to 1895, Krasnoyarsk 614 to 865 and Khabarovsk 52 to 133. In Moscow and St Petersburg a slight decrease was noted from 759 to 757 and 3857 to 3833, respectively. It was noted that there was a change in the relative number of opioid poisonings (heroin, methadone with substantial methadone prevalence in St Petersburg) and psychodisleptics including synthetic cannabinoid receptor agonists (SCRAs) in the European region. The ratio of opioids to psychodisleptics was reduced by 1.6 times in St Petersburg, 5 times in Omsk, 2.6 times in Krasnoyarsk and Khabarovsk with a simultaneous increase in poisoning cases with SCRAs by 1.1, 8.8, 1.4 and 6.3 times, respectively. In Moscow a 1.4 times decrease of SCRA cases was noted. Laboratory identification of PASs in Ekaterinburg showed the prevalence of synthetic psychostimulants (SPs) which increased 10-fold up to 2013, but in the last 2 years has abruptly dropped. By 2015 the prevalence of SPs to SCRAs was 1.3 times and in Moscow the proportion of SPs to SCRAs was 1.6 times. In addition Russian drugs including "Corvalol" for narcotic intoxication as an alcohol or opioid substitute (dosage 50–100 mL) and as a quieting drug (25–30 drops), containing phenobarbital 1.8%, mint of isovalerian acid and ethanol, the centrally-acting muscle relaxant baclofen and the antiepileptic pregabalin, reached 4.8%, 0.8% and 1.2% of PASs cases, respectively. Overall poisonings with narcotics and psychodisleptics totaled 12.2% of all admitted poisoning cases. In-hospital lethality was 5.0% and mortality due to acute poisonings with narcotics and psychodisleptics reached 4.1 per 100,000 in 2015; 78.5% of lethal cases involved opioids.
Conclusion: Poisonings with PASs occurs in Russia and there has been a marked increase in poisonings, mainly due to SPs and SCRAs. The data do not show regional differences and demonstrate common trends in psychoactive drug use across Russia.

274. Epidemiology of rattlesnake envenoming reported to an Arizona Poison Center

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Objective: To describe the demographics of victims of rattlesnake bites reported to a poison control center in Arizona.
Methods: A retrospective chart review of all rattlesnake exposures reported to a poison control center in Arizona from January 2002 to December 2014. Cases were reviewed for date of bite, patient age and gender, bite site, circumstances of bite, and involvement of alcohol. Bites were categorized as either legitimate or illegitimate based upon whether the risk of envenomation was known prior to the bite and whether action was taken to reduce the risk prior to being bitten.
Results: There were 1738 cases that met inclusion criteria out of 1937 identified in the study period. The average age of victims over the study period increased from 34 to 44 ($p < .005$). The majority of bites occurred from April to September (74.3%) and the majority of victims were male (63%). The number of bites to the hand/finger did not change significantly during the study period ($p = .487$), but the number of bites to the foot/ankle did ($p < .005$). Bites occurring while the victim was gardening or walking outside also increased significantly ($p < .005$). There was an upward trend in legitimate bites, but it did not reach significance.
Conclusion: The traditional profile of the victim of a rattlesnake bite has been a young, inebriated man provoking the animal prior to envenoming [1,2]. This study challenges that dogma for victims in Arizona by demonstrating the average victim to be a middle-aged man increasingly likely to be bitten on the lower extremity.

References

[1] Curry SC, Horning D, Brady P, et al. The legitimacy of rattlesnake bites in central Arizona. Ann Emerg Med. 1989;18:658–663.
[2] Warrell DA. Management of exotic snakebites. QJM. 2009;102:593–601.

275. Fatal poisoning by pharmaceuticals and illicit drugs: comparison of cases reported to a Poisons Centre with official death certificates

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Objective: To compare fatal poisonings by pharmaceuticals and illicit drugs recorded by the Federal Statistical Office (FSO) in the official death register of Switzerland to cases reported to the National Poisons Centre of Switzerland (PC).
Methods: Retrospective review of cases from the official death register and cases reported to the PC from 1999 to 2009. The number of cases from the FSO with ICD-10 codes X40–44 (accidental poisoning) and X60–64 (intentional self-poisoning) on death certificates were compared to the number of fatal poisonings by pharmaceuticals and illicit drugs reported to the PC. Cases with confirmed assisted suicide ($n = 1722$, coded by the FSO within the group X61) were excluded because of the unique circumstances of these poisonings.
Results: A total of 3274 poisoning deaths were recorded by the FSO; 80 cases were reported to the PC (Table 1). In both data sets about half of the deaths were registered in the ICD-10 groups X41/61. The second and third most frequent groups in both data sets were X44/64 and X42/X62, respectively. Few cases were registered in the remaining two groups.
Conclusion: Poisoning deaths by pharmaceuticals and illicit drugs recorded by the PC and the FSO show a very similar picture concerning the substances involved, even though the PC registered only a small fraction of the poisoning deaths in Switzerland over the study period. Most frequently substances with an effect on the central nervous system such as antidepressants, neuroleptics and sedative-hypnotics are involved.

276. Fatalities due to acute intoxications from 2000 to 2015: a survey of the Poisons Information Centre Austria

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Objective: To describe fatalities due to acute intoxication documented in the Poisons Information Centre (PIC) Austria from 2000 to 2015.
Methods: Fatalities were analysed, regarding age, circumstances and causative agents.
Results: The PIC documented 69 fatalities from 2000 to 2015. Sixty-six patients (95.7%) were ≥18 years old; 42 cases (60.9%) 18–70 years, 15 cases (21.7%) ≥ 70 years old, 9 adults (13%) with unknown age. Two fatalities were adolescents and one was a child. The main toxins were pharmaceuticals ($n = 40$; 58%), predominantly psychotropic, analgesic, and cardiac drugs. The remainder were: chemicals ($n = 10$, 14.5%), plants ($n = 4$; 5.8%), *Amanita phalloides* ($n = 3$; 4.3%), drugs of abuse ($n = 4$; 5.7%), detergents and disinfectants ($n = 5$; 7.2%), toxic gases ($n = 2$; 2.8%) and unknown agent ($n = 1$; 1.4%). The circumstances of exposure were suicidal ($n = 46$; 66.6%), accidental ($n = 13$; 18.8%), iatrogenic ($n = 3$; 4.3%), drug abuse ($n = 4$; 5.8%) and unknown ($n = 3$; 4.3%). In patients over 70 years fatalities occurred in 7 out of 15 cases after accidental exposure (46.7%); two cases after *Amanita phalloides* ingestion, a 91-year-old man after eating leaves of *Colchicum autumnale*, an elderly man due to inhalation of carbon monoxide, two women with dementia after drinking vinegar essence and after ingestion of an all-purpose cleaner and a 97-year-old woman died after drinking an unknown amount of drain cleaner. The remainder were suicidal cases ($n = 6$) involving ingestion of psychotropic ($n = 2$), cardiac ($n = 1$) and anticholinergic ($n = 1$) drugs, vinegar essence ($n = 1$), organophosphate ($n = 1$) as well as one iatrogenic case due to methotrexate and one unknown intent caused by a disinfectant. In the age group of 18–70 years suicide by pharmaceuticals was the most common cause of death (32 of 42; 76.2%). There were also fatalities after ingestion of vinegar essence, a disinfectant containing quaternary ammonium compounds, other chemicals, drugs of abuse and toxic plants. The remainder were: accidental ($n = 5$) exposure to *Colchicum autumnale*, chemicals, toxic gas; two cases of medical malpractice (lithium and selenium supplements); two unknown circumstances (pharmaceuticals, drugs of abuse) and one case of abuse (mephedrone). A 17-year-old adolescent died after consumption of ecstasy, a 17-year-old girl after suicidal ingestion of colchicine tablets and a 16-month-old boy after ingestion of a meal with *Amanita phalloides*.

Table 1. Fatal poisonings by pharmaceuticals and illicit drugs, comparing poison centre and Federal Statistical Office data, 1999–2009.

ICD-10 code and description		Federal Statistical Office (FSO)		National Poisons Centre of Switzerland (PC)	
X40/60	nonopioid analgesics, antipyretics and antirheumatics	24	0.7%	2	2.5%
X41/61	antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified	1683	51.4%	39	48.8%
X42/62	narcotics and hallucinogens, not elsewhere classified	676	20.6%	12	15.0%
X43/63	other drugs acting on the autonomic nervous system	15	0.5%	0	0.0%
X44/64	other and unspecified drugs, medicaments and biological substances	876	26.8%	27	33.7%
Total		3274	100%	80	100%

Conclusion: Suicide was the most common reason for fatal intoxications among those under the age of 70 years. Accidental fatalities were documented mainly in elderly people.

277. Liver injury in acute poisoning in children: specific issues of etiology and evolution

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Objective: To identify the etiology and evolution of acute liver injury in children with acute poisoning.
Methods: We performed a 5-year retrospective study of cases with acute toxic-induced liver injury admitted in two pediatric poisoning centers, taking into consideration the following criteria: age, gender, etiology and evolution.
Results: Out of the total number of the 4844 poisoned children admitted between 2010 and 2014, 77 cases (1.6%) presented acute toxic-induced liver injury, at admission or during hospitalization. There were 42 girls and 35 boys with an average age of 10.3 years. Non-pharmacological substances were implicated in the majority of cases ($n = 51$, 66.2%), and were mushrooms ($n = 40$, 78.4%), organophosphate compounds ($n = 8$, 15.6%), nitrites ($n = 2$, 3.9%) and novel psychoactive substances ($n = 1$, 2.0%). Paracetamol was the main pharmacological agent involved ($n = 13$, 50%), followed by isoniazid ($n = 3$, 11.5%), valproic acid ($n = 2$, 7.7%), antipsychotics ($n = 1$, 3.8%) and colchicine ($n = 1$, 3.8%). In 6 cases multidrug poisoning was noted (combination of paracetamol and non-steroidal anti-inflammatory drugs with other drugs). Neurological signs or coagulopathy suggesting evolution towards acute hepatic failure were present in 30 cases (38.9%), involving mushrooms ($n = 21$, 70%), paracetamol ($n = 7$, 23.3%), valproic acid ($n = 1$, 3.3%) and colchicine ($n = 1$, 3.3%). Mushroom exposure was associated with a 2.1 times higher risk of evolution to acute liver failure compared to other agents. Of the 77 patients, 64 (83.1%) survived and 13 (16.9%) died. The agents in the fatal cases were mushrooms ($n = 7$), organophosphates ($n = 4$), nitrites ($n = 1$) and colchicine ($n = 1$). Hypoglycemia, hyperbilirubinemia and increased INR values were the main risk factors for fatal evolution.
Conclusion: Despite low prevalence, mortality is higher in acute poisoning associated with liver injury, highlighting that the presence of toxic liver injury increases the severity of acute poisoning [1]. In our study, non-pharmacological agents were the main agents implicated in acute toxic-induced liver injury and in its fatal evolution too, while in the literature paracetamol is the main cause of acute toxic liver injury [2].

References

[1] Lee WM, Squires RH, Nyberg SL, et al. Acute liver failure: Summary of a workshop. Hepatology. 2008;47:1401–1415.
[2] Craig DG, Bates CM, Davidson JS, et al. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. Br J Clin Pharmacol. 2011;71:273–282.

278. Paediatric and adolescent poisoning in the Hunter region of Australia

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Objective: The aim of this study was to describe the demographic and clinical characteristics of paediatric and adolescent poisonings reported to a regional toxicology service in the Hunter region of New South Wales, Australia.
Methods: The Hunter Area Toxicology Service (HATS) handover database was searched for cases between 1 January 2015 and 31 August 2016 for all calls regarding patients aged under 18 years. Calls received from facilities outside the HATS referral area were excluded. Two subgroups were defined, aged 12 and under (paediatric) and 13–17 years (adolescent). Demographic data including age and sex was extracted in addition to clinical data including the reason for the consultation, presenting facility and the nature of the ingestants. The electronic medical record was searched for individual cases where data was insufficient or incomplete within the handover database. The study was approved by the area ethics committee. Descriptive statistics were used to analyse the data with medians describing continuous variables and proportions expressed as percentages used for categorical variables. Statistics were calculated using Microsoft® Excel.
Results: A total of 666 cases met the inclusion criteria, of these 4 cases were excluded due to inadequate data entry and 63 who had presented outside the HATS referral area. This left 599 cases in the final cohort. There were 220 paediatric presentations with median age of 2 years and 52% were female. This group accounted for 259 exposures, 66% of which were pharmaceutical ingestions. The adolescent group had 379 presentations. Median age was 16 years and 77% were female. There were 603 exposures of which 539 (89%) were pharmaceutical ingestions. Subgroups and further details are provided in Table 1.
Conclusion: Most paediatric exposures occurred in the toddler age group. Adolescent poisoning exposures have a significantly higher proportion of females and are more likely to be due to pharmaceutical ingestions.

Table 1. Paediatric and adolescent poisoning in the Hunter region of Australia

Variable		Paediatric Group $n = 220$ (%)	Adolescent Group $n = 379$ (%)
Median age in years		2 (0–12)	16 (13–17)
Female sex		114 (52)	292 (77)
Multiple ingestion (>1 toxin)		–	130/379 (34)
Presentation to rural facility		30/220 (14)	41/379 (11)
Ingestant categories		–	–
Pharmaceutical		172/259 (66)	539/603 (89)
Subgroups	Analgesics (paracetamol, NSAIDs, opiates)	NA	211/539 (39)
	Psychotropic agents (includes sedatives and antidepressants)	NA	179/539 (33)
	Miscellaneous groups	NA	149/539 (28)
Chemical exposure		42/259 (16)	29/603 (5)
Natural toxin		38/259 (15)	17/603 (3)
Recreational agents		0 (0)	16/603 (3)
Other		7/259 (3)	0 (0)

279. Characterizing benzodiazepine toxicities using the Toxicology Investigators Consortium (ToxIC) Registry

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Objective: Benzodiazepines are among the most widely prescribed drugs in the US. Benzodiazepine toxicity may result in significant respiratory and central nervous system (CNS) depression. Our objective was to characterize benzodiazepine exposures reported in the ToxIC Registry from January 2010 to July 2016.
Methods: The ToxIC Registry database was queried for all benzodiazepine exposures from January 2010 to July 2016. Data collected included age, gender, race, chronicity of exposure, presence of co-ingestants, pertinent symptoms, use of gastrointestinal (GI) decontamination techniques [gastric lavage (GL), activated charcoal (AC), whole bowel irrigation (WBI)], intubation (ET), hemodialysis (HD), multi-dose activated charcoal (MDAC), intravenous fluids (IVF), and use of flumazenil.
Results: Over the study period, 4658 cases met the inclusion criteria. Exposures were slightly more common in females (54.1%) than males (42.8%). The majority of exposures occurred in persons aged 19–65 years (78.9%), with significantly fewer exposures in patients aged 13–18 years (8.9%), >65 years (4.8%), and 0–12 years (4.4%). Race was recorded in only 1031 (22%) of cases. Of these, Caucasian (81.3%) and Black (11.2%) were the most commonly reported. Exposures were acute in 44.2%, acute-on-chronic in 11.3%, and chronic in 3.5% of exposures. Clonazepam (33.2%), alprazolam (29.8%), lorazepam (18.2%), and diazepam (8.9%) accounted for the vast majority of benzodiazepine exposures. Only 23.4% of benzodiazepine exposures occurred as a single-substance exposure, the remainder being part of a polysubstance ingestion. In terms of symptomatology, 34.6% of patients developed a sedative-hypnotic toxidrome, 55.1% exhibited central nervous system depression, and 13.1% exhibited respiratory depression. Few patients received a GI decontamination intervention (GL 0.2%, AC 3.6%, WBI 0.2%), or underwent enhanced elimination (HD 0.2%, MDAC 0.1%). Sixty-four percent of patients received some kind of treatment, with the most common being IVF (23.8%). Intubation was performed in 12.3% of patients, and 2.8% required vasopressors. Flumazenil was administered in 11.2% of cases, primarily in the 19–65 (84.5%) and >66 years (7.6%) age groups. Twenty-four patients were reported to have died.
Conclusion: Benzodiazepine exposures reported to the ToxIC Registry occurred primarily in females, people aged 19–65 years old, were acute in nature, and part of a polysubstance ingestion. Few GI decontamination or enhanced elimination interventions were performed or necessary, and only a small percentage of exposures were treated with flumazenil.

281. Acute poisoning in children with concentrated laundry detergent capsules

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Objective: In Moscow an increased number of cases of acute poisoning with concentrated laundry detergents in water soluble capsules was registered. Patients admitted to the Moscow Children's Poisoning Treatment Center due to ingestion of soluble capsules with concentrated laundry detergents has increased from 22 in 2011 to 133 in 2015 and most frequently occured in children during the first three years of life. We studied the severity of digestive tract injury and evaluated this household hazard in children.
Methods: We analysed case reports of poisoning by concentrated laundry detergents including evaluation of clinical picture, blood count and biochemical parameters, urine analysis, esophagogastroscopy, and chest X-ray examination for all children admitted to the treatment center.
Results: In total there were 104 children aged 8 months to 3 years with liquid concentrated laundry detergent exposure. Anxiety, hoarseness, increased salivation and refusal of food intake were reported in these children. In 47% of cases nausea and vomiting were observed. There was swelling, redness in the oral cavity mucous membrane and pharynx of all patients. In 3 cases respiratory failure developed due to pronounced pharyngeal edema, which required tracheal intubation. Esophagogastroscopy revealed chemical burns of the esophagus presenting as longitudinal sections of hyperemia, mucosal edema throughout the esophagus and single erosions in 29% of patients. In 10% of cases there was a chemical burn of stomach, and in rare cases damage was described as acute gastritis. Chest radiography showed increased vascular pattern in the lungs in 50% of cases and in one case aspiration pneumonia was registered. Blood count and urine analysis of most patients were in the normal range, except moderate leukocytosis with an increase in the number of neutrophils observed in some cases. During the first day mild increases in alanine aminotransferase (56–77 U/L [normal up to 55 U/L]) and aspartate transaminase (103 U/L [normal up to 40 U/l]) concentrations were observed in 11% of children. In some cases, there were increases in serum amylase (to over 100 U/L [normal up to 80 U/L]) and glucose (7–10 mmol/L [normal up to 6.2 mmol/L]). After treatment, normalization of laboratory parameters was registered and re-esophagogastroscopy showed complete esophagus and stomach mucous membrane healing.
Conclusion: Ingestion of water-soluble capsules with liquid laundry detergents pose a risk of chemical burns of the mouth, esophagus and stomach in children. This can lead to life-threatening conditions such as aspiration pneumonia and respiratory tract burns. Such cases require immediate hospitalization.

282. Characterization of endoscopic findings following ingestion of liquid laundry detergent packet products as reported to US poison centers

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Objective: Exposures to liquid laundry detergent packets (LDPs) have been well described. However, the role of upper-endoscopy and bronchoscopy in management remains unclear. This analysis aims to evaluate the clinical effects (CEs) leading to the performance of endoscopy and the severity of endoscopic findings after LDP ingestion.

Methods: LDP exposures reported to US Poison Centers were reviewed if any of the following occurred: death, major medical outcome, suspected suicide. Cases were also reviewed for children aged <6 years with medical outcome of moderate effect and admission to a healthcare facility or if any clinically significant CE (e.g., coma) or therapy (e.g., intubation) was reported. CEs were documented for each case. Endoscopic findings were reviewed by a physician who assigned a severity score (0 – normal findings, 1 – erythema and/or mild edema, 2 – superficial burns and/or moderate edema, 3 – deep burns and/or severe edema). Mean severity scores were calculated.
Results: In total 450 cases were reviewed. Upper endoscopy was performed in 102 (22.7%) patients with a mean severity score of 1.07. Bronchoscopy was performed in 30 (6.7%) patients with a mean severity score of 1.07. The mean severity score for any patient with endoscopy was 1.04. Drooling was reported in 49.0% of upper endoscopy patients and in 29.9% of patients where upper endoscopy was not reported. Vomiting was similarly reported between these two groups (86.3% upper endoscopy; 79.6% no upper-endoscopy). The mean severity scores for upper-endoscopy patients with reported vomiting (1.04), drooling (1.02), or neither (1.11) were similar. Both stridor (60.0% bronchoscopy; 33.3% no bronchoscopy) and respiratory depression (36.7% bronchoscopy; 19.8% no bronchoscopy) were reported more commonly in bronchoscopy patients compared to patients where bronchoscopy was not reported. When the presence of stridor or respiratory depression was evaluated, this combined endpoint was reported in 80.0% of bronchoscopy patients compared to 41.2% of patients where bronchoscopy was not reported. Mean severity scores for cases reporting stridor (0.81), respiratory distress (1.20), both (0.25), or neither (1.00) were similar.
Conclusion: Following LDP ingestion, upper-endoscopy and bronchoscopy findings were not associated with severe outcomes as the mean severity score was 1.04 with any endoscopy performed. Drooling, but not vomiting, appears to lead to the performance of upper endoscopy, while stridor and/or respiratory distress appear to lead to the performance of bronchoscopy. However, the presence or absence of these effects did not correlate with the severity of findings. The generally limited report of findings in both limits the strength of these observations.

283. Circumstances of liquid laundry pod exposure: a prospective study based on calls to the French Poison Control Centers

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Objective: Liquid laundry pods (LLPs) are widely used by households but are known to be a pediatric poisoning risk. As only a few studies have focused on the circumstances of exposure to LLPs, the French Toxicovigilance Coordination Committee network has provided a description of these circumstances to help health authorities take preventative measures.
Methods: We conducted a prospective study of the circumstances surrounding exposure of children under 6 years of age to LLPs, for whom an adult called a French PCC between 12 January and 15 February 2015. Based on a specific questionnaire conducted during the PCC call with the caller's consent, we studied the characteristics of containers and their storage locations, and interviewed callers (parents or other relatives) about their risk perception regarding household products.
Results: In total, 253 children under 6 years of age unintentionally exposed to LLPs were included in the population study. The survey participation rate was 82.7%. The sex ratio was 1.1 and the median age 1.9 years. Oral exposure was reported in 86.5% of cases; 78.0% of cases were symptomatic, including one Poison Severity Score (PSS) 3 case. The events occurred at the child's home in 93.1% of cases and were their first household accident in 94.5% of cases. While exposure occurred in the room containing the washing machine in 81.5% of cases, in only 38.5% of cases was someone in the process of doing laundry. Children managed to remove the pods from their containers themselves in 72.4% of cases (176/243 documented cases), a box or pouch in 93.1% and 6.9% of cases, respectively. Only 41.5% of these containers were stored in a safe place. Finally, while 61.9% of children succeeded in opening the containers themselves, the opacity or transparency of the packaging did not influence if children removed the pod from an already open or closed box. Of the remaining 27.6% of children who found pods already outside containers (67/243 documented cases), 35.8% removed them directly from the washing machine. 58.5% of interviewed adults declared they paid attention to the recommendations on household packaging products.
Conclusion: Our results highlight the need to improve education concerning LLP poisoning risks. Pod containers must be properly closed and stored in a safe place completely out of children's reach. Measures to enhance container security and reduce pod toxicity would also prevent such accidents. Furthermore, the monitoring of LLP exposure would make it possible to evaluate the impact of these initiatives.

284. Exposures to automatic dishwashing detergents examined by an Italian Poison Control Center

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Objective: Automatic dishwashing detergents (ADDs) are alkaline based and fairly aggressive household products that require precautions when in use. Oral and gastrointestinal tract irritation, corneal and skin damage has been documented. We analysed cases reported to our poison center.
Methods: We analyzed cases of ADD exposure from 2010 to 2014 by detergent type, route of exposure, and medical outcome. ADDs were divided into powder, liquid, powder tablets (PTs) and unit dose pouches delimited by soluble membrane (UDPs).
Results: During the study period we collected 1943 cases: 2010 $n = 390$, 2011 $n = 447$, 2012 $n = 417$, 2013 $n = 354$ and 2014 $n = 335$. We analyzed a random sample of 467 cases in which follow-up was successful. Exposures to ADDs occurred mainly as a result of ingestion alone in 243 cases: no symptoms were present in 153 cases ($n = 109$ PTs, $n = 13$ powders, $n = 29$ liquids, $n = 2$ UDPs); minor symptoms were present in 74 cases ($n = 40$ PTs, $n = 5$ powders, $n = 22$ liquids, $n = 7$ UDPs); moderate symptoms in 8 cases ($n = 3$ PTs, $n = 1$ powder, $n = 4$ liquids); severe symptoms in 2 cases ($n = 1$ liquid, $n = 1$ PT). Mucosal contact alone was involved in 184 cases: no symptoms were present in 163 cases ($n = 109$ PTs, $n = 22$ liquids, $n = 20$ powder, $n = 12$ UDPs); minor symptoms were present in 18 cases ($n = 14$ PTs, 3 liquids, $n = 1$ UDP); moderate symptoms were present in 2 cases ($n = 2$ liquids).Skin contact was involved in 5 cases: no symptoms were present in 3 cases ($n = 1$ liquid; $n = 2$ PTs); minor symptoms were present in 2 cases ($n = 1$ powder; $n = 1$ PT). Multiple routes

of exposure were involved in 21 cases: no symptoms were present in 14 cases ($n = 6$ PTs, $n = 3$ powders, $n = 5$ liquids); minor symptoms were present in 6 cases ($n = 3$ PTs, $n = 2$ liquids, $n = 1$ UDP); moderate symptoms in 1 case ($n = 1$ liquid).
Conclusion: Exposures to ADDs represent about 20% of the total exposures to household products. From data analysis PTs and powders represent the detergent types that are more involved in exposures (72.4%). However they do not present any particular toxicological problems. Liquids were involved in 6.6% of minor and in 1.9% of moderate poisonings. This study suggests that the market entry of UDPs, did not address the safety issues common to regular kinds of detergent (such as PTs, powders, and liquids). However, they do not show higher risks of toxicity since in 5.4% ($n = 25$) of certain exposure cases, 14 presented with no symptoms, 10 had minor symptoms, and 1 had a moderate ocular exposure.

285. Ocular exposures to household detergents and cleaning products

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Objective: Ocular exposure to household detergents and cleaning products is a public health event. We sought to analyze ocular exposures to household products reported to an Italian Poison Control Center.
Methods: Eye exposures from1 March 2014 to 28 February 2015 were analyzed.
Results: During the study period 446 eye exposures were collected. The age group distribution was: infants ($n = 8$), toddlers ($n = 224$), schoolchildren ($n = 16$), 2 adolescent 17 years, 193 adults, 20 elderly, and 3 unknowns. Overall there were 227 females, 217 males and 2 of unknown gender. All exposures were accidental, including 13 occupational; 5.6% of exposures involved products for professional use. In total 408 cases were followed-up successfully (91.5%). Overall 305/408 cases with completed follow-up were classified as minor (74.8%), 64 as moderate (15.6%), 1 as severe (0.2%), no symptoms were present in 36 cases (8.8%) while 40 cases could not be graded based on the dataset collected (9.8%). Frequent symptoms that were reported were signs of irritation. Moderate cases were caused by laundry detergents ($n = 14$), of these 9 were liquid laundry detergent capsules (LLDCs); textile bleaches ($n = 12$); all purpose and neutral cleaners ($n = 10$); hand and machine dishwashing detergents ($n = 7$); toilet cleaners ($n = 3$); oven and grill cleaners ($n = 2$); laundry additives ($n = 2$); others ($n = 5$); and unknown ($n = 9$). In 4 cases the eye irrigation was delayed and in one case the eyewash was performed with warm water and soap. Seventeen patients developed corneal damage; LLDCs were involved in 4 cases of corneal abrasion. One child with ocular exposure to a LLDC described yellow vision for a few minutes and corneal opacification for 7 days. In total 52 cases received hospital treatment, and 12 were not hospitalized. Full recovery was reported in 43 cases with healing expected in 20 cases, in 1 case the outcome was unknown. Of the 64 moderate cases, 42 have been identified with the exact brand name. The severe case was caused by a traditional liquid laundry detergent (TLLD). Two cases with residual eye damage over 21 days were collected: one patient suffered from persistent sensitivity to light and another patient suffered photophobia and reduced vision. Four asymptomatic cases and 36 mild cases became moderate after follow up.
Conclusion: Most patients exposed to household cleaning products suffer minor symptoms. LLDCs were involved in 4 cases of corneal abrasion and one severe case involved a TLLD, probably in relation to the dehydrating action of surfactants.

286. Paediatric poisonings from ethanol-based household products: a review of enquiries to the New Zealand National Poisons Centre, 2003–2015

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Objective: Ethanol is found in various household products, including hand sanitisers, teething gels, perfumes, cosmetics, methylated spirits, other therapeutics (homeopathic remedies and cough suppressants), and in consumables (alcoholic drinks and food essences). Ingestion of ethanol can cause concerning symptoms in children, including central nervous system (CNS) depression and hypoglycaemia. The aim of this study was to investigate paediatric poisoning following ingestions of ethanol-containing household products, based on calls received by the New Zealand National Poison Centre (NZNPC).
Methods: Data involving ingestion of ethanol-containing products in children (0–6 years) was extracted from the NZNPC database from 1 January 2003 to 31 December 2015. Data extracted included age, symptoms, product name and recommended treatment.
Results: The NZNPC received 3588 inquiries involving 3469 cases of ingestion. Hand sanitisers were the most common exposure (38%) followed by teething gels (20%), perfumes (11%), methylated spirits (10%), alcoholic drinks (6%) and insect repellents (5%). Other therapeutics, mouth washes, cosmetics and food essences were all <5%. There were no inquiries regarding hand sanitisers in 2003–2004 before a constant increase in calls was recorded, culminating in 206 calls in 2010 (587% increase from 2006 to 2010). Additionally, a significant increase in ingestions (220%) of other therapeutics was recorded from 2012 to 2015. Medical attention was required following 11% of hand sanitiser ingestions and 16% of other therapeutics, while alcoholic drinks, food essences and methylated spirits resulted in the highest amount of medical referrals (44%, 41% and 32%, respectively). Ages ranged from 1 month to 6 years; the majority being 1 and 2 years olds (38% and 34%, respectively). In children consuming alcoholic drinks, 20% displayed symptoms at the time of the call, most commonly dizziness/unsteadiness (48%), drowsiness (40%) and vomiting (35%).
Conclusion: Hand sanitisers showed an interesting trend with no or few inquiries early in the study period then increasing to become the most common source of exposure. The high incidence of hand sanitiser exposures is cause for concern as this product typically contains high concentrations of ethanol. However, only a small proportion of these exposures required medical attention suggesting only limited amounts were ingested. Although the incidence of alcoholic drinks ingestion is low (6% of exposures), they posed the highest risk of toxicity, as 44% of cases required medical intervention and 20% of children were symptomatic at the time of call. Awareness and poison prevention strategies, especially for hand sanitizers and alcoholic drinks, including ensuring products are out of reach of children, should be implemented to minimise exposures.

287. Effects of insulin on statin-induced myopathy and insulin resistance

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Objective: The goal of the study was to characterize the potential effect of insulin on statin-induced myopathy [1], investigating simvastatin-associated cytotoxicity, impairment of the Akt pathway [2] and induction of insulin resistance [3] in skeletal muscle cells.
Methods: Mouse C2C12 myotubes were used as a model of skeletal muscle cells. Cells were treated separately or in co-treatment with simvastatin (final concentration 10 µM) and insulin (from 10 to 100 ng/mL). Cytotoxicity assays, Western blots and polymerase chain reaction (PCR) as well as glucose uptake and reactive oxygen species (ROS) production assays were performed after 24 hours exposure.
Results: Simvastatin-induced cytotoxicity at 10 µM. Insulin exposure was able to prevent and rescue the cytotoxicity induced by simvastatin, reducing the latter by 50% with the highest concentration of insulin used (100 ng/mL). Phosphorylation status and activity of the insulin receptor, Akt, mTOR (target of rapamycin), and 4E-BP-1 (eukaryotic translation initiation factor 4E-binding protein 1) were suppressed by simvastatin 10 µM. Co-treatment with insulin was able to prevent these adverse effects associated with simvastatin. Atrophy genes, namely MaFbx and MuRF1, were upregulated with simvastatin to 2 fold, and this upregulation could be prevented by co-treatment with insulin. Furthermore, at 10 µM, simvastatin induced insulin resistance by decreasing the glucose transport rate into myotubes by half. This effect of simvastatin could be prevented by the addition of insulin.
Conclusion: This study highlights the importance of PI3K/Akt signaling in skeletal muscle and demonstrates the role of insulin in the prevention of myopathy and the insulin resistance associated with simvastatin.

References

[1] Dirks AJ, Jones KM. Statin-induced apoptosis and skeletal myopathy. Am J Physiol Cell Physiol. 2006;291:C1208–1212.
[2] Mullen PJ, Zahno A, Lindinger P, et al. Susceptibility to simvastatin-induced toxicity is partly determined by mitochondrial respiration and phosphorylation state of Akt. Biochim Biophys Acta. 2011;1813:2079–2087.
[3] Brault M, Ray J, Gomez YH, et al. Statin treatment and new-onset diabetes: a review of proposed mechanisms. Metabolism. 2014;63:735–745.

288. Electroencephalographic patterns of lithium poisoning: a study of the effect/concentration relationships in the rat

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Objective: Lithium overdose may result in encephalopathy and electroencephalographic abnormalities. Three poisoning patterns (acute, acute-on-chronic and chronic) have been identified based on the ingested dose, previous treatment duration and renal function. Whether severity of lithium-induced encephalopathy depends on the poisoning pattern is not established.
Methods: We designed a rat study to investigate lithium-induced encephalopathy and correlate its severity to plasma, erythrocyte, cerebrospinal fluid and brain lithium concentrations previously determined in rat models mimicking human poisoning patterns. Lithium-induced encephalopathy was assessed and scored using continuous electroencephalography.
Results: We demonstrated that lithium overdose was consistently responsible for encephalopathy, the severity of which depended on the poisoning pattern. Acutely poisoned rats developed rapid-onset encephalopathy which reached a maximal grade of 2/5 at 6 hours and disappeared at 24 hours post-injection. Acute-on-chronically poisoned rats developed persistent and slightly fluctuating encephalopathy which reached a maximal grade of 3/5. Chronically poisoned rats developed rapid-onset but gradually increasing life-threatening encephalopathy which reached a maximal grade of 4/5. None of the acutely, 20% of the acute-on-chronically and 57% of the chronically lithium-poisoned rats developed seizures. The relationships between encephalopathy severity and lithium concentrations fitted a sigmoidal Emax model based on cerebrospinal fluid concentrations in acute poisoning and brain concentrations in acute-on-chronic poisoning. In chronic poisoning, encephalopathy worsening paralleled the increase in plasma lithium concentrations.
Conclusion: Severity of lithium-induced encephalopathy is dependent on the poisoning pattern, previously shown to determine the lithium amount accumulated in the brain. Our data supports electroencephalography as a sensitive tool to score lithium-related neurotoxicity.

289. Mechanisms of cytotoxicity involved in metamizole-induced neutropenia

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Objective: Metamizole (dipyrone), a non-opioid analgesic prodrug can cause potentially life-threatening neutropenia, but it is rare. Currently, the mechanisms underlying metamizole-induced neutropenia (MIN) are poorly understood [1,2], and certain features are compatible with direct metabolic toxicity on circulating cells and/or their precursors in the bone marrow. Our objective was to investigate the mechanisms of cytotoxicity in neutropenia caused by the main metamizole metabolites 4-methylaminoantipyrine (MAA), 4-formylaminoantipyrine (FAA), 4-aminoantipyrine (AA), and 4-acetylaminoantipyrine (AAA).
Methods: We treated promyelocytic HL60 cells and neutrophil granulocytes with increased concentrations of metamizole metabolites (from 1 µM to 200 µM) with or without components of the oxidative system composed of horseradish peroxidase (HRP) and hydrogen peroxide (H_2O_2). We assessed the adenylate kinase release as a marker of cytotoxicity and adenosine triphosphate (ATP) content as a marker of cell viability.
Results: MAA, FAA, AA, and AAA were not cytotoxic nor did they decrease the ATP content in either cell line. MAA incubated with H_2O_2 was cytotoxic in HL60 cells starting at 1 µM and when we

co-incubated MAA with H_2O_2 and HRP together, cytotoxicity began at 100 µM. Furthermore, AA exposed with H_2O_2 solely or in combination with HRP showed cytotoxicity in HL60 cells at 100 µM. We observed decreased ATP content for all incubations containing H_2O_2 independent of added metamizole metabolites. However, in incubations containing H_2O_2 and MAA or AA the decrease in ATP content started before cytotoxicity. Furthermore, H_2O_2 alone decreased the ATP content in neutrophil granulocytes, but the co-treatment of MAA, FAA, AA, or AAA with H_2O_2 was not cytotoxic.
Conclusion: Since the co-incubation of H_2O_2 is needed to induce cytotoxicity by MAA and AA in HL60 cells, the associated decreased ATP content may amplify the sensitivity of cells to these metamizole metabolites. As the ATP content was decreased before cytotoxicity could be measured, impaired ATP-dependent processes could be part of the underlying mechanism for metamizole-induced neutropenia. As *in vitro* cytotoxicity was observed in the promyelocytic cell line HL60 but not in neutrophil granulocytes, this adverse drug reaction may affect only progenitor cells. Therefore colony-forming assays are now planned to investigate cytotoxicity of MAA, FAA, AA, and AAA on human myeloid progenitor cells.

References

[1] Andres E, Maloisel F. Idiosyncratic drug-induced agranulocytosis or acute neutropenia. Curr Opin Hematol. 2008;15:15–21.
[2] Garbe E. Non-chemotherapy drug-induced agranulocytosis. Expert Opin Drug Saf. 2007;6:323–335.

290. Neurobehavioral effects of lithium in the rat: an investigation of the effect/concentration relationships and the contribution of the poisoning pattern

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Objective: Severity of lithium poisoning depends on the ingested dose, previous treatment duration and renal function. No animal study has investigated neurobehavioral differences in relation to the pattern of lithium poisoning observed in humans, while differences in lithium pharmacokinetics have been reported in lithium-pretreated rats mimicking chronic poisonings with enhanced brain accumulation in rats with renal failure. Our objectives were 1) to investigate lithium-related effects in overdose on locomotor activity, anxiety-like behavior, spatial recognition memory and anhedonia in the rat; and 2) to model the relationships between lithium-induced effects on locomotion and plasma, erythrocyte, cerebrospinal fluid and brain lithium concentrations previously obtained according to the poisoning pattern.
Methods: Open-field, elevated plus-maze, Y-maze and sucrose consumption tests were used.
Results: In acutely lithium-poisoned rats, we observed horizontal ($p < .001$) and vertical hypolocomotion ($p < .0001$), increased anxiety-like behavior ($p < .05$) and impaired memory ($p < .01$) but no altered hedonic status. Horizontal ($p < .01$) and vertical ($p < .001$) hypolocomotion peaked more markedly 24 hours after lithium injection and was more prolonged in acute-on-chronically versus acutely lithium-poisoned rats. Hypolocomotion in chronically lithium-poisoned rats with impaired renal function did not differ from acutely poisoned rats 24 hours after the last injection. Interestingly, hypolocomotion/concentration relationships best fitted a sigmoidal Emax model in acute poisoning and a linear regression model linked to brain lithium in acute-on-chronic poisoning.
Conclusion: Lithium overdose alters rat behaviour and consistently induces hypolocomotion which is more marked and prolonged in repeatedly lithium-treated rats. Our data suggest that differences between poisoning patterns regarding lithium-induced hypolocomotion are better explained by the duration of lithium exposure than by its brain accumulation.

291. Neuro-respiratory toxicity of baclofen in the rat: study of the concentration/effect relationships and role of GABAergic receptors

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Objective: Baclofen, a GABA-B receptor agonist is used as a muscle relaxant agent and recently for the treatment of alcohol dependence. The number of poisonings has significantly increased since this new indication. Clinical presentation of poisoning mainly includes sedation, hypotonia, respiratory depression and seizures. To characterize the neurorespiratory toxicity of this molecule at high doses, we investigated alterations in Sprague-Dawley rat ventilation and brain electrical activity after baclofen administration and studied their reversal by GABA-receptor antagonists.
Methods: Rat ventilation was investigated using plethysmography and arterial blood gas analysis while brain electrical activity was studied using electroencephalogram (EEG) with one implanted frontal electrode. Three baclofen doses were used including 43.5 mg/kg (30% lethal dose 50%), 72.5 mg/kg (50%) and 116 mg/kg (80%). Baclofen concentrations were obtained using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay. We modeled baclofen pharmacokinetics and analyzed the doses/effects and effects/concentrations relationships.
Results: Baclofen induced early-onset and prolonged dose-dependent sedation ($p = .0002$), hypothermia ($p = .004$), EEG and respiratory depression ($p = .001$) characterized by significant increase in the inspiratory ($p = .0001$) and expiratory times ($p = .02$). Significant increase in $PaCO_2$ and decrease in arterial pH and PaO_2 were observed at 116 mg/kg ($p = .001$), peaking at 240 minutes. EEG showed signal slowing, burst-suppression aspects and spikes peaking at 5–6 hours post-injection without normalization at the end of the experiment at 24 hours. We reversed baclofen-induced decrease in tidal volume with saclofen (a GABA-B receptor antagonist) and interestingly no alteration of baclofen-induced respiratory depression was observed with flumazenil (a GABA-A receptor antagonist). Pharmacokinetic parameters of baclofen were obtained at the three doses and were

dose-dependent. Significant but non-linear relationships were observed between baclofen-induced effects and concentrations.
Conclusion: Baclofen causes dose-dependent neurorespiratory toxicity in rats. However, due to increased poisonings, its safety profile at high doses remains to be established in humans.

292. Tramadol-related neurotoxicity in the rat: contributions of the different neuromediators and effects of potential antidotes

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Objective: Tramadol, an opioid analgesic used to treat moderate to severe pain, causes coma, respiratory depression, seizures and serotonin syndrome in overdose. The exact role of naloxone to reverse tramadol-related effects is debated. We investigated the pathways involved in tramadol-related neurotoxicity and seizures in the rat, by using various antagonists of the different tramadol-mediated effects including naloxone, cyproheptadine, fexofenadine and diazepam and determining the turnover of brain monoamines.
Methods: Body temperature (using telemetry), respiratory effects (using plethysmography) and neurological effects (using clinical scales and electroencephalogram) were studied. Brain (frontal lobes) monoamines (serotonin, dopamine and norepinephrine) and their respective metabolites were measured using high-performance liquid chromatography coupled to fluorometry. For each animal and each time, we calculated the difference between the parameter value at that time and baseline and the area under the curve of its time course. Comparisons were performed using two-way ANOVA followed by post-tests using Bonferroni correction.
Results: Tramadol induced sedation ($p < .01$), seizures (early onset and peaking at 30 minutes) and increase in inspiratory time ($p < .001$) as well as a non-significant trend to hypothermia. Diazepam completely suppressed seizures. Naloxone prevented tramadol-related sedation and respiratory effects but did not inhibit seizures. In contrast to cyproheptadine which exhibited no effects, fexofenadine partially reduced seizures, suggesting the involvement of a histaminergic pathway. Turnover of monoamines was significantly reduced in the presence of diazepam ($p < .01$), suggesting that diazepam-mediated prevention of tramadol-induced seizures could be related to the inhibition of monoamine metabolism in addition to its usual GABAergic effects.
Conclusion: Tramadol-induced sedation and respiratory effects are mediated by mu-opioid receptors. Seizures involve complex mechanisms including histaminergic but not serotonergic pathways. Diazepam-related anticonvulsive activity to prevent tramadol-induced seizures may be related to the inhibition of monoamine metabolism in addition to its GABAergic effects.

293. A severe intoxication after ingestion of an infusion prepared with seeds bought over the Internet

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Objective: We report the case of a man who ingested an infusion prepared with *Mimosa hostilis* (MH), a plant containing N,N-dimethyltryptamine (DMT), used in combination with *Peganum harmala* (PA) seeds. PA (Syrian rue) is a psychoactive plant that grows in Asian and African deserts. Its seeds and roots contain harmine and harmaline (56.0 mg/g in the seeds [1]) that act as monoamine oxidase (MAO) inhibitors preventing the degradation of DMT and psylocibin. Moreover they contain tetrahydroharmine that is believed to inhibit serotonin uptake.
Case report: A 20-year-old man ingested an infusion made with seeds of PA and MH bought online. In a few minutes he developed kaleidoscopic visual hallucinations, vomiting, hypertensive crisis, tachycardia and agitation, and was brought to the emergency department. Our Poison Center suggested starting electrocardiogram (EKG) and arterial blood pressure (ABP) monitoring and to draw blood and urine samples. The patient was decontaminated with 30 g of activated charcoal and a dose of macrogol 4000. At 2 hours and 20 minutes after ingestion, ABP was still 188/92 mmHg, therefore an infusion of labetalol 1 mg/min was started. ABP lowered to 160/90 mmHg. Blood tests revealed mildly increased transaminases (AST 162 U/L, ALT 47 U/L, and creatine kinase 830 U/L) and urinary toxicological screening was positive (> 100 ng/mL) for 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (THCCOOH) and negative for cocaine. At four hours after ingestion, ABP was 186/66 mmHg which decreased to 150/90 mmHg 7 hours post-ingestion; the administration of labetalol was stopped. Meanwhile, hepatic functionality improved (AST 50 U/L, ALT 39 U/L), with stable complete blood count and decreased creatine kinase (605 U/L). The patient was discharged after 24 hours with ABP 140/70 mmHg.
Conclusion: Visual hallucinations, nausea, vomiting and sedation are common symptoms of harmine intoxication and they were all observed in this case. Hypertension, instead, seems to be associated with the effects of MH rather than to those of PA, since that is more likely to induce hypotension. New substances available over the Internet are an important source of intoxication. Clinicians should be aware of the risks connected with these atypical drugs and that information available online is often misleading for consumers who can underestimate the real dangers. Moreover, the combination of these herbs and the variability in the concentration of their active ingredients may lead to unexpected clinical effects.

Reference

[1] Moloudizargari M, Mikaili P, Aghajanshakeri S, et al. Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids. Pharmacogn Rev. 2013;7:199–212.

294. Aconite: rare but potentially serious poisoning

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Objective: Management of patients with exposure to plants may require toxicological advice from Poison Centers. We describe cases of aconite exposure reported to French Poison Centers (PCs).
Case series: Since 2000, the French PCs have received 101 cases of poisoning involving aconite. There were 57 accidental poisonings (58%), 42 voluntary exposures and 2 unknown; 76 cases involved only aconite. Signs included paresthesias (18% of cases), rhythm disorders (18%), tachycardia (13%), abdominal pain (9%), hypotension (9%), shock (7%), mydriasis (5%), seizures (3%), cardiac arrest (3%) and vomiting (24%). All recovered with supportive care without sequelae. Aconitine was measured in three cases with 1.95, 2.9 and 13 µg/L in blood and 403, 2412, 6700 µg/L in urine (liquid chromatography-tandem mass spectrometry [LC/MS-MS]). In recent years, the number of cases of plant exposures recorded annually by French PCs remains stable with about 50 cases per 1000 exposures (aconite 4/10000). In one aconite case a 21-year-old female called a Poison Center after ingestion of 7 g of aconite seeds (21 to 210 mg of aconitine). She complained of insomnia, paresthesia of the extremities and abdominal pain 30 minutes after ingestion. On examination 7 hours post-ingestion, she was alert, respiratory rate was 16/min, SpO_2 100%, blood pressure (BP) 108/80 mmHg, heart rate 110 bpm and glucose 4.8 mmol/L. Electrocardiogram (ECG) showed a sinusal rhythm, PR 17.8/100 s, thin QRS, QT_c 0.469s and multifocal ventricular ectopic beats. Coupled beats appeared at 11 hours with decreased BP 90/60 mmHg, with return to a normal heart rate with BP 120/89 mmHg at 15 hours. No therapeutic interventions (e.g., atropine or antiarrhythmic) were prescribed and troponin, pro-brain natriuretic peptide (proBNP) and routine blood samples were unremarkable. Aconitine concentrations (using LC/MS-MS) ranged from 1.9 to 2.9 µg/L in blood and was 403 µg/L in urine.
Conclusion: Approximately 5000 cases of aconite poisoning have been described worldwide between 2001 and 2015 including fatalities [1]. Deaths are known with aconitine at 10.8 µg/L in blood and 264 µg/L in urine [2]. Clinical symptoms are variable depending on the dose and concentration of aconitine in different parts of the plant that vary by a factor of 10. Early symptomatic treatment provides recovery in most cases.

References

[1] Li H, Liu L, Zhu S, Liu Q. Case reports of aconite poisoning in mainland China from 2004 to 2015: A retrospective analysis. J Forensic Leg Med. 2016;42:68–73.
[2] Elliott SP. A case of fatal poisoning with the aconite plant: quantitative analysis in biological fluid. Sci Justice. 2002;42:111–115.

295. *Amanita phalloides* poisoning in Slovenia, 1999–2015

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Objective: *Amanita phalloides* is the most poisonous mushroom. Widely distributed across Slovenia, it resembles several edible species that are commonly picked and consumed. The aim was to evaluate epidemiology and treatment of *Amanita phalloides* poisoning in Slovenia.
Methods: In this retrospective study we analyzed the incidence, clinical course, interval from ingestion to therapy, treatment and outcome in *Amanita phalloides*-poisoned patients treated in the Poison Control Centre in Ljubljana between 1999 and 2015. The diagnosis was based on clinical evaluation and identification of the mushroom by a mycologist. Patients were graded according to the Poisoning Severity Score in four categories: none, minor (PSS1), moderate (PSS2) and severe poisoning (PSS3) [1].
Results: In total 150 patients were hospitalized due to mushroom poisoning, 32 of them due to *Amanita phalloides* between 1999 and 2015. Three cases were non-toxic exposures due to early recognition and decontamination in the first hours after ingestion. Of the other 29 patients, 8 were PSS1, 8 PSS2 and 13 PSS3. All 29 patients received silibinin therapy and continuous intravenous fluid therapy according to the protocol on admittance. The mean time interval between mushroom ingestion and the start of the therapy was 27.6 ± 5.1 hours for PSS1, 22.8 ± 2.3 hours for PSS2 and 41.8 ± 7.6 hours for PSS3 ($p = .10$). In PSS3 group AST reached 77.8 ± 16.3 µkat/L, ALT 87.6 ± 14.6 µkat/L and INR 3.78 ± 0.96. The creatinine value in the phase of acute liver failure in PSS3 (185.6 ± 40.7 µmol/L) was significantly higher compared to the creatinine concentrations in PSS1 and PSS2 groups ($p = .03$). Three patients graded as PSS3 fulfilled the King's College criteria for non-paracetamol related acute liver failure used by Eurotransplant (INR >6.5). One had urgent liver transplant, one was too old for liver transplant and one had a significant improvement between the 3rd and 4th day after ingestion and fully recovered without liver transplantation. The decision not to proceed with transplantation was based on Escudie's criteria.
Conclusion: The study revealed the decreasing number of *Amanita phalloides* poisoning, probably due to public health campaigns. In the 17-year period we recorded only one death and one liver transplantation. The remaining 30 patients recovered fully. The study indicates that severity of *Amanita phalloides* poisoning according to PSS does not depend on silibinin and hydration therapy.

Reference

[1] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.

296. Anticholinergic toxicity associated with ingestion of water containing lupini bean extract

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Objective: A case of anticholinergic toxicity associated with ingestion of water containing lupini (lupin) bean extract.
Case report: A 63-year-old man with no significant past medical history presented to the emergency department (ED) three times in the same day for gradually worsening anticholinergic symptoms. The patient had returned from Ecuador and brought back lupini beans. He soaked the beans in water for several hours, and then drank approximately 300 mL. His initial symptoms included generalized weakness and emesis that began 15 minutes after ingestion. Initial vital signs and screening laboratory tests were unremarkable and the patient was discharged. He returned to the ED almost immediately complaining of difficulty urinating. Placement of a urinary catheter removed 150 mL of yellow urine and he was again discharged. He returned 2 hours later with confusion, visual hallucinations, distended abdomen with quiet bowel sounds, urinary retention, dry skin and dilated pupils. Vital signs at this time were blood pressure of 120/69 mmHg, heart rate 93 bpm, and respiratory rate 18/minute. The patient was admitted overnight for observation. He was symptom free and discharged the following day. The patient's wife ingested 100 mL of the same water and presented simultaneously with symptoms including vision changes, anxiety, decreased bowel movements, nausea, and generalized weakness. She was also admitted for overnight observation and discharged the next day with resolution of symptoms. Laboratory analysis of the water revealed concentrations of lupanine at 3.10 mg/mL and sparteine at 0.89 mg/mL. Serum concentrations of lupanine were 170 ng/mL, and 71 ng/mL in the husband and wife, respectively. Serum concentrations of sparteine were below the lower limit of quantification (<1 ng/mL) and 1.3 ng/mL in the husband and wife, respectively.
Conclusion: *Lupinus albus* is a member of the Leguminosae family. Lupini beans derive their bitter flavor from the quinolizidine alkaloids which include, among others, lupanine and sparteine. Prior to consumption, raw lupini beans must undergo a de-bittering process to remove the alkaloids. This typically occurs by repeatedly soaking the beans in water and can take four days [1]. This is an unusual case of a delayed anticholinergic toxidrome resulting from ingestion of water containing lupini alkaloid extract with novel reports of the corresponding water and serum alkaloid concentrations.

Reference

[1] Carvajal-Larenas FE, Linnemann AR, Nout MJ, et al. *Lupinus mutabilis*: composition, uses, toxicology, and debittering. Crit Rev Food Sci Nutr. 2016;56:1454–1487.

297. Case report: a relaxing cup of poppy seed tea goes toxic

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Objective: We present a case of a patient who became intoxicated and developed hearing loss following ingestion of tea made from poppy seeds.
Case report: A 51-year-old healthy female with a history of consuming poppy seed tea for "relaxation" one to two times per week switched tea suppliers the evening prior to presentation. The patient reported feeling "odd" after her evening tea and suspected she took too much. In a proactive attempt to resolve ongoing symptoms, the patient consulted a local pharmacist who provided her with a naloxone kit. The patient utilized the naloxone kit, which provided transient resolution of her symptoms, and then went to bed without ingesting any additional tea. The following morning, the patient was found unresponsive with difficulty breathing and pinpoint pupils. Her husband called emergency medical services (EMS), who provided a rescue dose of naloxone. Upon arrival to the emergency department, the patient presented with symptoms including loss of hearing, dry skin and mouth, and decreased cognitive abilities. The patient's labs indicated an elevated creatinine 1.67 mg/dL, ammonia 53 µmol/L, white blood cell count 19,400/mm^3, and anion gap 17. Five hours after EMS administered naloxone, the patient self-reported a return to baseline cognitive and auditory functions. She denied use of any other opioids, benzodiazepines (within the last week), or sedatives. Urine confirmation was positive for morphine, codeine, and benzodiazepines. Additional lab work-ups were unremarkable. On follow-up, the patient confirmed discontinuation of tea and full resolution of symptoms with continued baseline auditory abilities.
Conclusion: Consuming poppy seed tea can result in significant opioid toxicity, and can present even when merely switching suppliers. Additional monitoring of poppy seed tea's varying potencies and associated adverse reaction to consumption is needed to identify its toxicity profile.

298. *Cerbera manghas* intoxication: a case report

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Objective: *Cerbera manghas,* also known as sea mango, is a poisonous tree containing cardiac glycosides [1]. It is a very common evergreen plant and readily accessible in Taiwan, especially in coastal areas. Cardiac glycoside intoxication results in predominantly digestive, cardiac and neurological symptoms. Non-specific anorexia is an early symptom of poisoning that may be neglected if the clinician is unaware of the possibility of intoxication. Here, we present a patient with *Cerbera manghas* intoxication.
Case report: A 28-year-old female without known systemic disease was transferred to our emergency department due to *Cerbera manghas* intoxication with a history of persistent vomiting for one day. She had been seen at a local hospital with intermittent bradycardia and persistent vomiting, but had not revealed the intentional ingestion of three *Cerbera manghas* fruits one day prior to hospital admittance. Digoxin intoxication was highly suspected due to electrocardiographic (ECG) changes, and the patient finally confessed to attempting suicide. On arrival, her vital signs were temperature 36.2 °C, pulse 42–56 beats/minute, respiratory rate 19/minute and a blood pressure of 140/79 mmHg. Physical examination was normal except for hyperactive bowel sounds. ECG showed sinus rhythm with ST depression over inferolateral leads with scooped appearance. Her blood tests revealed potassium 4.63 mmol/L and digoxin <0.09 ng/mL. Renal function and other laboratory findings were unremarkable. She was admitted to the intensive care unit due to fluctuating pulse rate and persistent vomiting. During hospitalization, supportive management was given, and she was discharged stable five days after ingesting *Cerbera manghas*.
Conclusion: The diagnosis of *Cerbera manghas* intoxication can be made by the exposure history and digoxin-like clinical manifestations. Detection of digoxin by fluorescence polarization immunoassay further supports the diagnosis. However, digoxin-like toxicity, such as digestive, cardiac and neurological symptoms, can occur in patients with normal digoxin and potassium

concentrations. The key to successful treatment is early recognition and digoxin-Fab fragments in patients with life-threatening poisoning. The possible ECG findings of cardiac glycoside intoxication include any type of cardiac dysrhythmia, although rapid atrial fibrillation/flutter and bundle branch block are rare. Physicians should be alert to clinical appearance and ECG findings of cardiac glycoside intoxication.

Reference

[1] Tsai, Y-C, Chen, C-Y, Yang, N-I, et al. Cardiac glycoside poisoning following suicidal ingestion of *Cerbera manghas*. Clin Toxicol. 2008;46:340–341.

299. *Cerbera odollam* poisoning in the western world: a potentially serious public health epidemic

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Objective: *Cerbera odollam* (pong pong tree) is a highly toxic, cardenolide-containing plant, belonging to the same family as oleander species. It is found throughout Southeast Asia where cases are quite common due to ease of access, but ready availability of the seeds on the Internet at a modest cost is resulting in more widespread occurrence [1]. Ingestion is potentially life-threatening. We describe a patient who presented on two occasions with significant cardenolide poisoning following deliberate ingestion of *C. odollam* seeds, purchased over the Internet.
Case report: A 49-year-old woman with depression was receiving inpatient psychiatric treatment. She researched "suicide tree" and "pong pong tree" on the Internet and purchased two seeds online, which were delivered to her home address. She went home and ingested the seeds and later returned to tell members of staff of her act. She was transferred to our hospital 2 hours post-ingestion. Within 2 hours of arrival she developed features of cardenolide poisoning with protracted nausea and vomiting, hyperkalaemia (7.1 mmol/L) and 2nd degree atrioventricular block with intermittent sinus pauses, which responded to boluses of digoxin specific antibody fragments (a total dose of 5 mg/kg, 10 × 40 mg vials over 2 days). She also received one dose of insulin/dextrose (Actrapid® 10 units/50% dextrose 50 mL), to control her hyperkalaemia. Vomiting and hyperkalaemia subsided on day 4 but 1st degree heart block and digitalis effects were evident on her electrocardiogram (ECG) up to day 6. She was discharged to the psychiatric hospital on day 9. One month later, she again bought two seeds online and ingested them. However, on this occasion, she vomited most of the seeds within a few hours resulting in milder symptoms, lower potassium rise (peaked at 5.7 mmol/L) and less protracted atrioventricular block. She was treated with one dose of digoxin specific antibody (1.5 mg/kg, 3 × 40 mg vials) and made a good recovery.
Conclusion: *Cerbera odollam* poisoning is rare outside Southeast Asia but the modest cost, wide availability online and expensive antidote is potentially a public health concern. This is also the first case reporting the use of high dose digoxin specific antibody fragments for *C. odollam* poisoning.

Reference

[1] Kassop D, Donovan MS, Cohee BM, et al. An unusual case of cardiac glycoside toxicity. Int J Cardiol. 2014;170:434–437.

300. Classic appearances of aconitine intoxication: do physicians recognize the signs?

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Objective: With increasing world acceptance of Chinese herbal medicine, *Aconitum* species are commonly used to treat musculoskeletal disorders, gastroenteritis, rheumatism, etc. However, the alkaloid aconitine has cardio- and neurotoxic properties and is present in the roots of *Aconitum* species [1]. We present two cases with aconitine intoxication, accompanied by altered mental status (AMS) and signs mimicking anaphylactic shock, respectively.
Case reports: Case 1: A 60-year-old man presented to our emergency department (ED) with altered mental status two hours after drinking a decoction prepared by boiling aconite for 30 thinsp;minutes. He also had disorientation, diaphoresis and vomiting. His vital signs were blood pressure 75/53 mmHg, pulse 90 beats/minute, body temperature 35.2 °C and Glasgow Coma Score $E_2V_2M_5$. Other physical examinations were normal. Electrocardiography (ECG) revealed normal sinus rhythm. Fluid resuscitation with 500 mL normal saline was prescribed because of hypotension. Aconitine-related shock was highly suspected after a comprehensive series of investigations, including laboratory data, brain and abdominal computed tomography (CT). Twelve hours after ingestion, his conscious level and vital signs were markedly improved. Case 2: A 29-year-old man arrived at our ED with numbness of the lips and all limbs after taking a decoction of 15 g of aconite made from inadequate boiling. He presented unstable vital signs with pulse 92 beats/minute, body temperature 36.5 °C and blood pressure 75/51 mmHg, but normal mental status. Other physical examinations and laboratory data were within normal limits. Anaphylactic shock was suspected and epinephrine and fluid resuscitation with normal saline were prescribed resulting in clinical improvement. After consulting the Taiwan National Poison Control Center by telephone, aconitine intoxication was diagnosed on the basis of classic signs and supportive care was suggested.
Conclusion: Although aconitine intoxication is sometimes reported, there may be a delay in diagnosing it due to unfamiliarity with the typical signs. The usual signs of aconitine intoxication include chest tightness, palpitations, numbness, hypotension, dizziness, shortness of breath and even altered mental status. Our two cases were both diagnosed by complex procedures involving extensive laboratory analyses and computed tomography in one patient; the other was initially misdiagnosed. Aconitine intoxication will continue to occur and in a patient reporting use of herbal medicine, physicians should be alert to the risk of poisoning with some herbs.

Reference

[1] Lin C-C, Chan TY, Deng J-F. Clinical features and management of herb-induced aconitine poisoning. Ann Emerg Med. 2004;43:574–579.

301. *Colchicum autumnale* or why autumn may be dangerous even if you are not depressed

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Objective: To describe a series of cases of accidental and deliberate intoxications with *Colchicum autumnale*.
Cases series: Cases 1–3: A family of three (father aged 68 years, mother aged 59 years, son aged 30 years) ate a preparation of herbs containing the leaves of *Colchicum autumnale* (autumn crocus), mistaken for *Allium ursinum* (wild garlic). After 12 hours all of them developed vomiting, abdominal cramps and diarrhea of varying severity. The father was significantly more affected and was admitted to our intensive care unit (ICU) with mild thrombocytopenia (possibly confounded by underlying chronic leukemic disease). He received activated charcoal and supportive therapy and recovered within 48 hours without further distress. The mother and son also received activated charcoal, developed only minor symptoms and recovered rapidly. We obtained colchicine concentrations from the leaves and the blood of the patients at different time points by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The leaves contained 0.48 mg/g. The father had a serum colchicine concentration of 5.4 ng/mL at 20 hours, 5.1 ng/mL at 36 hours and 2.8 ng/mL at 60 hours. The serum colchicine concentrations in the mother were 3.1 ng/mL at 22 hours, 1.2 ng/mL at 46 hours and 0.75 ng/mL at 70 hours. The serum colchicine concentrations in the son were 2.0 ng/mL at 22 hours and 0.56 ng/mL at 70 hours. Case 4: A 35-year-old female ingested an unknown quantity of *Colchicum autumnale* leaves in a suicide attempt. She developed nausea, vomiting and profound diarrhea 8 hours after ingestion and was transferred to our ICU 10 hours thereafter. Only supportive care was given. We observed atrioventricular conductance disturbances (first degree AV block) on admission; all signs resolved within 24 hours. After 48 hours, the AV-block reoccurred for about 12 hours, resolving thereafter. The patient was discharged to a psychiatric ward after 72 hours without further symptoms. The serum colchicine concentrations in blood drawn approximately 12 hours after ingestion was 5.0 ng/mL.
Conclusion: We report 4 cases of mild to moderate colchicine intoxication. Detection of colchicine concentrations in blood by LC-MS/MS seemed to correlate to the clinical course of our patients, with lower concentrations associated with milder symptoms, suggesting a dose-response relationship. Cardiac toxicity was detected in one patient after more than 48 hours after ingestion, emphasizing the need for cardiac monitoring for an appropriate time.

302. Enquiries to a poisons information service concerning sycamore (*Acer pseudoplatanus*)

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Objective: In the UK *Acer pseudoplatanus* (sycamore) is a common tree with large five lobed leaves and winged seeds which are attractive to children. In horses a fatal muscle disease (equine atypical myopathy) has been linked to ingestion of sycamore leaves and seeds [1] but there are no reports of human toxicity in the literature. The objective was to investigate enquiries to the UK National Poisons Information Service (NPIS) concerning the sycamore tree.
Methods: Enquiries to the NPIS, citing sycamore tree exposure, were retrieved from the NPIS electronic enquiry database (UKPID), for the period 1 January 2004 to 30 September 2016. These enquiries derived from all four UK NPIS Units (Birmingham, Cardiff, Edinburgh and Newcastle) from October 2006 to 2016 and from 2 or 3 Units in earlier years.
Results: Seventy-five enquiries were identified, of which 73 concerned potential exposures. In 69 cases sycamore alone was mentioned. In 3 others ash seeds, laburnum leaves or hazelnuts were also ingested and in another oak and *Platanus* (plane) leaves were also ingested (none symptomatic). Enquiries concerned a single patient in 70 cases and groups of children in the other three. Where known ($n = 65$), the age ranged from 7 months to 46 years with 92% aged 10 years or less. There were 33 males and 34 females (remainder unknown or groups). There were no deliberate exposures. Seventy-one enquiries were about ingestion, one about ingestion and skin contact and one about skin contact. In 60 cases the patients were asymptomatic. The Poisoning Severity Scores (PSS [2]) in the 73 enquiries were: none $n = 60$, minor $n = 6$ (2 nausea, one each rash/swelling, vomiting, burning in mouth, feeling unwell); moderate $n = 4$ (3 prolonged vomiting, 1 allergic reaction with dyspnoea, coughing, bronchospasm); severe $n = 0$; and unknown $n = 3$. Exposures were to seeds/fruit ($n = 38$), leaves ($n = 30$), spore on leaf ($n = 1$), resin ($n = 1$) and unknown ($n = 3$). Limitations of the report are that none of the trees involved were definitely identified.
Conclusion: Ingestion of seeds and leaves of the sycamore tree seldom cause symptoms in humans. In a few cases there may be prolonged vomiting or allergic reactions.

References

[1] Westermann CM, van Leeuwen R, van Raamsdonk LW, et al. Hypoglycin A concentrations in maple tree species in the Netherlands and the occurrence of atypical myopathy in horses. J Vet Intern Med. 2016;30:880–884.
[2] Persson HE, Sjöberg GK, Haines JA, et al. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36:205–213.

303. *Erycibe henryi*-induced acute cholinergic syndrome

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Objective: Chinese herbal therapy is common in Taiwan but some herbs can cause toxic effects. There are few reports in the literature of toxicity from usage of *Erycibe henryi* [1]. Here, we present a case of acute *Erycibe henryi* Prain poisoning due to misidentification.
Case report: A 42-year-old male presented to emergency department (ED) due to nausea, vomiting, watery diarrhea and diaphoresis, developing acute cholinergic syndrome 30 minutes after

ingesting an *Erycibe henryi* Prain decoction. At the ED, he was noted to have hypothermia (34.5 °C), miosis, bradycardia (heart rate 61 beats/mins), and hyperactive bowel sounds. Laboratory examination revealed leukocytosis (white blood cell count 14060/μL), elevated blood glucose (160 mg/dL), and normal plasma cholinesterase activity. Atropine was administrated following diagnosis of acute cholinergic syndrome and it improved the patient's condition immediately. He was well after one day's observation. The herb in this case was identified by Chinese herbal pharmacists at the China Medical University, Taiwan.
Conclusion: *Erycibe henryi* Prain is a herb commonly used for muscloskeletal pain management in Taiwan. Our patient and others previously reported, all developed acute peripheral cholinergic manifestations. A few reports have found tropane alkaloids in this plant which may act as agonists on the muscarinic receptor. Thus, atropine would be an effective antidote in patients with *Erycibe henryi* poisoning. Some other herbs have similar Chinese names and *Erycibe henryi* can easily be misidentified, resulting in possible toxicity. It is important to study how to prevent misidentification amongst users of herbal medicine.

Reference

[1] Huang HH, Yen DH, Wu ML, Deng JF, Huang CI, Lee CH. Acute *Erycibe henryi* Prain ("Ting Kung Teng") poisoning. Clin Toxicol. 2006;44:71–75.

304. Gastrointestinal toxicity and acute kidney injury following ingestion of suspected *Amanita ochrophylla*

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Objective: In Australia there is concern that white topped and gilled mushrooms are the hepatotoxic *Amanita phalloides*. Despite reports being limited to southern Australia, recent deaths create angst regarding treatment of potential exposures. However, non-phalloides *Amanita species* exist in Australia but epidemiological data are limited. We report a case of suspected *Amanita ochrophylla* poisoning with a favourable outcome.
Case report: A 77-year-old male in Southern Queensland picked and cooked white-coloured wild mushrooms; 16 hours later he experienced abdominal cramps, but ate a second meal 8 hours later. At 12 hours (34 hours after the initial meal) he experienced vomiting but no diarrhoea. Persistent vomiting prompted presentation to hospital 48 hours after the first meal (24 hours after latest meal) and examination noted stable haemodynamics and minimally tender abdomen without marked dehydration. Investigations noted mild transaminitis (ALT 57 IU/L, AST 81 IU/L) and normal creatinine 94 μmol/L despite oliguria. Clinical toxicology advice was supportive care and regular blood tests without antidote therapy given the absence of diarrhoea and exposure in an area where *A. phalloides* is unreported. The patient subsequently developed hypotension that persisted despite 4 litres of crystalloid (92/56 mmHg, pulse 105/min); other observations were normal, urine output returned, but generalised central abdominal pain increased without diarrhoea. Blood gas analysis revealed lactic acidosis (7 mmol/L). The patient was transferred to ICU for pressor support and a computerised tomography (CT) scan noted normal bowel with peri-hepatic fluid. Biochemistry deteriorated over the following 12 hours: ALT 79 IU/L, AST 134 IU/L, creatinine 118 μmol/L and arterial lactate 9.6 mmol/L. During this time the patient presented photographs of the mushrooms prior to cooking, which were noted to be white-topped and gilled. Further discussion with clinical toxicology prompted initiation of acetylcysteine, multiple doses of activated charcoal and rifampicin for possible *A. phalloides*. Subsequent mycology advice was that the mushrooms were possibly *Amanita ochrophylla*. The patient made a favourable recovery. The clinical course was similar to that of the few reports of poisoning with this mushroom in the literature.
Conclusion: Ingestion of white topped and gilled mushrooms by patients who subsequently develop gastrointestinal symptoms requires prompt and careful consideration of the identity and treatment. This involves attention to the clinical effects and collaboration with local mycology services. Depending on the epidemiology of mushroom poisonings in that region and in the absence of other explanations, it may not be unreasonable to treat as *A. phalloides* until counter information is available.

305. Suicide attempt by infusion of rotenone-containing plant extracts: a case report from French Polynesia

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Objective: Several species in the Fabaceae contain ichthyotoxic rotenoids and are traditionally used for fishing in numerous tropical areas. Rotenone is also toxic for arthropods and was consequently widely used as an insecticide [1]. Human ingestion of rotenone and rotenoids at low concentration is relatively harmless (isolated digestive symptoms) but high concentrations can induce neurological symptoms including coma and central respiratory depression [2]. The purpose of this report is to describe a case of poisoning after drinking an infusion of a rotenone-containing plant.
Case report: In Nuku Hiva island, French Polynesia, a 63-year-old male, without medical history, intentionally drank an infusion containing several leaves of a plant identified as *Derris trifoliate* in a suicide attempt. He drank the same infusion again 12 hours later. A few hours later, he was admitted at the emergency department with seizures and Glasgow Coma Scale 3. A brain scan showed no abnormalities, and blood tests showed only liver cytolysis (AST 92 UI/L, ALT 108 UI/L). After intubation and assisted ventilation, he was transferred to the intensive care unit in Papeete Hospital, Tahiti. N-acetylcysteine infusion was given for 24 hours for liver protection. At day 2 the biological disturbances had improved (both <30 UI/L). There were no further neurological symptoms and he was extubated.
Conclusion: In the literature, most cases of rotenone intoxication involve exposure to concentrated formulations used in insecticides [2]. Very few published cases in Asia and French Guiana, have involved ingestion of rotenone containing plants [1]. The typical clinical picture is characterized by digestive manifestations (abdominal pain, vomiting, and diarrhea) rapidly followed by dizziness, loss of conscience and respiratory insufficiency. Some patients also have liver cytolysis associated with metabolic acidosis. In our report, this patient had typical signs of rotenone poisoning, with coma requiring intubation/ventilation and isolated liver cytolysis. No metabolic acidosis was observed, however, and seizures are unusual for such a poisoning. In patients who survive the initial phase, symptoms usually regress quickly [1]. The therapeutic protocols are based on symptomatic management including endotracheal intubation.

References

[1] Chesneau P, Knibiehly M, Tichadou L, et al. Suicide attempt by ingestion of rotenone-containing plant extracts: one case report in French Guiana. Clin Toxicol. 2009;47(8):830–833

[2] Wood DM, Alsahaf H, Streete P, et al. Fatality after deliberate ingestion of the pesticide rotenone: a case report. Crit Care. 2005;9:R280–R284.

306. Methanol poisoning inadvertently treated with vodka via intravenous administration

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Objective: Methanol is a clear, flammable liquid often found in industrial fluids and illicit alcohol. Ingestion of methanol can result in metabolic acidosis, ocular toxicity and death. Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then, via aldehyde dehydrogenase, to formic acid resulting in retinal toxicity [1]. Irreversible retinal damage and blindness can occur when treatment is delayed. We report the clinical outcome of severe methanol poisoning, resulting in basal ganglia hemorrhage, accidentally treated with oral ethanol via intravenous administration.

Case report: A 16-year-old male was found comatose by family members after drinking "homemade" alcohol purchased two days prior. He presented in an outside hospital lethargic with disconjugate non-reactive pupils. Initial vital signs: heart rate 90, blood pressure 155/100 mmHg, pulse oximetry 100% (via face mask). Initial blood work revealed: metabolic acidosis (arterial pH 6.81, pCO_2 13, HCO_3 <5), renal failure (creatinine 221 mmol/L; reference range 45–90) and elevated lactate (12.9 mmol/L; reference range 0.5–1). The patient was intubated and our poison center was contacted for transfer and treatment advice. Due to a lack of fomepizole, an oral ethanol load was recommended prior to transfer. Upon arrival to our facility, the patient immediately received hemodialysis for severe metabolic acidosis; subsequent testing (approximately 24 hours after ingestion) revealed a serum methanol of 34 mg/dL. It was later discovered that the referring hospital accidentally administered oral ethanol (vodka), through a filtered needle, into a peripheral intravenous site (PIV) in his antecubital fossa. The metabolic acidosis resolved rapidly and the patient's neurological status improved. On hospital day (HD) 2 he was extubated; he had dysarthria and a diffuse upper extremity tremor, but normal vision. The PIV site was normal and there was no evidence of phlebitis. On HD 9, magnetic resonance imaging (MRI) of the brain revealed bilateral hemorrhagic putaminal necrosis with less extensive areas involving the basal ganglia, frontal cortex and temporal cortical areas. He was discharged home on HD 19.

Conclusion: Delayed treatment for methanol toxicity, and the resulting metabolic acidosis, many result in permanent neurologic deficits (seen on MRI) without visual impairment. The inadvertent administration of oral ethanol through a peripheral intravenous site did not appear to adversely affect the patient's clinical course.

Reference

[1] Liu DM, Zhou S, Chen JM, et al. The intoxication effects of methanol and formic acid on rat retina function. J Ophthalmol. 2016; Article ID4087096.

307. Acute beta-blocker overdose management: factors associated with cardiovascular mortality in a Caribbean intensive care unit

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Objective: Beta-adrenergic antagonists are commonly used worldwide to treat hypertension, tremor, migraine, ischemic heart disease, heart failure, arrhythmias, portal hypertension, angina and panic attacks. Propranolol, a beta-adrenergic antagonist with membrane-stabilizing proprieties, is the most common cardiotoxicant used in suicide attempts in Martinique. Though respiratory depression, bronchospasm, bradycardia, severe hypotension, and seizures may result from beta-blocker intoxication, cardiovascular depression appears to be the most common cause of morbidity and mortality in severe acute beta-blocker poisoning [1]. Massive beta-blocker ingestion can cause prolonged QRS interval and may be associated with refractory cardiac failure. Our objectives were to determine factors that are associated with the development of cardiovascular mortality in beta-blocker overdose.

Methods: We conducted a retrospective study over 10 years (January 2005 to December 2015), including all poisoned patients admitted to and treated in the Emergency Department and the Intensive Care Unit (ICU). During this period, there were over 10 beta-adrenergic antagonist exposures per year reported by the medical records department. These poisonings accounted for an average of 5 deaths annually.

Results: In total 308 patients (173 males/135 females) were admitted to the ICU for severe acute poisoning (median age 46.5% years [16–79]; Simplified Acute Physiology Score (SAPS) II score 120 [49–94]). Among these 308 patients, 100 had ingested high doses of cardiotoxicants (class I ant-arrhythmic drugs 40%, beta-blockers 15%, calcium channel blockers 10%). Fifty patients (50%) survived, including 18 that suffered prolonged cardiac arrest. Poor prognostic factors in Extracorporeal Life Support (ECLS)-treated poisoned patients for beta-blocker poisoning were as follows: QRS enlargement on admission, SAPS II score on admission, ECLS performance under massage, potential coingestants, arterial pH and lactate concentration (10.5 mmol/L).

Conclusion: The most important factor associated with an increased risk of cardiovascular mortality in beta-blocker poisoning is the exposure to a beta-blocker with stabilizing activity. The identification of risk factors allows physicians to identify patients at greatest risk. ECLS appears to be an efficient salvage technique in case of refractory toxic cardiac failure or arrest.

Reference

[1] Love JN, Howell JM, Litovitz TL, et al. Acute beta blocker overdose: factors associated with the development of cardiovascular morbidity. J Toxicol Clin Toxicol. 2000;38:275–81.

308. Advances in a knowledge-based decision support system for the diagnosis of human toxic exposures

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Objective: In conjunction with the Florida Poison Information Center Network, a computer program known as a knowledge-based system (KBS) is being developed to aid medical personnel in diagnosing exposures to unknown toxins. The KBS utilizes data elements defined by the National Poison Data System (NPDS) that must be gathered electronically by all constituent members of the American Association of Poison Control Centers, potentially enabling the KBS to serve as a decision support tool for all American poison control centers and practicing clinical/medical toxicologists.
Methods: Data mining is used to extract and filter information regarding human toxic exposures and their related clinical effects from a database. Further processing the extracted information, the KBS is trained by computing pre-test probabilities and likelihood ratios for use in diagnosing toxic exposures with at least 10 occurrences in the dataset. Given a set of clinical affects associated with an unknown toxic exposure, the KBS generates a ranked list (i.e., differential diagnosis) indicating the toxins most likely to produce these signs and symptoms. During training and testing, 10-fold cross validation was used to verify the KBS at various exposure severities as well as different levels of identification (diagnosis by substance, NPDS major and minor categories, and NPDS major category alone). System accuracy was calculated as the percentage of correct diagnoses in the top 10% of all viable diagnoses.
Results: Previously, the KBS was tested assuming no prior knowledge in the field of toxicology. In this study, cases resulting in death were removed from the database as they typically include extraneous clinical effects not normally associated with the involved toxin. Furthermore, vague categories and unhelpful substance diagnoses were removed from the dataset prior to training and testing, resulting in 168,545 usable single exposure cases. For exposures involving severe symptoms, the system attained accuracies as high as 86.4% diagnosing by substance, 84.1% diagnosing by major and minor categories, and 79.9% diagnosing by major category alone. These accuracies represent an increase in overall system accuracy by +0.5% for substances, +1.7% for major and minor categories, and +2.5% for major categories alone.
Conclusion: The removed diagnoses generally represent unknown or miscellaneous categories containing a variety of substances producing varied clinical effects and requiring different management strategies. Their removal not only improves system accuracy, it also improves utility for the user. Future work will include the examination of database substance listings to determine whether better groupings for clinical diagnosis exist.

309. An outbreak of foodborne botulism due to stuffed pizza with olives

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Objective: Food borne botulism is a neuro-paralytic disease caused by ingestion of food contaminated with botulinum toxin. Diagnosis of botulism is still a challenge for physicians, due to the variability of clinical presentations that may progress to respiratory failure. We report the clinical course and the multi-professional management of a botulism outbreak involving four people (three from the same family) due to the consumption of a stuffed pizza with black olives.
Cases report: Father, mother and daughter as well as a fourth patient, consumed a takeaway stuffed pizza with ham, mozzarella, tomato and olives on the same day. After 24 hours all patients developed nausea, vomiting, and diplopia. Some hours later, they presented xerostomia, dysphagia, dysphonia, weakness, ptosis, diplopia, blurred vision, mydriasis and constipation. The fourth patient also had respiratory failure. This patient was admitted to the hospital 24 hours after consumption of the contaminated food, whilst the family, presented 5 days later. Foodborne botulism was suspected and after Poison Control Centre consultation Botulinum Antitoxin® was administrated with no adverse reactions. Rectal swabs, enema and blood, collected from all patients, were sent to the National Reference Centre for Botulism in order to perform laboratory diagnosis. Through the epidemiological investigation the fourth case was connected to the family and the suspected food, as well as the restaurant, were identified. Some pizza ingredients were collected and tested for the detection of botulinum toxins and *Clostridium botulinum* spores. Clinical suspicion of foodborne botulism was confirmed through the detection of proteolytic type B *C. botulinum* in fecal samples and in the black olives used for the pizza stuffing. No botulinum toxins were recovered from blood samples. Patients progressively improved. Gastrointestinal symptoms resolved after a week, while mild symptoms and signs related to ocular and swallowing disorders persisted for over a month. The father still had mild dysphagia 72 days later. Isolated *C. botulinum* strains submitted to molecular sub-typing confirmed the outbreak and the epidemiological correlation with the consumption of stuffed pizza containing black olives.
Conclusion: Physicians should maintain a high index of suspicion of botulism when evaluating patients with a clinically compatible picture. The diagnosis is easy if a suspected outbreak is evaluated but laboratory diagnosis is essential for definitive diagnosis. The prompt administration of antitoxin blocks the progression of the symptoms, although full recovery can be slow.

310. Appropriateness of assessment of acute recreational drug toxicity in on-site nightclub medical facilities

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Objective: Acute recreational drug toxicity is common in night-time economy settings (e.g., nightclubs/bars) [1]. Unwell individuals are often assessed by non-specialist workers (club medics) in on-site medical facilities (club medic rooms). European guidelines exist for club medics to determine whether emergency services should be called to transfer a patient to hospital [2]. This study aimed to determine compliance of assessment with these guidelines.
Methods: Prospective study of presentations to club medic rooms in a South London nightclub over 3 months (June-August 2016). Standardised data forms filled by club medics collected data on basic demographics, self-reported drugs used and presenting clinical features.
Results: Data were available for 76 individuals; 54 (71.1%) were male. The majority ($n = 56$, 73.7%) were brought in by club staff; 25 (32.9%) presented following lone alcohol use, 24 (31.6%) for combined drugs/alcohol, 22 (28.9%) for lone drug use and 5 (6.6%) unrelated to drugs/alcohol. Regarding drug-related presentations: 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') was the most common drug ($n = 30$, 65.2%); followed by gamma-hydroxybutyrate (GHB) ($n = 15$, 32.6%), ketamine ($n = 4$, 8.7%) and cocaine ($n = 1$, 2.7%). Most ($n = 40$, 87.0%) only used one drug; 44 (95.7%) were not naïve drug users and 50% had previously presented to a club medic room. Complete clinical observations were recorded for 20 (46.5%). In 19 forms (41.3%) the only clinical observation documented was "alert, voice, pain, unresponsive" (AVPU) scale. The commonest clinical parameter not recorded was blood pressure ($n = 23$, 50.0%); temperature ($n = 21$, 45.7%) and heart rate ($n = 20$, 43.5%) were also poorly recorded. Most ($n = 41$, 89.1%) were discharged after assessment, 1 (2.2%) was transferred to hospital by ambulance; data incomplete for 4. Of those discharged, this was inappropriate in five (10.9%) as they fulfilled the European criteria for emergency services to be contacted: 3 (6.5%) with AVPU of P/U; 1 (2.2%) with a seizure; and 1 (2.2%) with blood pressure >180/110 mmHg on two readings.
Conclusion: Acute recreational drug toxicity remains common in nightclub settings. The majority are not naïve users and have utilised on-site medical facilities previously. Whilst the assessment of individuals was broadly acceptable, there is a need for additional targeted training to ensure full documentation and that emergency services are called for those with potentially serious/life-threatening toxicity.

References

[1] Wood DM, Nicolaou M, Dargan PI. Epidemiology of recreational drug toxicity in a nightclub environment. Subst Use Misuse. 2009;44:1495–1502.
[2] Wood DM, Dines AM, Heyerdahl F, et al. Review of European Drug Emergencies Network (EuroDEN) training package for non-specialist workers to assess acute recreational drug and NPS toxicity in night-time economy environments. Drugs Educ Prev Polic. 2016;23:73–77.

311. Avoidable management errors in acute salicylate poisoning

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Objective: Salicylate overdose remains a somewhat common and often life-threatening poisoning. Errors in treatment often lead to worse outcomes. This case report illustrates a series of errors which led to a fatal outcome.
Case report: A previously healthy 49-year-old man in a personal crisis took a deliberate overdose of unknown quantities of acetylsalicylic acid (aspirin) and melatonin with approximately 40 tablets of hydrocodone 7.5 mg/acetaminophen 325 mg and 30 tablets of an unidentified muscle relaxant over the course of a day. Paramedics observed a single generalized seizure before transport to an urban, academic hospital. On emergency department (ED) arrival (23:30 hours), he was "agitated", "confused", tachycardic, and tachypneic (vital signs heart rate 170 bpm, respiratory rate 44/minute, temperature 39.5 °C, blood pressure 212/92 mmHg). The electrocardiogram (EKG) showed sinus tachycardia at 153 bpm with normal intervals and no R wave in aVR. Significant laboratory results included sodium 139 mmol/L, potassium 4.4 mmol/L, chloride 127 mmol/L, bicarbonate 15 mmol/L, calculated anion gap <3 mmol/L, BUN 9 mg/dL (3.3 mmol/L), creatinine 1.2 mg/dL (106 µmol/L), glucose 137 mg/dL (7.5 mmol/L), AST 479 IU/L, ALT 279 IU/L, myoglobin >500 ng/mL. Toxicology studies revealed salicylate 104.9 mg/dL, acetaminophen 35.3 µg/mL, ethanol 3 mg/dL, and urine drug screen positive for opiates. All chemistry results were available 45 minutes after ED arrival with critical values conveyed by telephone to the ED nurse. A head computerised tomography (CT) scan was normal. Tachycardia persisted despite 2 L of 0.9% saline. The ED physician requested admission to the intensive care unit (ICU) and delegated all further care to the ICU intern and junior resident. Two hours after ED arrival, the ICU resident ordered IV sodium bicarbonate 100 mEq and 20 mEq potassium chloride added to 1 L of 0.9% saline at 125 mL/hour and IV N-acetylcysteine infusion. Vital signs at 3.5 hours after arrival included heart rate 137 bpm, respiratory rate 37/minute and temperature 39.2 °C. The ICU resident attempted to intubate him before moving to the ICU. He received IV etomidate 20 mg and IV succinylcholine 100 mg. Intubation was successful on the third attempt 11 minutes later when his heart rhythm changed to asystole. Resuscitation attempts were unsuccessful.
Conclusion: At least six avoidable errors occurred in the management of this case including reliance on the low anion gap despite a low bicarbonate, failure to request emergency hemodialysis, failure to give adequate sodium bicarbonate, failure to give dextrose for altered mental status, focus on non-toxic acetaminophen concentration, and endotracheal intubation.

312. Dexmedetomidine for alcohol withdrawal: looks can be deceiving

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Objective: Alcohol is a gamma-aminobutyric acid (GABA) agonist and an N-methyl-D-aspartate (NMDA) antagonist. Although benzodiazepines and barbiturates are the standard treatments for alcohol withdrawal (AW), there has been some recent interest in adding dexmedetomidine (DEX). We report a patient with severe AW to highlight a limitation of DEX.

Case report: A 58-year-old male with a history of delirium tremens requiring intensive care unit (ICU) admission presented to the emergency department (ED) with AW. His last drink was the night before. Vital signs were: heart rate 100/min, blood pressure 160/90 mmHg, respiratory rate 18/min; oxygen saturations 97% (room air), afebrile and normoglycemic. He had tremors in his extremities and tongue but no hallucinations. He was started on the institutional AW protocol and admitted. By 48 hours after admission he had received a total of 1150 mg chlordiazepoxide orally and 560 mg IV diazepam without any resolution of his symptoms. He was transferred to the ICU and 65 mg IV phenobarbital was given. Within 30 minutes he was asleep with normal vital signs. Unfortunately over the next 24 hours he only received a total of 200 mg chlordiazepoxide and became increasingly agitated with obvious signs of AW. Psychiatry recommended the patient be placed on DEX. He was given a 24 hour infusion of DEX (0.2 µg/kg/h), with no other therapy during which time he was sedated with a heart rate 80/min, blood pressure 126/80 mmHg, respiratory rate 18 and afebrile. Then 7 hours after stopping the DEX he was once again in moderate AW. When seen at the bedside the patient was requesting phenobarbital. "I only want phenobarbital, that's the only stuff that works". When asked further about his concern he stated that over the previous 24 hours while on the DEX infusion he "had been laying in bed staring at the ceiling feeling like hell". He said he "felt extremely agitated in my head" during that time period. He was subsequently restarted on the institutional AW protocol with resolution of his severe AW over the following week.
Conclusion: DEX is an α_2-receptor agonist commonly used for sedation in the ICU. Although DEX appears to control the autonomic instability and behavior associated with AW, it does not address the underlying pathophysiology. This leaves patients to suffer the psychologic effects of AW as illustrated in this case. We recommend that benzodiazepines remain the first-line treatment for AW, with refractory cases being treated with barbiturates or propofol. The role of DEX remains to be determined with studies that address cognitive and long-term outcomes of AW.

313. Does a patient with severe aluminum phosphide intoxication pose a danger to healthcare providers?

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Objective: A 62-year-old man, 100 kg, took 2 tablets of 3 g of mole poison containing 56% aluminum phosphide (AlP) 30 minutes prior to arrival at hospital. On arrival he was placed in a decontamination tent, because of fear of secondary contamination from phosphine gas by hospital staff. This went against the advice from the Poisons Information Center. Our aim is to show that ventilation and space significantly lowers the maximum phosphine concentration that health workers could be exposed to.
Methods: There are few studies on the toxicokinetics of phosphine and metal phosphides in mammals [1,2]. For the calculations, we used the following: a 3 g tablet of 56% aluminum phosphide releases 1 g of phosphine; 30% of the total phosphine formed after ingestion will be exhaled; first-order elimination of phosphine gas from the lungs, with an elimination constant ke =0.01, based on a rat study [1]; legal requirements for intensive care unit (ICU) rooms, i.e., a floor area of 18 m^2 and 100 m^3 fresh air/person/hour.
Results: During the first 30 minutes after ingestion, 0.16 g of phosphine would have been exhaled at home and in the ambulance. After arrival at the ICU, he would exhale another 0.20 g phosphine in the next 60 minutes. In an ICU room of 46 m^3, this equates to $(200/46) \times 0.72 = 3.1$ ppm. With the required ventilation of 100 m^3/hour in an ICU room, a concentration of 3.1 ppm exhaled by a patient would never exceed 0.03 ppm, during the hour following arrival.
Conclusion: A potentially lethal ingestion of 6 g aluminum phosphide does not give rise to a substantial exposure for health workers, though the immediate release of phosphine may be relatively high. The required ventilation in an ICU room is sufficient to decrease the phosphine concentration to harmless concentrations very quickly [3]. Likewise, in an ambulance, the calculated release of phosphine from the patient rapidly decreases to harmless concentrations when windows are opened.

References

[1] Meredith C. Toxicological studies on zinc phosphide. University of Birmingham (MSc Thesis). 1981. Cited in: World Health Organization. Environmental Health Criteria 73. Phosphine and selected metal phosphides. Geneva: WHO; 1988. [cited 2017 Mar 29]. Available from: www.inchem.org/documents/ehc/ehc/ehc73.htm
[2] Chan LT, Crowley RJ, Delliou D, et al. Phosphine analysis in post mortem specimens following ingestion of aluminium phosphide. J Anal Toxicol. 1983;7:165–167.
[3] Sudakin DL. Occupational exposure to aluminium phosphide and phosphine gas? A suspected case report and review of the literature. Hum Exp Toxicol. 2005;24:27–33.

314. Effect of extracorporeal treatments in a patient with prolonged phenytoin toxicity

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Objective: The management of acute phenytoin poisoning is complicated by prolonged central nervous system toxicity which often requires hospital admission lasting many days. Therefore, treatments to enhance phenytoin elimination have been trialled. Data are conflicting for multiple doses of activated charcoal (MDAC) and a recent systematic review suggested haemodialysis has a role in selected cases of severe poisoning, but based on limited data. We report a case of prolonged phenytoin toxicity treated with extracorporeal elimination.
Case report: A 30-year-old man was admitted with dysarthria, ataxia and nystagmus and then coma requiring intubation, following ingestion of up to 20 g of phenytoin. In addition to supportive care, MDAC and haemodialysis (either high flux or low flux) were initiated to enhance elimination. Phenytoin clearance by haemodialysis was determined using the extraction ratio and plasma flow, and the amount of phenytoin removed was calculated using the median overall clearance. The maximum plasma phenytoin concentration was 100 mg/L at 1.2 days post-admission. Haemodialysis and MDAC were commenced at this time which was followed by a decrease in plasma concentration to 64 mg/L 24 hours later. The plasma concentration decreased to 55 mg/L over the next 48 hours, but then increased. MDAC and haemodialysis were again initiated and the plasma concentration decreased from 60 mg/L to 37 mg/L. Ileus restricted further MDAC so he received repeat haemodialysis sessions, but a

consistent decrease in phenytoin plasma concentrations was not noted when haemodialysis was used alone. The concentration-time profile was not log-linear so half-lives during treatments could not be reliably determined. Extracorporeal clearance during haemodialysis was 31 mL/min ($n = 6$) for low flux and 49 mL/min ($n = 3$) for high flux modality, ($p = .5476$). Over the 18 day admission to intensive care, the patient received a total of 6 days of haemodialysis which removed approximately 16.4 grams of phenytoin.

Conclusion: A decrease in plasma phenytoin concentrations was associated with MDAC and haemodialysis co-treatment (two occasions), but not consistently when haemodialysis was used alone. Haemodialysis may be potentially useful if the duration of haemodialysis is prolonged, but this has logistic and cost implications.

315. Glucose-6-phosphate hydrogenase (G6DP) deficiency induced by 6-aminonicotinamide in hepatocytes: a protective factor in phosphine exposure

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Objective: Aluminum phosphide (AlP) causes severe toxicity with a 30–70% mortality rate [1–3]. However, several case reports presented AlP-poisoned patients with G6PD deficiency and extensive hemolysis who survived the poisoning [1,2]. We investigated whether G6PD deficiency could protect patients from severe fatal poisoning by this pesticide.

Methods: In a prospective animal study Sprague Dawley rats (150 to 200 g) were anesthetized by intraperitoneal administration of 0.2 mg/kg ketamine and 0.1 mg/kg xylazine. After heparinization, the abdominal cavity was opened. Isolation and incubation of the hepatocytes was performed by collagenase perfusion of the liver through the portal vein. After complete perfusion of the liver with buffer II (containing collagenase), the liver was excised and immersed in the buffer III (Krebs-Henseleit buffer supplemented with 12.5 mM HEPES) [4]. The hepatocytes were separated by pincers, centrifuged, and the precipitated hepatocytes were extracted. The viability of the hepatocytes were checked under the light microscopy and by administration of 300 µL of buffer IV (containing HEPES) and 200 µL of trypan blue to be over 80%. The hepatocytes were then transferred into three different flasks containing only hepatocytes; hepatocytes + phosphine and hepatocytes +6-aminonicotinamide + phosphine. Cell toxicity in the three groups was then compared by re-evaluating the viability of the liver cells. Production of reactive oxygen species (ROS) was also checked by ROS test.

Results: Cytotoxicity and the intracellular ROS concentration significantly decreased in the 6-aminonicotinamide + phosphine cells demonstrating that G6PD-deficiency induced by 6-aminonicotinamide had a significant protective effect on hepatocytes.

Conclusion: G6PD deficiency significantly reduces the hepatotoxicity of phosphine. Future drugs that can induce this deficiency may be promising in the treatment of AlP poisoning.

References

[1] Zamani N, Mehrpour O. Protective role of G6PD deficiency in poisoning by aluminum phosphide; are there possible new treatments? Eur Rev Med Pharmacol Sci. 2013;17:994–995.

[2] Farnaghi F, Owliaey H, Hassanian-Moghaddam H, et al. Intravascular haemolysis due to glucose-6-phosphate dehydrogenase deficiency in a patient with aluminum phosphide poisoning. Indian J Forensic Med Toxicol. 2013;7:79.

[3] Hashemi-Domeneh B, Zamani N, Hassanian-Moghaddam H, et al. A review of aluminium phosphide poisoning and a flowchart to treat it. Arh HigRadaToksikol. 2016;67:183–193.

[4] Hsu C, Quistad GB, Casida JE. Phosphine-induced oxidative stress in Hepa 1c1c7 cells. Toxicol Sci. 1998:46:204–210.

316. Hyperbaric treatment for hydrogen peroxide poisoning associated with portal venous gas and neurological symptoms: a case report

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Objective: Hydrogen peroxide (H_2O_2) is an oxidizing agent and the strength of the oxidizing reaction is determined by the concentration. The release of oxygen may cause gastrointestinal distension, as well as venous or arterial gas embolization. Ingestion of a small amount of 3% H_2O_2 can cause gastrointestinal irritation; concentrated (>10%) solution can cause caustic injury and gas embolization. The volume of oxygen liberated from the decomposition of 30 mL of 35% H_2O_2 solution is 3.5 L. We present a symptomatic case of portal vein gas embolism due to concentrated H_2O_2 ingestion, successfully treated with hyperbaric treatment.

Case report: A 47-year-old female presented to our emergency department (ED) after unintentional ingestion of a mouthful of 30% H_2O_2 solution used for swimming pool cleaning. She had a large self-induced frothy non-bloody vomiting episode at home. On admission her pulse was 67 bpm, blood pressure 157/86 mmHg, and oxygen saturation 94% (room air). She complained of headache, abdominal pain, dizziness, and upper limb weakness. A thorough neurological examination revealed no objective findings. Abdominal computerized tomography (CT) scan showed multiple portal vein gas emboli. Electrocardiogram (ECG), biochemistry and hematological laboratory workup, laryngoscopy, brain CT and cardiac echocardiography were normal. She was treated in a hyperbaric chamber with US Navy Diving Manual Treatment Table 6 (4.75 hours of oxygen and air intermittently up to 18 m depth) 8 hours after ingestion, with resolution of symptoms. Post-treatment upper gastrointestinal endoscopy revealed diffuse gastritis. Follow up abdominal CT performed 8 hours after completion of hyperbaric treatment showed complete disappearance of the gas emboli.

Conclusion: We present a case of concentrated H_2O_2 ingestion with mild neurological symptoms and diffuse gastritis, which resolved after hyperbaric treatment. Concentrated H_2O_2 ingestion is an uncommon poisoning but it can cause severe complications, including hemorrhagic gastritis, respiratory collapse, cerebral gas embolism, pneumomediastinum, and death. Clinical manifestations are usually evident shortly after ingestion, but they may be delayed and abrupt. Abdominal CT is a sensitive measure to detect portal gas emboli. Although a favorable outcome was reported even with delayed hyperbaric treatment,

permanent disability has been recorded. Early hyperbaric treatment can cause rapid resolution of gas emboli and may prevent neurologic complications. We recommend preforming abdominal CT in patients ingesting concentrated H_2O_2, and considering early hyperbaric treatment in the presence of portal or systemic gas emboli, even if patients are asymptomatic.

317. Management of a mixed overdose in the prehospital setting: a case report

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Objective: To discuss the prehospital management of a mixed overdose including a beta-adrenergic antagonist and a tricyclic antidepressant.
Case report: A 71-year-old woman was found unconscious after ingesting unknown quantities of modified-release propranolol, amitriptyline, modified-release oxycodone, bupropion, citalopram, lorazepam, rosuvastatin, fesoterodine, levothyroxine and pantoprazole. The paramedics were called to the scene and arrived at 07:30 with the patient in pulseless electrical activity arrest. Advanced cardiac life support was initiated. She was given 2 mg of epinephrine, 100 mEq of sodium bicarbonate and 5 mg of glucagon with return of spontaneous circulation (ROSC) at 08:12 and subsequent rhythm analysis showing a wide QRS bradycardia. The paramedics called other teams to obtain additional doses of antidotes pending transport and she was administered a total of 200 mEq of sodium bicarbonate and 13 mg of glucagon over the 30 minutes following ROSC. She was then transported to a hospital less than 5 minutes away and arrived in the emergency department at 08:51 with a heart rate of 43 beats per minute and a blood pressure (BP) of 41/19 mmHg. Ten units of regular insulin were administered intravenously (IV), followed by a 0.7 unit/kg/hour IV infusion and dextrose infusion to maintain euglycemia. Her BP remained low despite an IV epinephrine infusion so IV insulin was adjusted to 1 unit/kg/hour. Hemodynamic parameters stabilized afterwards and the epinephrine was stopped. She remained hemodynamically stable and the insulin infusion was stopped 36 hours after hospital arrival. Life support was withdrawn 8 days post-overdose for anoxic brain injury secondary to prolonged hypotension during the initial resuscitation.
Conclusion: This case illustrates the prolonged treatment of a mixed overdose in a prehospital setting without poison control centre backup while a hospital was within 5 minutes transport time. No confirmatory concentrations were obtained, however, at the time of administration, tricyclic antidepressant overdose should have been considered and insufficient sodium bicarbonate was given. The effectiveness of glucagon in treating beta-adrenergic antagonist overdose is also debated. Poison centers and emergency medical services should collaborate to revise protocols and better define goals of therapy, prioritize interventions and establish appropriate dosage of antidote and transportation times to avoid unwarranted reliance on glucagon for suspected beta-adrenergic antagonist toxicity and transport delays to healthcare facilities.

318. Metformin poisoning in the intensive care unit: a clinical, prognostic and pharmacokinetic study

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Objective: Metformin is the most prescribed anti-diabetic drug in the world. Its main complication, metformin-associated lactic acidosis (MALA) is rare, but potentially fatal. The most common cause is incidental metformin overdose, often triggered by acute renal failure or sepsis. Self-poisoning seems to have a better prognosis. We aimed to compare cases of self-poisoning and incidental overdose and assess the prognostic factors of mortality. We also wished to investigate the relationships between plasma metformin and blood lactate concentrations as well as describe the pharmacokinetics of metformin when possible.
Methods: We conducted a single-center retrospective observational study including all successive patients admitted in our intensive care unit between 2007 and 2016 for metformin poisoning defined by plasma metformin concentration >2 mg/L and analyzed data from the Laboratory of Toxicology for all metformin concentration measurements obtained in poisoned patients hospitalized in our region.
Results: Eighty-seven patients were included. Chronically metformin-overdosed patients differed from self-poisoned patients mainly by their co-morbidities and their presentation severity like the Sepsis-related Organ Failure Assessment (SOFA) score on admission ($p < .0001$). Based on a univariate analysis, risk factors of death were plasma lactate concentration >10 mmoL/L (OR =8.80), blood metformin >10 mg/L (OR =10.40) and prothrombin ratio <50% (OR = 12.9). A pharmacokinetic model was obtained from our metformin-poisoned patients with enough available data, showing two elimination phases and confirming the dialyzability of metformin. The lactate/metformin relationship fitted an Emax sigmoid model ($n = 109$ poisoned patients with concomitant measurements in the laboratory registry).
Conclusion: Metformin intoxication is severe and responsible for significant complications. Our study confirms the likely different mechanism of toxicity between self-poisonings and incidental overdoses. Measurement of intra-erythrocyte metformin concentration may be helpful to better understand the mechanisms of metformin-related toxicity and predict a metformin-poisoned patient's prognosis.

319. Need hemodialysis? Only during business hours!

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Objective: The treatment of severely poisoned patients is a primary goal of poison control centers (PCCs). Recommending hemodialysis (HD) is occasionally necessary to enhance removal

of select toxins. HD is often not performed despite strong recommendations from the PCC. The objective of this study is to identify barriers to performing HD when it is recommended by the PCC.
Methods: The study used PCC data from a single center from 2000 to 2015. We identified 413 adult patients (aged ≥8 years) for whom the PCC recommended HD and reviewed whether HD was performed. Univariate logistic regression was conducted with the performance of HD as an outcome and the following covariates: year, age, sex, and location (in or out of the PCCs primary catchment area), time of day (daytime [6 am to 5:59 pm] versus night time [6 pm to 5:59 am]), and day of week (weekday [Monday 6 am to Friday 11:59 pm] versus weekend [Friday Midnight to Monday 5:59 am]). We then performed multivariate logistic regression model using the outcome and potential confounders that were statistically significant at $p < .05$ in the univariate analysis.
Results: Among the 413 patients who had HD recommended by the PCC, 366 (89%) had HD, and 47 (11%) did not. Men were 54% of cases and most patients (79%) resided within the PCC's primary catchment area. About half (54%) of patients were reported during daytime and 70% were reported on weekdays. The univariate model showed that there were a significantly increasing number of HD performed throughout the study period (Odds Ratio [OR] = 1.08 [1.01–1.16]). Compared with cases who had HD, patients who did not have HD were significantly more likely to be reported during night time (44.3% versus 63.8%; OR =2.22 [1.18–4.17]) and during the weekend (27.1% versus 48.9%; OR = 2.59 [1.40–4.79]). These two factors remained significant after controlling for patient's age, sex, and year (adjusted OR for call hour and day of week: 2.18 [1.14–4.16] and 2.49 [1.32–4.70], respectively).
Conclusion: This study suggests that when the PCC recommends HD the actual performance of HD is associated with the time and day that it is recommended. Patients who have HD recommended outside regular business hours (i.e., night time and weekends) were less likely to be treated. Administrators and providers need to be aware of this potential barrier and work towards resolution.

320. Outcome of intoxicated patients admitted to the Intensive Care Unit (TOXIC study)

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Objective: Admission rates of intoxicated patients from the Emergency Department (ED) are often high. A proportion of these intoxicated patients are admitted to the Intensive Care Unit (ICU) and approximately 4% of the ICU population consists of intoxicated patients. We investigated the triage of intoxicated patients at the ED, with specific follow-up of ICU patients.
Methods: All intoxicated patients who were presented at our ED between January 2015 and June 2016, and subsequently admitted to the ICU of our hospital were included in the study. Data on exposure, clinical course and applied treatment were collected from electronic patient files.
Results: A total of 450 intoxicated patients visited the ED of whom 73% was admitted to a ward. For 59 patients (13%) ICU admittance was considered necessary, of whom 30 were referred to other hospitals due to capacity problems. The remaining 29 patients were admitted to our ICU and included in this study. The median age of these patients was 42 years (6 months-78 years) and males were overrepresented (59%). The majority of the patients had one or more co-morbidities (72%), including psychiatric and somatic diseases (59% and 38%). Based on medical history, most patients (55%) had exposure to only one substance. Reported exposures frequently involved medication (48%), illicit drugs (21%), alcohol (17%), caustic/cleaning products (10%), and inhalation of smoke (17%). At the ED, around three quarters of these patients presented with severe symptoms including cardiac arrest ($n = 5$), acute respiratory insufficiency ($n = 5$) and coma ($n = 11$). At the ICU, 93% of the patients received one or more treatments requiring ICU admission, including mechanical ventilation ($n = 23$), vasopressors ($n = 9$), antidotes (N-acetylcysteine $n = 2$, flumazenil $n = 2$, antivenom $n = 1$), hemodialysis ($n = 4$) and other treatment ($n = 4$). Overall 7% of the patients were under observation for rhythm disturbances or respiratory insufficiency, but remained without severe symptoms. The median Acute Physiology and Chronic Health Evaluation (APACHE) IV score [IQR] was 63 [28–82] ($n = 20$). Mortality of intoxicated ICU patients was 4/29 (14%). The median length of stay [IQR] at the ICU was 27 [11–58] hours. One patient who was admitted to a medium care ward was in need of ICU transfer.
Conclusion: Admission rates of intoxicated patients who visit the ED are generally high. Often this is for observational reasons and a large number of patients only develop mild symptoms. As these data show, the triage of patients who need ICU treatment is quite optimal with a sensitivity of 0.96 and a specificity of 0.99.

321. Poisons information at the frontline: use of the TOXBASE app by UK ambulance service staff in the prehospital setting

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Objective: The TOXBASE app (for iOS/Android) was re-launched in September 2015 becoming free for NHS healthcare professionals. It provides up-to-date, evidence-based poisons information both online and off-line to healthcare professionals at the point of care. Our objective was to compare use of the TOXBASE app with TOXBASE online amongst UK ambulance staff in the prehospital setting.
Methods: We retrospectively analysed ambulance staff use of the TOXBASE app and TOXBASE online from 1 October 2015 to 30 September 2016. We compared user profile, product page accesses, and daily pattern of use by ambulance service users across both platforms.
Results: TOXBASE app accounts are registered to individual healthcare professionals. A total of 6813 app accounts (an increase of 1388% from 458 on 31 March 2015) were registered during this period; 51.7% (3521) were ambulance staff. By contrast, TOXBASE online accounts are registered by unit. During the same period 4.1% (244) of total TOXBASE accounts were registered to ambulance units. During the 12-month period, ambulance healthcare professionals made 62.0% (27,364) of total TOXBASE app product accesses compared to 10.8% (156,555) of

Table 1. Top accesses to TOXBASE online/TOXBASE app over a 12 month period.

TOXBASE online accesses (by ambulance units)			TOXBASE app accesses (by individual ambulance healthcare professionals)		
Rank	Product page	Number	Rank	Product page	Number
1	Paracetamol	9.5% (14,951)	1	Paracetamol	8.7% (2,386)
2	Ibuprofen	4.6% (7277)	2	Amitriptyline	2.7% (726)
3	Codeine	2.2% (3,465)	3	Ibuprofen	2.0% (541)
4	Sertraline	1.8% (2752)	4	Diazepam	1.9% (526)
5	Diazepam	1.3% (2037)	5	Citalopram	1.9% (515)
6	Tramadol	1.3% (1992)	6	Sertraline	1.9% (513)
7	Citalopram	1.2% (1939)	7	Zopiclone	1.7% (473)
8	Zopiclone	1.0% (1642)	8	Codeine	1.5% (418)
9	Co-codamol	1.0% (1597)	9	Mirtazapine	1.5% (406)
10	Amitriptyline	1.0% (1507)	10	Tramadol	1.3% (366)

total TOXBASE online product accesses. The most commonly accessed product pages by ambulance healthcare professionals across both platforms are shown in Table 1. Analgesics and antidepressants were commonly accessed via both platforms. The hourly pattern of product pages accessed throughout the day across both platforms showed a lowest point around 7 am, followed by a steady rise over the course of the day, rising to a peak at around 9–10 pm.

Conclusion: The profile of top product page accesses made by ambulance users was similar across both platforms reflecting UK poisoning epidemiology. Since the TOXBASE app re-launch there has been a significant uptake of this new platform for poisons information, particularly among ambulance healthcare workers in the prehospital environment.

322. Protective effect of erythropoietin in visual disturbances due to methanol poisoning: a preliminary report

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Objective: Methanol poisoning may cause visual disturbances ranging from blurred vision to complete blindness. These complications may be permanent [1] and therefore, introduction of new treatments alleviating visual complications are important. Previous case reports suggest possible therapeutic effect of erythropoietin in preserving the visual acuity of these patients [2].

Methods: In an ongoing prospective case-control study that started in September 2014, all methanol-poisoned patients who presented with visual disturbances after methanol poisoning and survived were prospectively enrolled. They were assigned into the case group (prednisolone + erythropoietin; group 1) if they consented to receive this new experimental therapy and control group (prednisolone alone; group 2) if they did not. They were followed with visual evoked potential (VEP) and complete ophthalmology examination afterwards. The dosing regimen was erythropoietin 10000 U every 12 hours for three days and prednisolone 250 mg every 6 hours for 3–5 days. The two groups were then compared regarding their final visual status.

Results: A total of eleven patients have been enrolled up to May 2016 (8 in group 1 and 3 in group 2). All were dialyzed. All three patients in group 2 and 5 patients in group 1 reported that their visual acuity improved with treatment given (at discharge). However, two of them in group 2 declared their visual acuity deteriorated 1–2 months after discharge. Two other patients in group 2 reported that their visual acuity deteriorated even after treatment and continued to be worse after discharge and one reported no change in vision. There was no statistically significant difference between the VEP results and ophthalmologic examination of the two groups in long-term follow up.

Conclusion: At the moment, it seems that although erythropoietin may have protective effects on visual acuity of methanol-poisoned patients in the short-term, the effects do no persist in long-term follow-up. Further study is required.

References

[1] Sanaei-Zadeh H, Zamani N, Shadnia S. Outcomes of visual disturbances after methanol poisoning. Clin Toxicol. 2011;49:102–107.

[2] Pakravan M, Sanjari N. Erythropoietin treatment for methanol optic neuropathy. J Neuroophthalmol. 2012;32:325–328.

323. Recalled to life: prolonged action of pancuronium in a neonate suggesting death reversed with neostigmine

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Objective: To report the very rare use of neostigmine in a neonate.

Case report: A male neonate born at 24 weeks +2 gestation, required transfer to a tertiary centre at 25 days of age for a laparotomy due to a necrotic bowel complicating a severe Gram negative infection. Prior to transport, the neonate received pancuronium. Twelve hours after surgery there were no noticeable movements. Testing for brain-stem death was undertaken. Subsequently staff realised that the child had been given a 10 times overdose of pancuronium, receiving 540 µg in error. The National Poisons Information Service was contacted and was advised that the child remained stable from a cardiac, respiratory and metabolic perspective and was currently intubated, ventilated and receiving ionotropic support. There was no data sheet available on TOXBASE and no medical scientific literature available regarding pancuronium overdose in neonates. Neostigmine and atropine were advised by the on call consultant. The neonate received 0.02 mg/kg neostigmine 26 hours post-overdose, developed bradycardia within four minutes of administration of neostigmine which responded to 11 µg atropine. Return of spontaneous movements was noticed within 20 minutes of receiving neostigmine. Continuing care was provided for underlying sepsis and the child was discharged from hospital.

Conclusion: Pancuronium is a non-depolarizing neuromuscular blocking agent, which acts on the neuromuscular junction nicotinic receptors. Neostigmine is a competitive acetylcholinesterase inhibitor that prolongs the action of acetylcholine at the neuromuscular and ganglionic nicotinic receptors. The temporal relationship between the return of spontaneous movement and the onset of bradycardia following neostigmine are suggestive of a pharmacological antagonism. The half-life of pancuronium is estimated to be between 89 and 161 minutes, but this is thought to be doubled during renal failure and cirrhosis and biliary obstruction. Pancuronium is cleared through the biliary (11%) and renal (40%) routes. Pharmacokinetics in the premature neonate are not well described. At the time of enquiry approximately 10 half-lives would have elapsed, suggesting that the half-life in this case was considerably prolonged. Careful consideration of toxicological causes should be evaluated before brain stem death is concluded.

324. Suicide attempt with acetonitrile treated with sodium thiosulfate: a case report

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Objective: To report a suicide attempt with acetonitrile (ACN) successfully treated with sodium thiosulfate.
Case report: A 75 kg nursing mother of a 2-month-old baby ingested 200 mL of ACN 99.5% (estimated dose approximately 2 g/kg) in a suicide attempt; ACN had been purchased via Internet. She was admitted to a local emergency department (ED) a few hours post-ingestion complaining of dizziness and lethargy, with no other remarkable clinical features being detected after a short-stay observation, and was discharged. Next morning (approximately 20 hours post-ingestion; T20), she was taken again to the same ED, with the same symptoms and skin pallor; at this time, our Poison Center was contacted. In the face of the estimated ingested dose and potential risk of cyanide poisoning, we decided to start treatment with sodium thiosulfate IV at T34 (15 mg/kg; 12.5 g). Blood and urine samples collected before starting the infusion (T24) revealed ACN concentrations of 200 mg/L and 235 mg/L, respectively. Subsequently, blood samples collected every 24 hours for ACN determine revealed 140, 80, 56, 37, 27 and 17.5 mg/L, allowing calculation of the elimination half-life of 40.4 hours. The infant showed no signs of intoxication, and ACN was not detected in the child's blood at D7. Concomitant samples of maternal milk and blood obtained at D7 revealed ACN values of 21 mg/L and 27 mg/L, respectively, suggesting a 1.2:1 relationship between blood and breast milk. She remained asymptomatic during treatment and, after receiving 5 days of sodium thiosulfate IV, she was discharged in good condition (D7).
Conclusion: ACN is an organic solvent of the aliphatic nitrile group used in laboratory extraction processes, and in the synthesis of polymers, plastics, resins, dyes, and medicines. ACN is rapidly absorbed through the lungs and gastrointestinal tract. It is widely distributed, and metabolized to cyanide ion (CN^-), formaldehyde and formic acid, by cytochrome P450 2E1. Its toxic effects are related to cyanide formation, and its elimination half-life ranges from 32 to 36 hours. Signs and symptoms have a lag time of 2–18 hours [1]. In the present report, despite the large dose of ACN ingested, treatment with sodium thiosulfate alone, for 5 days, started approximately 34 hours post-ingestion, was successful in preventing cyanide toxic effects. An elimination half-life of ACN of 40.4 hours was calculated in this case.

Reference

[1] Aliphatic nitriles. Acute exposure guideline levels. In: Acute Exposure guideline levels for selected airborne chemicals. Washington (DC): National Academy of Sciences; 2014. [cited 2016 Nov 2]. Available from: http://www.nap.edu/catalog.php?record_id =18707.

325. Update after 20 years of take home naloxone programs

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Objective: The first Take Home Naloxone program began in 1996 [1]. We report the results of a survey of sites providing naloxone kits to laypersons [2].
Methods: In 2014, the Harm Reduction Coalition, surveyed 140 US overdose education and naloxone distribution (OEND) programs [2]. Managers at 136 organizations completed the survey.
Results: From 1996 through June 2014, 644 sites had distributed naloxone to 152,283 laypersons with 26,463 overdoses reversed. Half of the responding programs only began operating during the last 1.5 years of the survey period. Naloxone recipients were primarily drug users (81.6%) and friends and family members (11.7%). Those who administered naloxone were mainly persons who use drugs (82.8%) and friends and family members (9.6%). Only injectable naloxone was provided by 50.7%, only intranasal by 37.5%, and both were provided in 11.8%. Intranasal naloxone is preferable because it avoids needle-stick risks to rescuers and is simple to learn and use. Heroin was reversed in 81.6% of reversals and prescription opioids in 14.1%. Heroin predominated because early OEND programs were based at syringe exchanges. Later, other programs based at substance use treatment facilities, primary care clinics and pharmacies appeared. The latter sites are better suited to enrol persons who witness prescription opioid overdoses, which account for many deaths. The price of intranasal naloxone more than doubled in the second half of 2014 and naloxone prices have doubled again since then. Cost increases are reducing the quantity of naloxone distributed to laypersons. While OENDs recommend calling emergency medical services (EMS), a survey of trainees reported that fewer would do so for fear of police involvement. Passage of Good Samaritan laws to protect bystanders from legal consequences from calling EMS improve compliance with this recommendation.
Conclusion: These data show that persons at risk for overdose and bystanders are able to be trained to prevent overdoses and administer naloxone. Other countries have also developed OEND programs but only a few studies have evaluated the efficacy of OEND in reducing opioid deaths, most with positive results. Greater emphasis must be place on enrolling high risk opioid prescription users. Facilitating the growth of OEND programs appears to be worthwhile in fighting the opioid mortality epidemic.

References

[1] Darke S, Hall W. The distribution of naloxone to heroin users. Addiction. 1997;92:1195–1199.
[2] Wheeler E, Jones TS, Gilbert MK, et al. Opioid overdose prevention programs providing naloxone to laypersons – US, 2014. MMWR Morb Mortal Wkly Rep. 2015;64:631–635.

326. When an international vacation almost kills your teenager: case report of severe *Bothrops asper* envenomation of an American teenager while in Belize with common and not so common manifestations

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Objective: While on a trip to Belize from California, a young teenager was bitten by one of the world's deadliest snakes, the fer-de-lance (*Bothrops asper*), leading to respiratory arrest and severe exsanguination, almost to death. Aggressive treatment in Belize, and in Florida, collaboration between local Belize physicians, pediatric intensivists, and venom response specialists led to significant recovery of this young girl, to be able to return home to play with her friends and return to school, despite severe coagulopathy, and cerebrovascular issues. We highlight this important case that crosses the span of toxinology, international travel medicine, critical care transport, neurology, hematology, emergency medicine, wilderness medicine and prehospital medicine. This case also highlights common but not classic human reactions to deadly venoms.

Case report: A teenage female patient was traveling with her family in Belize and walking along a hotel path, when she was bitten by *Bothrops asper*. The patient reportedly syncopized and went into respiratory arrest, witnessed by her father, and was immediately taken to a local clinic, where she was ventilated and administered the first antivenom dose. She was then immediately transferred 45 minutes to a hospital. At this hospital, the patient received another eight vials of antivenom, was intubated and resuscitated with significant blood in her urine, and orogastric suctioning. An air critical care service transported her to a Florida pediatric intensive care unit with consultation of Miami's toxicologist, poison control center, and the Venom One Team. The patient soon thereafter was extubated, however she did not appear to regain full neurologic function immediately despite normalization of labs and decreased visible bleeding, and exhibited stroke-like symptoms. Emergent imaging confirmed feared right frontal ischemic pathology. The patient ultimately returned home to California with aggressive physical therapy and now is happily recovering and able to attend school and play with her friends.

Conclusion: *B. asper* is a known extremely deadly venomous snake in Belize. This case highlights the importance of quick thinking, and quick consultation with true specialists like experienced toxicologists and an experienced wilderness emergency medical services (EMS) physician and a venom response team, such as the unique Venom One Team out of Miami Dade, Florida. Furthermore, this highlights the unique pathological timeline of coagulopathy and neurologic outcomes not described in specialty textbooks and advanced training.

327. When new therapies fail and old therapies are forgotten: a case of a late nortriptyline death with failed lipid emulsion therapy

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Objective: Most deaths from tricyclic antidepressant overdose occur within 6 hours. We present a delayed nortriptyline death in a patient who was not decontaminated. We hypothesize that death in this case was likely due to delayed absorption following re-perfusion of the gastrointestinal tract. Following deterioration, lipid rescue failed in this patient.

Table 1. Clinical course in a patient with nortriptyline overdose.

Time from arrival	Vital signs	QRS (msec)	Blood biochemistry	Intervention	Notes
00:00	98/68 mmHg HR 100/min	122		$NaHCO_3$ bolus	QRS narrowed
00:45		149	pH 7.33 PCO_2 51	Lorazepam $NaHCO_3$ bolus $NaHCO_3$ drip	Seizure
03:00	64/48 mmHg	150	pH 7.41 PCO_2 30	Vasopressors $NaHCO_3$ bolus $NaHCO_3$ drip Hyperventilation	Intubated NG inserted No decontamination
09:00	SBP 130 mmHg HR 90/min	<100		Hyperventilation $NaHCO_3$ drip	Stabilized
15:00			pH 7.45 PCO_2 "low"	RR decreased to 14/min	Vent adjusted
15:30	SBP 80 mmHg HR 140/min	140		$NaHCO_3$ bolus	
15:35		117			
16:00	SBP 80 mmHg HR 130/min	135	pH 7.7 Na^+ 152 mmol/L	$NaHCO_3$ drip stopped Activated charcoal	
17:00	SBP 80 mmHg HR 150/min		pH 7.38 PCO_2 37	$NaHCO_3$ bolus $NaHCO_3$ drip	Cardiopulmonary resuscitation
17:30	PVT	>220		$NaHCO_3$ bolus ILE bolus Hyperventilation	
17:38	HR 150/min	>220		$NaHCO_3$ bolus $NaHCO_3$ drip	Return of spontaneous circulation
18:00	Pulseless ventricular tachycardia	>220		$NaHCO_3$ bolus ILE bolus ILE infusion	
19:00					Dead

HR: heart rate; ILE: intravenous lipid emulsion; $NaHCO_3$: bicarbonate; NG: nasogastric; RR: respiratory rate; SBP: systolic blood pressure.

Case report: A 25-year-old suicidal woman presented 3 hours after ingesting nortriptyline (1200 mg). Vitals were: heart rate 100/min, blood pressure 98/68 mmHg, oxygen saturation 98% (room air), temperature 36.1 °C, and Glasgow Coma Scale (GCS) 9. Her clinical course is summarized in the Table 1. At hour 15.5 the respiratory therapist (RT) reduced the respiratory rate to 14 because of her respiratory alkalosis and she became unstable again. She remained unstable and at hour 17.5 she went into a pulseless ventricular tachycardia (PVT). Cardiopulmonary resuscitation (CPR) was started and she received bicarbonate boluses and lipid emulsion therapy (ILE). Return of spontaneous circulation was achieved after 8 minutes. The bicarbonate infusion was restarted, but at hour 18 she went back into PVT. CPR was again started and another ILE bolus was given followed by an infusion. After 60 minutes of CPR the patient was pronounced dead at hour 19. Her blood nortriptyline concentration was 2800 ng/mL.

Conclusion: This case illustrates a second, delayed, phase of toxicity after hemodynamic stabilization possibly resulting from inadequate gastrointestinal decontamination. Once gastrointestinal perfusion was restored, the drug remaining in the gut becomes available for absorption leading to recurrence of toxicity. This re-bolus effect can be amplified when standard therapy is withheld. The best treatment is likely to limit gastrointestinal absorption as there is no effective antidote. In this case, there was no benefit administering ILE, possibly because ILE enhanced gastrointestinal absorption.

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