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ABSTRACTS

EAPCCT Abstracts

1. Toxicity Mediated via Receptor Interactions. The Example of Opioids

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Opiates belong to the group of the longest used drugs in human history. Their toxic effects are well known since ancient times. However, insight into the mechanisms of their actions comes from investigations over the last 40 years, but little is known and the findings give a puzzling and not always conclusive picture. This article will highlight some of the best investigated effects of opioids on their receptors. Since the 1970s, opiate receptors (OR) are grouped according to their ligand-specificity and are differentiated into three types: μ, k, d, and subtypes. Substrates of OR are endogenous oligopeptides as are endomorphines, enkephalines, dynorphine or exogene opiates, opioids, and synthetic oligopeptides. These ligands differ in specificity/cross-reactivity, intrinsic activity, and receptor-kinetics. OR are unevenly distributed in the CNS. μ-OR are concentrated in CNS-areas responsible for spinal and supraspinal pain processing, respiratory-control, and parts of the reward system such as medial thalamus, limbic system, and frontal region of the cortex. Their natural substrates are the endomorphines. μ1-OR are responsible for supraspinal analgesia and euphoria. μ2-OR mediate spinal analgesia, respiratory depression, physical dependence, inhibition of intestinal motility, miosis, bradycardia, k-OR mediate spinal analgesia and miosis, sedation, and dysphoria. They are concentrated in pain processing areas and in substantia nigra. Dynorphin is the natural ligand. d-OR are involved in modulation of stress- and pain-induced reactions like excretion of ACTH and superior regulatory mechanisms. d-OR are predominantly distributed in the cortex, medulla, and spine. Their natural substrate are enkephalines. d-OR inhibit the cough-reflex and alter nigrostriatal dopamine release. s-Receptors are no longer considered to belong to the OR-family. However, they too are involved in pain processing, vigilance, and psychomimesis. They are substrates for drugs such as ketamine, phencyclidine, and dextromethorphan. The opioid-like-receptor (ORL) shares some homologies with OR and mediates spinal analgesia and in contrast supraspinal hyperalgesia. The classic pharmacological model of the three classes of OR and their subtypes does not explain the incomplete crosstolerance between codeine and fentanyl which are both μ-agonists. This effect is known clinically and used in pain management with the so called "opioid-rotation." A possible explanation is the existence of different splice variants of one OR as shown in mouse models with the μ1-OR. This would postulate a much greater multiplicity of μ-OR than assumed so far. Distinct OR can heterodimerize. Heterodimeric OR exhibit signalling properties different from their monomers. μd-heterodimer-OR have an enhanced morphine-activation when incubated with a d-antagonist. Likewise in a mouse model, spinal analgesia of morphine is enhanced by co-treatment with a d-antagonist. There are clinically known interactions between agonists, partial agonists, and partial antagonists, such as morphine and buprenorphine, which cannot be explained satisfactorily by classical pharmacological models. Possibly, these observations find better explanations with this new multiplicity of OR. OR belong to the family of G-coupled-receptors (GPCR). They have a seven-transmembrane-spanning domain architecture. They modulate intracellular metabolism by activation of heterotrimeric (abg)-GTP-binding proteins (G-proteins). Ligand binding to the OR stimulates GTP-binding at the a-subunit of the G-protein, and its dissociation from the receptor-G-protein-complex. The a-subunit as well as the bg-dimer of the G-Protein bind to and influence their effectors. One effector of OR is adenylatcyclase, which is inhibited dependent from the concentration of the opioid. In excitatory neurons, inhibition of adenylat-cyclase causes alterations in K^+/Ca^{++} ion-channels leading to a decreased excitability. cAMP activates factor CREB (see below) in the locus coeruleusm, which is involved in addiction and withdrawal of the transcription. One target gene of CREB encodes tyrosin-hydroxylase, which is necessary for dopamine-synthesis. OR are a subject of desensitisation. Desensitisation may be the correlative of tolerance. Tolerance means the adaption to chronic opiate exposure with diminishing intrinsic activity of the actual opiate. Arrestines and GCPR-kinases such as GRK3 are involved in desensitisation. KO-mice lacking GRK3 show reduced tolerance to fentanyl; KO-mice lacking b-arrestin-2 exhibit enhanced morphine antinocireception and reward but do not develop tolerance. However, the manifestations of naltrexone-precipitated withdrawal are not altered. This means, physical dependence is modulated by other mechanisms. The desired effects of an opioid and its toxic side-effect may result from an activation of the same OR-type. Newer investigations give some insights into the most prominent toxic effects of opioids: respiratory depression and addiction. Respiratory depression is μ2-OR mediated. μ-OR are concentrated in the ventral respiratory column of the medulla oblongata. There, opioids desensitize CO_2 receptors which attenuates the respiratory drive. By different additional mechanisms opioids attenuate respiratory frequency, tidal volume, and chest wall compliance. Application of μ-specific-opioids into the prae-Bötzinger complex disrupts the inspiratory rhythm generating network causing dose-dependent lower frequencies. With fentanyl, μ-OR mediated activation of inhibitory synapses at exspiratory neurons causes tonic stimulation of phrenic and abdominal muscles and subsequently a diminished chest wall-compliance and lower tidal volume. The natural substrates of μ2-OR, endomorphines, at equianalgesic doses compared with morphine, exhibit no respiratory depression in another experiment. Dependence/addiction is the consequence of chronic stimulation of μ2-OR in the reward system of the brain. There, acute opioid stimulation suppresses the intracellular second messenger cAMP. By chronic stimulation, cAMP is upregulated and activates the transcription factor CREB. This effect is shared with other reinforcing substances like cocaine and ethanol. Increased CREB-expression diminishes the rewarding effects of opioids. One target gene of CREB encodes dynorphin which in the case of opiate withdrawal causes dysphoria by stimulation of k2-OR. Chronic μ2-OR-stimulation in the rewarding system also causes an accumulation of the transcription-factor ΔfosB. Mice overexpressing ΔfosB show increased sensitivity to the rewarding effects of opioids. However, ΔfosB also upregulates the synthesis of dynorphin. There are other toxic/side effects of opioids, e.g., intestinal paralysis is μ2-OR mediated and not subject to tolerance. Bolus injection fentanyl causes μ-OR mediated dopamine depletion in the striatum and thus chest wall rigidity. This is an additional effect to that described above. *Conclusion:* New techniques in molecular-biology have gained new insights into the mechanisms of opioid – receptor interactions including the toxic side effects of opiates. However, many clinical observations still need better pathophysiological explanations.

2. Toxicity Mediated by Ion Channel Dysfunction. The Example of Calcium–Channel-Blocker Poisoning

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Calcium-channel-blockers (CCB) are responsible for life-threatening poisonings, with an increasing incidence. In 2005, CCB poisoning was associated with the highest number of reported fatalities among cardiovascular agents in the U.S., with 75 deaths among 10,500 exposures (1). There are five pharmacological classes of CCB, including the phenylalkylamine (verapamil), the dihydropyridine (nifedipine and amlodipine), the benzothiazepine (diltiazem), the diphenylpiperazine (mibefradil), and the diarylaminopropylamine (bepridil). On the other hand, there are five different types of voltage-gated calcium channel, designated L, T, P, Q, and N. CCB act by binding to the L (or long-lasting)-type channels. These L-type channels are located on the heart, the arterial smooth muscles, and the pancreatic beta cells. Muscle cells are able to maintain a huge calcium concentration gradient across their membranes by allowing calcium influx only through these voltage-gated channels, sequestering free calcium in the sarcoplasmic reticulum and maintaining an adenosine triphosphate (ATP)-driven calcium export pump (2). Activation of the L-type channel (following phosphorylation by intracellular cyclic adenosine monophosphate (cAMP)-mediated protein kinases) results in an increase of intracellular calcium concentrations from less than a 10^{-7} molar to more than a 10^{-6} molar range. Available intracellular calcium is then necessary for the muscle excitation-contraction coupling. Thus, CCB toxicity, by reducing the calcium influx and the muscle excitation-contraction coupling, results in a reduction in the cardiac and vascular smooth muscle contractibility. The CBB phenylalkylamine and benzothiazepine classes affect both the myocardium and the cardiac pacemaker cells. They induce myocardial negative inotropic effects, conduction deficits, and dysrhythmias. The dihydropyridine class mainly inhibits the arterial vascular tone, causing vasodilatation. Thus, the usual clinical features include hypotension, bradycardia, sinus nodal suppression, junctional rhythms, atrioventricular blocks, idioventricular rhythms, congestive heart failure, and asystole (3). Toxicity also results in extensive extra-cardiac abnormalities, including mental status deterioration, seizures, metabolic acidosis from hyperlactacidemia, and adult respiratory distress syndrome (or non-cardiogenic edema) (4). Metabolic consequences of CCB poisoning may enhance cardiotoxicity; hypoinsulinemia adversely affects cardiac myocyte glucose uptake, which appears crucial in stress conditions and mitochondrial calcium intake decrease inhibits pyruvate dehydrogenase activity, causing hyperlactatemia. Management of CCB poisoning focuses on restoring hemodynamic function. Conventional therapies consist of fluid replacement and administration of atropine and various catecholamines (3,5). Calcium salts, for which efficacy remains controversial, are helpful. In severely poisoned patients, repeated 1 g IV bolus /15–20 min to a total of 4 doses is recommended, followed by an infusion of 20–50 mg/kg/h, in those with beneficial hemodynamic response to initial calcium infusion (5,6). Serum calcium concentration should be measured at least twice daily and maintained at normal levels, given the lack of evidence for benefit in supra-physiological levels. Although only supported by evidence from animal studies, glucagon (5–10 mg IV bolus followed by 1–10 mg/h infusion) use may be beneficial (7). Hyperinsulinemia (0.5–1 IU/kg/h), combined with glucose to maintain euglycemia, has been proposed as an adjunctive approach. However, to date, recommendations are only based on limited case series (8–10). Insulin allows the switch of the myocardial cell metabolism from fatty acids to carbohydrates which is required in stress conditions, improving cardiac contractility and restoring peripheral resistance. Administration of multidose activated charcoal is indicated in case of sustained-release preparation ingestion. Due to large distribution volumes and high protein binding ratios, extracorporeal elimination enhancement techniques are not feasible options. However, despite all these aggressive resuscitative measures, ventricular arrhythmia, sudden cardiac arrest or refractory cardiovascular failure cause death in the most severe cases. When catecholamine-refractoriness is evidenced, central hemodynamic monitoring is mandatory. High-dose titrated vasopressor therapy, ventricular pacing, intra-aortic balloon pump, or percutaneous cardiopulmonary bypass (extracorporeal life support systems) should be considered as lifesaving measures (6,11). However, the value of intra-aortic balloon pump use is limited, due to the need for intrinsic cardiac rhythm for synchronization and diastolic augmentation. Interestingly, available data allowing the benefit analysis of these exceptional therapies are still limited. Other "antidotal therapies" have been recently shown as promising, including phosphodiesterase III inhibitors (inamrinone), vasopressin analogues (terlipressin) (12), and potassium-channel-antagonists used as non-depolarizing neuromuscular blocking agents (4-aminopyridine and two potent dihydropyridines, the 3,4-diaminopyridine and the Bay K8664) (13,14). All these agents proved interesting effects in animal studies or if tested, in limited human cases. However, their availability still limits their utilization. In conclusion, toxicity mediated by calcium channel dysfunction is life-threatening. Although mechanisms of toxicity are now rather well-understood, poisoned patient management remains difficult and may be unsuccessful in a significant proportion of cases. *References*: 1. Lai MW, Klein-Schwartz W, Rodgers GC, et al. Clin Toxicol 2006; 44:803–932. 2. Brent J. Critical care toxicology. Philadelphia, USA:Elsevier Mosby, 2005:413–426. 3. Mokhlesi B, Leikin JB, Murray P, et al. Chest 2003; 123:577–592. 4. Brass BJ, Winchester-Penny S, Lipper BL. Am J Emerg Med 1996; 14:459–461. 5. Salhanick SD, Shannon MW. Drug Saf 2003; 26:65–79. 6. Albertson TE, Dawson A, de Latorre F, et al. Ann

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3. Toxicity Mediated by Interference with Membrane Pumps - Underlying Mechanisms of Cardiac Glycoside Toxicity

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Globally, cardenolide poisoning is common due to unintentional poisoning in patients taking medicinal cardiac glycosides (digoxin, digitoxin), and intentional poisoning in people ingesting toxic plants (oleanders, sea mango). Although anti-digoxin Fab fragments have revolutionized treatment in rich countries, the antitoxin is not routinely available in many countries due to cost and here patients are treated with more classical therapies. Cardenolides inhibit the Na^+/K^+-ATPase on the myocardial membrane, increasing the intracellular concentration of Na^+. This stimulates the activity of a Na^+/Ca^{2+} transporter, which exchanges intracellular Na^+ for extracellular Ca^{2+}. The increase in intracellular Ca^{2+} enhances the Ca^{2+}-triggered Ca^{2+} release from the sarcoplasmic reticulum, increasing the force of contraction. However, further increases in cardenolide load lead to toxicity manifesting as dysrhythmias and cardiac standstill in systole ('stone heart'). Changes in intracellular Ca^{2+}, K^+, and Na^+ homeostasis produce partial membrane depolarisation, increased automaticity, and the generation of early after-depolarisations that may trigger dysrhythmias. Additional mechanisms include variable sodium channel blockade, augmented or reduced sympathetic activity, increased vascular tone, and vagotonic effects. The most common dysrhythmias in acute overdose are bradycardias and AV block. The speed of onset of clinical effects relates to the time for these processes to occur, and the dose of cardenolide ingested. Inhibition of the Na^+/K^+-ATPase induces hyperkalaemia, which decreases membrane excitability and impairs cardiac conduction. Hypokalaemia may be noted due to concomitant medical conditions or therapies; this increases membrane excitability and the incidence of dysrhythmias, potentiating cardenolide cardiotoxicity. Standard management involves resuscitation, activated charcoal if a patient presents early (vomiting is a symptom of toxicity), antiemetics, and treatment of dysrhythmias, especially bradycardia. Sinus bradycardia is treated with a bolus dose of 0.6 mg atropine to reduce vagal tone; bradycardia with marked hypotension may require bolus doses of 2–3 mg. Anti-digoxin Fab bind to free cardenolides intra-vascularly, creating a concentration gradient that draws cardenolides out of the extravascular space, including cardiac tissue. The antitoxin can rapidly reverse high degrees of AV block and sinus block unresponsive to atropine, hyperkalaemia, and ventricular dysrhythmias. In the absence of antitoxin, temporary cardiac pacing may be considered but there is little evidence that pacing offers benefit and some evidence of harm. Lidocaine and phenytoin have been used to suppress enhanced ventricular automaticity without impairing AV node conduction. The effect of reducing serum K^+ concentrations with insulin dextrose when antitoxin is absent is currently unclear. While it is sensible to reverse hypokalaemia with K^+ infusions, this feature is uncommon in acute overdose. The most important future advance for treatment of cardenolide poisoning will be the development of anti-digoxin antitoxin affordable to the developing world.

4. Mechanisms and Clinical Effects of Interference with Enzyme Function using Cholinesterases as an Example

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Of the various macromolecular targets of toxic compounds enzymes play only a minor role. If, however, such an enzyme is centered in a key position, inhibition to a high degree may be detrimental. Well-known examples are cyanide, fluoroacetate, and the anticholinesterase agents. Nature developed the most sophisticated poisons compromising cholinergic transmission, such as fasciculin 3, a green mamba venom that has a dissociation constant of just 0.4 pM and is probably the most potent reversible inhibitor of acetylcholinesterase (AChE). The extraordinarily high potency of fasciculin, a 61 amino acid peptide, is due to its ability to occlude the entrance to the gorge of mammalian AChE. The high affinity deduces from the particularly low dissociation rate constant of the complex with a half-life of about 2 days (rat brain AChE) (1). Another low-molecular AChE inhibitor which also forms a reversible complex with the enzyme is huperzine A, which was isolated from the fir club moss. The (-) enantiomer has a dissociation constant of about 7 nM with a dissociation half-life of about 4.6 min (human red blood cells; 2). Huperzine A binds to the rim of the gorge of AChE. While the above-mentioned compounds form non-covalent complexes with AChE and thus impede substrate hydrolysis, the well-known acylating inhibitors are covalently linked to the active site serine. It is the group of carbamates and phosphororganic compounds which are responsible for millions of intoxications per year world-wide and some 300,000 deaths. Both carbamates and organophosphorus compounds are hemisubstrates for the cholinesterases. The enzyme splits the ester bond similarly to acetylcholine. But in contrast to the physiological substrate, the ensuing serine ester is not split within submilliseconds, but within fractions of hours up to several days. Therefore, hydrolysis of carbamates and organophosphorus compounds by cholinesterases is reminiscent to a suicide reaction when the catalyst becomes irreversibly inactivated. While the acylation reaction by carbamates may virtually completely inhibit the physiological function of AChE, resulting in endogenous acetylcholine intoxication, spontaneous deacylation by hydrolysis of the serine carbamate is significant and carbamates are therefore frequently termed as reversible inhibitors. While this misnomer appears handy when dealing with the toxicological consequences, one should be aware that the inhibition reaction is in fact irreversible, because the leaving group of the carbamate is no longer bound to the liberated carbamic acid and the parent carbamate is thus used up in the inhibition/reactivation cycle. With organophosphorus compounds spontaneous reactivation of the acylated cholinesterases is slow and competes with another true suicidal reaction. A tryptophane residue of the hydrophobic choline binding subsite near the catalytic triade accomplishes another ester hydrolysis and gives rise to liberation of an alcohol, leaving behind a negatively charged phosphate residue bound to the catalytic serine. This conjugate can neither hydrolyze spontaneously nor be reactivated by nucleophilic oximes, partly because the negatively charged phosphate is no longer electrophilic. These various post-inhibitory events are decisive whether the blocked enzyme regenerates or must be substituted by de novo synthesis. While inhibition of AChE (EC 3.1.1.7) plausibly explains the toxic signs and symptoms, inhibition of other B-esterases, such as butyrylcholinesterase (BChE; EC 3.1.1.8) or carboxylesterase (EC 3.1.1.1) is apparently not linked with physiological disturbances. While BChE with its low substrate specificity is involved in ester hydrolysis of a variety of substrates and drugs (succinyldicholine, mivacurium, cocaine, bambuterol), its natural absence in people bearing a silent gene is not associated with any illness under normal conditions. Recently, two knock-out mice strains were created in the laboratory of O. Lockridge: a homozygous AChE-deficient and a homozygous BChE-deficient strain. While BChE-deficient animals showed no abnormal behavior, AChE-deficient animals exhibited muscular weakness, did not eat solid food, did not engage in mating behavior, and never became pregnant. Yet, they had a surprisingly long life-span of 120 days on average. Most surprisingly, the AChE–/–mice were extremely sensitive towards organophosphorus compounds. This behavior pointed to a rescue role of BChE in AChE-deficient mice. In fact, selective inhibition of BChE was detrimental to these AChE-deficient mice, but hardly toxic to AChE+/+ animals (3). The BChE–/– mice, however, were extremely sensitive towards selective AChE-inhibitors, such as huperzine A and donepezil. These novel findings foster the role of the increase in endogenous acetylcholine as the ultimate toxic mechanism of anticholinesterase agents and they extend our view that BChE plays an auxiliary role in acetylcholine hydrolysis, which may be luxurious under normal AChE function, but life-saving when AChE is selectively inhibited (Duysen *et al.*, 2007). Despite these new insights, other actions of organophosphorus compounds cannot be ruled out: there are much more macromolecules which are phosphylated as shown by tandem mass spectrometry, and it appears conceivable that phosphylation of signal peptides, which could show selective sensitivity to a particular organophosphorus compound, could well contribute to acute and chronic toxicity. Finally, other serine hydrolases such as neuropathy target esterase or enzymes, which may process signalling peptides from pre-proteins, are target candidates of anticholinesterase agents. Hence, refinement of our view on toxic mechanisms that interfere with enzyme function and clinical effects remains an exciting task for the future. *References:* 1. Marchot P, Khelif A, Ji YH, et al. Binding of 125I-fasciculin to rat brain acetylcholinesterase. The complex still binds diisopropyl fluorophosphate. J Biol Chem 1993; 268:12458–67. 2. Eckert S, Eyer P, Mückter H, et al. Kinetic analysis of the protection afforded by reversible inhibitors against irreversible inhibition of acetylcholinesterase by highly toxic organophosphorus compounds. Biochem Pharmacol 2006; 72:344–357. 3. Lockridge O, Duysen EG, Voelker T, et al. Life without acetylcholinesterase: the implications of cholinesterase inhibitor toxicity in AChE-knockout mice. Environ Toxicol Pharmacol 2005; 19:463–469. 4. 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5. The Role of Cell Transport Systems in Medicating the Toxic Effects of Drugs and Chemicals. Mechanisms of Paraquat Poisoning

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Because the lung is responsible for all gaseous exchange necessary for oxidative metabolism, it is inevitably exposed to toxic gases, vapors, and particles (small enough to be present in the atmosphere). Apart from exposure through inhalation, the lung is also exposed to compounds or drugs that have been absorbed into the blood stream or in the form of metabolites formed either in the lung or extra pulmonary tissue. In order to carry out its respiratory function, the lung requires numerous cell types. More than 40 have been identified and are necessary to provide the diverse architecture associated with cartilage and smooth muscle, connective tissue, submucosal glands, vascular system, and epitheliae lining of the airways and alveoli. Paraquat (1,1-dimethyl, 4,4-bipyridinium) is a contact herbicide that can cause death from pulmonary damage when it is ingested. The discovery that paraquat is specifically accumulated into the lung compared with other tissues provides a plausible explanation for its selective toxicity. The uptake system for paraquat is energy dependent and obeys saturation kinetics. As part of an investigation to explain why paraquat is accumulated, it has been shown that various endogenous substrates are accumulated into the lung by the same uptake process. Among these are a series of diamines and polyamines that share specific structural similarities to paraquat. This uptake process for paraquat and polyamines is specifically located in the alveolar type I and type II cells, and clara cells in the respiratory airways. With the development of our understanding of the structural requirements for chemicals to be accumulated by this process, it is possible to predict which endogenous and exogenous chemicals and drugs will be taken up by the lung. For example, the diamino sulphate cystamine is accumulated by the polyamine uptake system and then metabolically converted in the lung to taurine. This led to the identification of the beta-amino acid uptake system in the lung, which is energy dependent and obeys saturation kinetics, analogous to that found in the liver. The purpose of the system in the lung has not yet been established, but is possibly related to the requirement of the lung to respond to the formation of hypohalide acid (HOCL) during inflammatory episodes. The lung has particularly high concentrations of taurine, which will interact with HOCL and in the process reduce its toxicity to the epithelium. In the wider perspective the polyamine uptake system has been found to be present in a number of other cell types, notably some tumour cells. With the knowledge of the structural requirements for this system, it is possible to design chemicals that will be specifically concentrated in cells that possess this uptake system. Also, drugs with appropriate molecular features, not targeted to the lung, but present in the circulation system, will be taken up into the lung by what appears to be a promiscuous accumulation system.

6. Metabolic Acidosis

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Acid-base disorders are a common feature of acute poisoning. Metabolic acidosis may result from exogenous administered acids, metabolic production of organic acids, disruption of mitochondrial function, or inadequate tissue delivery of oxygen because of respiratory or circulatory insufficiency. In addition to these primary causes of metabolic acidosis, secondary sources of metabolic acidosis are also commonly encountered in a critically ill patient. In contrast to other pathological conditions like chronic kidney disease, metabolic acidosis after poisoning is

usually of abrupt onset and short duration. Acid-base balance is precisely regulated by two organs, the kidneys and lungs, while intra- and extracellular buffer systems prevent changes in pH. At the clinical level, acid-base physiology is really the study of blood pH. While intracellular acid-base balance is certainly of great interest, it varies widely between cell types and cannot be measured clinically. For the clinician, it is only possible to evaluate acid-base balance in the blood. The determinants of blood pH are the physical chemical determinants of hydrogen ion concentration in aqueous solutions where water dissociation (into H^+ and OH^-) is a critical factor. H^+ concentration is determined by three variables: CO_2, the weak acids and the strong ions. The Henderson-Hasselbach equation defines equilibrium for only one of these variables, CO_2. The system as a whole can be accurately described using this single equation, but the determinants of blood pH include all three variables. Therefore, pH (really H^+ concentration) is not an independent variable and neither is bicarbonate ion. It is impossible to separate the effects of pH *per se* from the effects of the independent variables controlling it. Changes in blood pH due to alterations in CO_2 versus those secondary to metabolic causes often appear to produce very different clinical effects. The presence of powerful homeostasic systems emphasize that maintaining a constant H^+ concentration must be considered critical for the organism. Changes in blood pH could modify critical metabolic pathways. In particular, enzymatic reactions are usually characterized by a pH optimum value. Also, the tertiary structure of proteins will change when pH rises or falls, with possible structural changes and modifications of the function of the protein. Finally, changes in pH could also induce variations in hormones and their metabolic activities; this is probably the case with chronic metabolic acidosis. Another question is to know whether acidemia itself causes clinical effects, or whether these effects are caused by variables producing the acidosis. There are differences in clinical effects between respiratory and metabolic acidosis which are probably due to the differences in diffusibility of CO_2 compared to strong ions that must be actively transported or move through channels. When acidosis is exogenous or regional (increased lactate production after exercise), its effects will not be rapidly or evenly distributed across all cells in the body. Most clinical effects associated with acidosis, and particularly metabolic acidosis, are undesirable. For example, lowering the arterial pH has been shown to cause a decrease in cardiac contractility. This has been demonstrated in isolated and whole heart preparations. However, *in vivo*, this effect may be balanced by the concomitant stimulation of the sympathetic-adrenal axis. It is also said that the responsiveness of adrenergic receptors to circulating catecholamines is decreased. Different effects on left ventricular function have been described according to the type of extracellular acidosis (inorganic, respiratory, or lactic). It is not surprising that the treatment of metabolic acidosis is a matter of debate. In acute poisoning, the sources of metabolic acidosis are either exogenous (ingestion of mineral acids) or endogenous (metabolic production of organic acids). In a general setting, the correction of abnormal pH (excess H^+) via administration of bicarbonate has been questioned. There is a fear that the administration of bicarbonate may actually worsen intracellular acidosis. However, all the situations with metabolic acidosis are not strictly comparable. For example, in methanol poisoning there is an accumulation of an endogenous acid produced by hepatic metabolism. It appears logical not only to block the biotransformation of methanol, but also to remove by hemodialysis the excess of acids and strong ions. Buffering with sodium bicarbonate could also reduce visual toxicity by impairing the entrance of formic acid into the visual pathway. There are other toxicological indications for sodium bicarbonate (cardiac dysrhythmias in tricyclic antidepressants poisoning). In conclusion, metabolic acidosis is not rare after acute poisoning. The pathophysiology may be complex and acidosis may be related to exogenous or endogenous sources. Bicarbonate therapy remains useful in selected cases.

7. When the Simple Becomes Complex – Problems in Postmortem Toxicology

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Introduction: Pediatricians go to great lengths to point out that, for medical purposes, children cannot just be considered small adults; they operate by different rules. Unlike pediatricians, pathologists, and far too many clinical and forensic toxicologists, still don't seem to understand that cadavers and living humans also operate by different rules. This confusion may explain why many believe that the rules of Therapeutic Drug Monitoring can be applied after death. The purpose of this article is to explain some of the reasons why they cannot. When investigating a death, far too many toxicologists make the same three mistaken assumptions: 1) that postmortem blood concentrations accurately reflect drug concentrations at the time of death, 2) that a very high drug concentration can only be the result of taking too much drug, and 3) that an autopsy can be considered "negative" even though histological examination and genetic testing of the heart and liver are omitted. *Postmortem Redistribution:* The reddish fluid collected at autopsy is not a living tissue. It is an inhomogeneous mixture of proteins, ions, etc., in a soupy liquid. If there has been exposure to drugs or other poisons during life, there may be redistribution from tissues or from the gastrointestinal tract into blood after death. Do drug concentrations measured in liquid aspirated from the liver accurately reflect the plasma concentration at the time of death? The process of drug redistribution virtually guarantees that concentrations measured in blood taken from the left ventricle, which is supplied by thin walled pulmonary vessels, may be many times higher than in samples drawn from the right ventricle; many drugs diffuse from the lung back into the heart. The rate of diffusion depends on the drug, the storage temperature, the position of the cadaver, the number of hours elapsed from death till tissue collection, site of collection, and size of the sample collected. These variables are usually impossible to measure. When combined with the problem of tolerance, which cannot be measured after death, the interpretation of a single post-mortem measurement is often difficult, if not impossible. These realities have several consequences. For one, it is often impossible to back-calculate how much drug was taken, or even estimate body burden, from post-mortem blood measurements. Every drug's volume of distribution at steady-state (Vss) is different in every person. More obviously, Vss has never been measured in a cadaver, nor will it ever be, because it was designed for work in the living. Parent drug:metabolite ratios measured in blood cannot be used to estimate time of ingestion, because metabolites are often more polar (with perhaps a lower Vss) than the parent compound (1). Morphine, for example, has a Vss of 3–4 L/kg, while the value for the morphine glucuronides is closer to 0.8 L/kg. As a consequence, at steady state parent drug is distributed mainly to tissue, but most of the metabolite remains in the plasma, and even a minimal redistribution of drug after death can completely alter the drug:metabolite ratio. As a further example, the Vss of cocaine is 2–3 L/kg, but the Vss of benzoylecgonine is barely 1 L/kg. Thus, it is not possible to add together blood cocaine and benzoylecgonine concentrations and determine how much drug was taken or, knowing their plasma half-lives, estimate time of ingestion, because there are too many uncertainties. *Pharmacogenetics:* Then there is the problem of genetic heterogeneity. Recently, a 62-year-old male with a history of chemotherapy taking valproate for a seizure disorder, was admitted to hospital with bilateral yeast pneumonia and was treated with ceftriaxone, clarithromycin, and voriconazole (2). He was also given codeine. He became comatose, and testing showed high plasma concentrations of codeine, morphine, and morphine glucuronides. Genotyping showed multiple duplications of CYP2D6. Normally CYP2D6 converts 10 % of codeine to morphine, but additional morphine seems to have been produced. In addition, CYP3A4, the enzyme responsible for codeine N-demethylation, may have been inhibited by other medication. The data suggested that too much morphine had been produced from codeine, and moreover the patient couldn't adequately excrete the morphine metabolites because of renal failure. What does it mean when a report states that a particular drug was detected in the face of an otherwise unremarkable autopsy? It is commonly accepted (amongst pathologists at least) that a heart can't be diagnosed as normal just by looking at it; inspection under the microscope is required. But now even this is known to be false (3). Recently, 24 patients with myocardial infarction but negative angiograms underwent myocardial biopsy at the time of cathertization. The specimen was divided in half – with one half sent for routine histology, and one half for PCR. Only one of the biopsies actually met the Dallas criteria for diagnosis of myocarditis, but the presence of virus (usually Parvo-19) was demonstrated with PCR in all but one. *Conclusions:* It is clear that the mere detection of a drug in a post-mortem sample does not prove causation, especially if the autopsy is incomplete. And an autopsy without DNA testing may, in fact, be incomplete. DNA arrays for P450 analysis are already available, and work well in the postmortem setting. Similar devices for the diagnosis of heart disease are not quite so advanced, but should be available shortly. This poses a practical problem. Who is going to pay for this additional testing? The dead don't vote, and the public doesn't appreciate the importance of the tests. And what are we to say in court when we well know that we have not adequately ruled out other possibilities that could account for our findings? *References:* 1. Drummer O, Forrest ARW, Goldberger B, Karch SB. 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8. The Forensic Toxicology of Drugs that affect Performance and Behavior

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Drugs can affect the performance or behavior of criminals, victims of crime, and injured parties in civil cases. In this review, I consider briefly how drugs have effects on performance and behavior and those circumstances that are most important in criminal cases. A wide variety of chemicals can affect behavior, but three main groups merit discussion: drugs affecting neurotransmission; drugs affecting other endogenous chemicals; and other exogenous drugs. Frontal cortical pathways moderate aggression, prevent antisocial behavior, and reduce destructive urges. Gamma-amino-butyric acid (GABA) is the major inhibitory neurotransmitter. Ethanol and benzodiazepines act as GABA agonists. Low doses increase aggression, presumably because subtle pathways controlling social function are inhibited. As doses increase, GABA agonists affect thought processes, motor co-ordination, wakefulness, consciousness, and brainstem activity. They also cause amnesia, and this can be relevant both for the criminal and the victim. Dopaminergic neurons reinforce pleasure-seeking behavior, notably drug-taking, and addictive drugs of abuse share the common property of stimulating cortical dopaminergic neurons. Classical addictive drugs and other drugs of abuse – a group that includes opioids, ethanol, amphetamines, cocaine, lysergide, cannabis, and gammahydroxybutyrate, for example – all activate specific dopaminergic pathways by direct excitation, disinhibition, or blockade of dopamine reuptake. The behavioral consequences of addiction are drug-seeking and drug-taking in disregard of negative consequences, and these lead directly to crime. The high cost of drugs, and their high value to dealers, lead to crime indirectly. Serotoninergic neurons inhibit aggressive motor and sexual behavior, and experimental lesions of these neurons in animals result in unbridled aggression, failure to respond to punishment, and sexual disinhibition. The serotoninergic system also moderates appetite, and increases in serotonin improve depression. Amphetamines are serotoninergic, and this accounts for appetite suppression, hallucination, and psychosis. Other serotoninergic agents such as lysergide and mescaline, are also hallucinogenic. Endogenous chemicals other than neurotransmitters include testosterone and related sex hormones, that lead to aggression; and insulin that can cause behavioral disturbance by reducing brain glucose and so causing neuroglycopenia. Most exogenous drugs that impair behavior or performance – benzodiazepines, barbiturates, phenothiazines, opioids, methyldopa – act via neurotransmitters. Other exogenous drugs whose actions are unknown, can be invoked as causes of criminal behavior, or, more commonly, as causes of impaired performance. Potential examples include ketotifen, stavudine, and anastrazole, which can cause drowsiness; tibolone and infliximab, suspected of causing amnesia; and montelukast, pizotifen, and ribavirin, which are associated with aggression. Dopamine agonists such as ropinerole and pramipexole can cause sudden onset of sleep. Defects in performance, for example, in driving a motor car, can be the result of incoordination, visual disturbance, and inattention, and these too may be drug-induced. There is a large criminal workload associated with driving under the influence of ethanol, drugs of abuse, and prescribed drugs. These cases can raise difficult pharmacokinetic and pharmacodynamic issues. The criminal can sometimes argue that, but for prescribed drugs, he or she would not have committed a crime. In English law, deliberate self-intoxication is not a defence, but the occurrence of an unpredictable adverse drug effect might be. For example, a man who became aggressive and set fire to a building was charged with arson. He had taken diazepam tablets "to calm his nerves," believing they would make him sleepy and not knowing that they might cause paradoxical aggression. His conviction was quashed on appeal. By contrast, a man who killed his lover because he thought, as a result of taking lysergide, that she was a serpent at the center of the earth, was convicted of manslaughter on the grounds that this was the result of voluntary intoxication. Criminals may also argue that they were insane in the sense that they could not understand the nature of the act that they committed. This defence is only acceptable if insanity is the consequence of a physical disorder. A woman who drank nearly 700 ml of vodka then killed her daughter, was convicted of murder because alcoholism was not brain damage. Occasionally, criminals take refuge in amnesia induced by benzodiazepines to

deny (truthfully) that they have any recollection of crimes they have in fact committed. This is unlikely to help them if they are caught on closed-circuit television or leave fingerprints at the scene of a crime. After a crime, drugs can play a role in interrogation and confession. The use of "truth drugs" such as amilobarbital and thiopentone for narcoanalysis, an extension of the idea that *in vino veritas*, has long been discredited: some subjects are able to maintain a false story even under the influence of the drug, while others make false confessions. By the same token, confessions made under the influence of psychoactive drugs are suspect. The Cameron case, where a man confessed to murder under the influence of ethanol, and subsequently of chlorpromazine, emphasized the problem. A victim or other witness to a crime who is under the influence of drugs may be unable to perceive or recollect the events, or may alternatively fabricate them. Women can, under the influence of benzodiazepines or nitrous oxide, misinterpret medical or dental intervention as sexual assault, and this has led to criminal prosecutions. By contrast, drugs that impair resistance or consciousness can be used by rapists and abductors to further their criminal ends. Flunitrazepam and gamma-hydroxy butyrate have become used increasingly for date rape; ethanol remains popular; and there are still occasional victims of such agents as chloroform. In conclusion, agents that affect behavior are of great forensic importance, as they are relevant both to the criminal and the victim. Agents that affect performance are most often encountered in criminal road traffic cases. *Further Reading:* Curran WJ. Medical management and confession to crimes. New England Journal of Medicine 1969; 280:1008. Dession GH, Freedman LZ, Donnelly RC, Redlich FC. Drug-induced revelation and criminal investigation. The Yale Law Journal 1953; 62:315–347. Ferner RE. Forensic pharmacology. 1996. Lüscher C, Ungless MA. The Mechanistic classification of addictive drugs. PLoS Medicine, at www.plosmedicine.org. 2006; 3:11:e437. Schlapp MG, Smith EH. The new criminology; a consideration of the chemical causation of abnormal behavior. 1928.

9. Poisoning in Childhood

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Introduction: The poisons encountered and analytical methods available for use in clinical and in forensic toxicology are often the same. However, the method of presentation and samples available for analysis, and the circumstances in which such samples are collected and analysed, are sometimes vastly different. Nowhere is this more apparent as when investigating poisoning in childhood. The aim of the clinical toxicologist and the clinical scientist is to help with diagnosis and treatment, and in some cases prevention, of poisoning or other injury. Speed of response is often important, as is a broad understanding of all aspects of therapeutics, and of analytical chemistry and toxicology. *Background:* There are legal implications to all incidents of confirmed poisoning in childhood because either a parent or a legal guardian has responsibility for the welfare of the child, or another person such as a healthcare worker or an agency such as a local authority has assumed that responsibility. This being said, there are practical limits to the extent to which legal guardians can be held to account, for example as regards substance abuse in older children. Ironically, there are also instances where a guardian or other person will make repeated claims that a child is being or has been poisoned in the absence of any evidence that this is indeed the case, sometimes causing much distress to the child or the parents in the process. Evidence of exposure does not always equate to toxicity, a stricture that is as true when assessing exposure to environmental or other contaminants as when assessing the possible contribution of a prescribed drug when a child has died. As in any case of suspected poisoning, analytical results must always be interpreted in the context of the full clinical picture. *Fatal Poisoning:* Regarding fatal poisoning, information as to trends can often be gained from national mortality data. In Flanagan et al., in children aged < 10 years the number of deaths certified as due to poisoning fell from 165 (20.6 per million children) in 1968 to 30 (4.6 per million) in 2000, a decrease of approximately 80% (1). Accidental deaths declined from 151 in 1968 to 23 in 2000, but homicides and open verdicts varied from 5–20 per year, with no clear trend. Currently, a verdict of homicide or an open verdict is recorded by the coroner or by a higher court in some 50% of poisoning deaths in England & Wales. Opioids have superseded tricyclic antidepressants as the most common agents encountered in fatal poisoning with drugs in children, a reflection on the success of poisoning prevention campaigns on the one hand, and on the increased prevalence of illicit drug use on the other. *Malicious Poisoning:* The deliberate, covert, chronic poisoning of a child by a parent or guardian is almost by definition extremely difficult to diagnose, can continue even in a supposed place of safety such as a hospital, and in extreme cases only comes to light after the death of a sibling that was not thought suspicious (2,3). If poisoning is suspected, the traditional poisons information framework (accessed by poison) may be of limited use, the diagnostic skills of the experienced clinician or clinical scientist being in turn tested to the full. The hospital laboratory drug screen, often immunoassay-based, may also be unhelpful even if a sample of appropriate size collected at an appropriate time is available. The forensic laboratory, whilst perhaps possessing the necessary equipment and expertise to help in such cases, may be ruled out of the equation because of procedural and cost issues. So the analytical response may also be wanting. Even if a drug or other poison is detected, interpretation of the finding may not be straightforward if the compound may have been given legitimately either at home, or in hospital. Here knowledge of the epidemiology of poisoning in childhood can be helpful - with paracetamol (acetaminophen), for example, serious accidental self-poisoning is almost unknown in young children. *Accidental Poisoning:* This includes not only the traditional self-poisoning of childhood, but also iatrogenic and environmental poisoning. Analytical confirmation of the diagnosis may be required to give weight if a care or other court order is contemplated, but again an appropriate sample or choice of suitable analytical facilities may be lacking. Iatrogenic poisoning can of course sometimes be difficult to diagnose, and may not be confined to individuals (4). *Conclusions:* The resources devoted to the prevention of poisoning in the home in Western countries, including improved fire safety precautions, have paid dividends in that morbidity and mortality from accidental poisoning in childhood is now much reduced. A range of measures, including increased availability and use of therapeutic drug monitoring (TDM) services, have enhanced the safety of drug therapy in children. Vigilance and of course resources still need to be maintained, however, to deal with mental health issues. These include domestic situations where illicit drugs are to be found and deliberate poisoning, a category that includes deliberate self-poisoning and substance abuse in older children. The analytical resources that may be required do not always fit well with a cost/test model – how does one put a value on the life of a child? *References:* 1. Flanagan RJ, Rooney C, Griffiths C. Fatal poisoning in childhood, England & Wales 1968–2000. Forensic Sci Int 2005; 148:121–9. 2. McClure RJ, Davis PM, Meadow SR, Sibert JR. Epidemiology of Munchausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation. Arch Dis Child 1996; 75:57–61. 3. Bartsch C, Risse M, Schutz H, Weigand N, Weiler G. Munchausen syndrome by proxy (MSBP): an extreme form of child abuse with a special forensic challenge. Forensic Sci Int 2003; 137:147–51. 4. Fell JM, Reynolds AP, Meadows N, Khan K, Long SG, Quaghebeur G, Taylor WJ, Miller PJ. Manganese toxicity in children receiving long-term parenteral nutrition. Lancet 1996; 347:1218–21.

10. Drugs and Driving

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Introduction: The question as to the concentration of a drug and/or metabolite(s) in blood above which driving ability can be said to be impaired has been studied extensively. However, interpretation of the results obtained is often not straightforward. In many studies, the data are highly selected since they originate from blood samples seized or otherwise obtained by police after an accident or other incident. A true control group is thus lacking. Moreover, it is not possible to select subjects as regards either their general health, or other parameters such as, for example, recent food ingestion, fatigue, time of drug use, and nature and amount(s) of drug(s) ingested. This is in contrast to the situation with alcohol where data from drivers involved in accidents has played a large part in establishing limits taken to indicate impairment. Even with alcohol, however, application of the law may acknowledge different grades of impairment. In Germany, for example, while the blood alcohol concentration above which it is illegal to drive a motor vehicle is 0.50 g/kg, a limit of 1.10 g/kg for aggravated driving is also acknowledged. *Current Situation:* What, then, is the current situation for some common illicit drugs? A) Cannabis. Some studies have suggested that there is a positive relationship between accident risk and blood tetrahydrocannabinol (THC) concentrations ≥ 5 ng/mL (1). Recent research from Germany, however, has shown that the risk actually increases when blood THC has decreased to concentrations even approaching the limit of accurate measurement (1 ng/mL) (2,3). B) Heroin. Impairment has been demonstrated across the range of blood morphine concentrations encountered in heroin users, but there was no clear relationship between blood morphine concentration and driving ability. A distinctive feature here is the occurrence of withdrawal symptoms as the effect of the drug diminishes, withdrawal itself being associated with impairment (4,5). C) Amphetamines. Our own work as well as that of Jones (6), has not found any correlation between blood amphetamine concentration and driving impairment. The same applies for MDMA. D) Cocaine. The situation is similar to that with amphetamine. *Conclusion:* Use of illicit drugs by drivers is a fundamental problem for road safety. To conform with the data, jurisdictions should lower their requirements as to the degree of impairment that has to be demonstrated by psychomotor testing before ruling that an offence has been committed. *References:* 1. Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, Swann P. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004; 36:239–48. 2. Daldrup Th. Akute beeinträchtigung der fahrsicherheit durch cannabis aus toxikologischer sicht - Ein nationaler Zustandsbericht. Berichte der Bundesanstalt für Straßenwesen M171, Wirtschaftsverlag NW, Bremerhaven 2005:41–4. 3. Drasch G, von Meyer L, Roider G, Staack RF, Paul LD, Eisenmenger W. Accidents and genuine endangering of road traffic under the influence of cannabis. Blutalkohol 2006; 43:441–50. 4. Bachs L, Høiseth G, Skurtveit S, Mørland J. Heroin-using drivers: importance of morphine and morphine-6-glucuronide on late clinical impairment. Eur J Clin Pharmacol 2006; 62:905–12. 5. Daldrup Th. Drugs in road traffic with special focus on heroin. (Available at www.uni-duesseldorf.de/daldrup) 2002. 6. Jones AW. Age- and sex-related differences in blood-amphetamine concentration in DUID suspects. Lack of association with clinical evidence of impairment. 44th scientific meeting of The International Association of Forensic Toxicologists (TIAFT), Ljubljana, Slovenia August 26th - September 1st 2006.

11. Ethical and Legal Problems in Poison Information Centre Work

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Background: In the day-to-day work of poison information centres answering enquiries related to poisoning exposure calls that pose ethical and legal problems are not uncommon. Amid the often hectic pace of the call center work and demand for rapid response to the problems of the caller, the poison information staff has to be able to recognize and handle these demanding and potentially fateful calls properly. Education can help in preparing for such situations and sharing of experience with other centers could be useful. However, to discuss practical legal issues within an international audience is challenging due to differences in national laws. Ethical perceptions are also influenced by cultural backgrounds. To prepare the staff of the Nordic poison information centers to better handle ethical and legal problems, we arranged a course on the subject at the 2005 Annual Meeting of the Nordic Association of Poison Information Centres. *Methods:* The course was based on discussions of actual cases in groups. The participating centers were requested to send in advance cases representing problems relating to questions a) when is the PIC allowed or required to disclose information on individual call or calls received?, and b) when is the PIC allowed or required to make an intervention on the basis of call or calls received? *Results:* From the submitted cases, 26 were selected for the educational course. A physician-lawyer, who is an expert in medicolegal affairs and also has experience from working with a poison information center, gave a brief introductory lecture on the relevant legal framework. He remained available as a resource person during the course. The cases were discussed one by one in small groups of poison information staff from different countries and with different professional backgrounds. There was a summary discussion after each case. Selected examples of the cases used will be presented for discussion in the lecture. The cases displayed problems like disclosing information related to a previous call when contacted by the police, a parent, spouse or other close relative, a lawyer representing a client, a commercial company or media. Also, cases where the right or obligation for the person taking the call to make an intervention by contacting emergency services, a hospital, police, public health, or regulatory authorities, a company producing or distributing a product or media, were discussed. No formal evaluation of the course was made. *Conclusion:* Preparing the staff to properly handle acute ethical and legal problems in poison information work should be included in the continuous professional development plans. Group discussions based on actual cases provided in advance by participants is an educational format, which seemed to be well suited to facilitate exchange of views and experiences on questions significantly influenced by possible differences in local laws and ethical guidelines.

12. Harmonization of Categorization Systems for Agents: First Data from German Poisons Centers

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Objective: Categorization systems for agents (CSA) play a crucial role in Poisons Centers' (PC) daily work, particularly for the preparation of annual reports. The German research project "Toxikologischer Dokumentations- und Informationsverbund" (TDI) generated a harmonized CSA (1,2). As a final part of the project, a collection of all exposures of humans in 2005 categorized by the TDI-CSA was performed. *Aims of this Report:* 1. Description of the methods of the harmonization process. 2. Presentation of the first corporate data collection as well as the preliminary evaluation of the data pool. 3. Description of future steps of the harmonization process. *Methods:* 1. Evaluation of the situation in German PC before using the TDI-CSA. 2. Development of a common CSA, taking into account established systems (e.g., ATC-Code for drugs, COLIPA frame formulations for cosmetics, etc.), and extension with self created sectors (e.g., foods, drugs of abuse, etc.). 3. Test phase with integration and experimental use of the draft CSA in two PC (Erfurt, Mainz). 4. Distribution of the first official version of the TDI-CSA (3) in 9/2006 to all German PC. 5. Providing a form for data collection, to be filled out with selected data of all exposures of humans in 2005. The cases were sorted according to the first three levels of the TDI-CSA, age groups (Children (<18 years), adults and unknown), and the poisoning severity score by the regional PC, 9–11/2006. 6. Data pooling and first evaluation by an independent PC (Zurich) and returning the complete data set to the participating PC in 11/2006. 7. Common evaluation and quality control in 11/2006. *Results:* Originally in 10 PC, 7 different CSA were used in a variable manner. In 7 of 10 PC (Bonn, Erfurt, Freiburg, Goettingen, Homburg, Mainz, Munich), the new TDI-CSA could be implemented at least up to the first 3 levels, within 2 months. This hierarchically structured system covers 40 categories on the first three levels (e.g., plants, fungi, animals as a part of the group natural environment; foods and food additives, cosmetics, human drugs, pesticides, etc. as a part of the group products). With the 2005 data collection of all human exposure, 137,689 cases could be assembled from 7 of 10 PC, which represented 78% of all cases registered in German PC. There were 71,361 paediatric cases (52%) (range among PC 24–59%), 60,387 adult cases (44%) (range: 24–59 %), and 5,941 cases (4%) with unknown age (range: 1–13%). In 131,688 cases (95.6%), the agents could be unambiguously classified by the TDI-CSA. The three categories with most paediatric exposure are: human drugs 18,270 (25.3%), plants 14,520 (20.3%), and cleaning agents, detergents and care products 10,276 (14.4%). Most adult cases occurred with human drugs 34,989 (57.9%), cleaning agents, detergents and care products 4,423 (7.3%), and foods and food additives 3,644 (6.0%). In about 11,000 cases (8%), medical follow up information could be obtained within the daily routine of the PC. In these cases the final outcome and the maximum severity are known. In all other cases severity grading refers to the situation at the time of consultation. The distribution of severity grading is shown in Table 1. Considering the frequency of severe and fatal cases within one category, categories with the highest risk can be identified (see Table 2 for details (3)). *Limitations:* In about 5–10% of cases, data attribution to the TDI-CSA is currently not completely reliable, due to incompatibility of the systems, internal quality control arises. Currently the system is completely integrated until the deepest level, in only two PCs. Since follow-up is performed in only 8%, there is probably a bias towards lower severity grades. *Conclusion:* In 7 of 10 German PC, the first step to a harmonized CSA was successful. A procedure for a multi-center maintenance and update of the TDI-CSA has been established. A dataset with more then 137,000 exposures of humans is ready to be subjected to internal quality control measures. The results will lead to further development of the TDI-CSA. For the first time within the 40-year history of the German PC, common data of human exposure and poisonings in Germany are available for preliminary risk assessment and epidemiological analysis. *Future:* The complete integration of the TDI-CSA to all participating PC will approximately take another 5 years. A detailed evaluation of the data is planned for the next 6 months. Since the TDI project has been terminated the maintenance of the system will be ensured by a recently formed working group within the Society of Clinical Toxicology of German-speaking PC (4). The experience of harmonization as well as the TDI-CSA may serve as a basis for further harmonization on a European level. *References:* 1. Stürer A, et al. J Toxicol Clin Toxicol 2003; 41:498–499. 2. Stürer A, et al. Clin Toxicol 2006; 44:422–423. 3. Available at www.tdi-network.org 4. Available at www.klinitox.de

Table 1. Severity grading (n = 128,059)

Age/severity*	Asymptomatic	Minor	Moderate	Severe	Fatal	Unknown
Children	76.3%	18.2%	1.3%	0.2%	0.02%	4.0%
Adult	27.8%	49.5%	10.5%	3.6%	0.25%	8.4%

*Poisoning severity score.

Table 2. Categories with high risk

		Category	Total number of cases	Severe and fatal cases	%
Children	1.	Drugs of abuse	293	11	3.8%
	2.	Human drugs	18,051	90	0.5%
	3.	Foods, additives	2,541	11	0.4%
Adult	1.	Drugs of abuse	1,594	111	7.0%
	2.	Human drugs	34,989	1698	4.9%
	3.	Pesticides	1,347	65	4.8%

13. Notification of Product Information in 15 EU Countries and the Possibility of European Harmonization

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Objective: Article 17 of the European Directive No. 1999/45/EC states that each EU Member State must appoint an authority where information regarding dangerous preparations must be notified. The appointed authority is responsible for supplying information exclusively for medical purposes when curative and preventive measures need to be taken. The Directive does not define which information should be notified and how. In the Netherlands, the Poisons Information Centre (PIC) was appointed for this task. Article 17 of the Directive was implemented in national legislation, making use of a special form and notification of the exact composition and concentration mandatory. Ten years after implementation, the Dutch PIC still experiences problems with the notification of adequate product information. For suppliers it is most efficient to use the Material Safety Data Sheet (MSDS) for this purpose, a well established format designed to inform professional users. They are reluctant to use different formats because of the increased workload and also to provide more specific ingredient information. In the opinion of the Dutch PIC the MSDS doesn't provide sufficient detail to make a good risk assessment. Consequently, it is more difficult to inform healthcare personnel in cases of acute intoxications. As described in the European Directive No. 2001/88/EC, only dangerous substances above specified concentration thresholds have to be stated on the MSDS. The absence of guidelines for the required accuracy of the ingredient concentrations brings the use of wide concentration ranges into general practice. A renewed discussion with industry and trade organizations' representatives to improve notification was started. In line with this project, the Ministry of Health asked the Dutch PIC to conduct a survey in EU countries and make an overview of the various procedures and requirements. Before changing the Dutch situation only, it would be a good moment to evaluate whether there is basis for harmonization on a European level, especially with the forthcoming GHS and REACH legislation. *Methods:* For this survey, the initial 15 European Union Member States (the EU15) were included, being Belgium, France, Spain, Portugal, Italy, Austria, Germany, Ireland, Denmark, Sweden, Finland, Luxembourg, Greece, the United Kingdom, and The Netherlands. Norway was included to complete the group of Scandinavian countries with Product Registers. A questionnaire on three major topics, i.e., information on the competent authority, requirements on product composition and ingredient concentrations, and the notification procedures was sent to the competent authorities. When necessary, further questions were asked by e-mail, telephone, or through personal communication. Fourteen countries responded. *Results:* In six countries it is the PIC that directly receives the information on dangerous products (6/14). In the other countries, a governmental authority is appointed. Most of them (6/8) make the information available to the PIC(s). Just as in the Netherlands, in most countries (10/14) the competent authority requires more precise information on the composition of the product and concentration of its ingredients than present on a MSDS. Only four countries accept the MSDS for notification of product information. Variable additional requirements are set to improve the quality above the MSDS level. For the composition, the additional requirements fall roughly into two categories. In 6/10 countries, the exact composition is required, i.e., all dangerous as well as non-dangerous substances have to be notified. In 4/10 countries, additional thresholds for substances are used, e.g., for non-dangerous substances and/or for specified dangerous substances. For the concentration, 4/10 countries require the exact concentration of the ingredients, one country uses self-defined concentration ranges. In 5/10 countries it is a combination of these two, e.g., for some or all dangerous substances exact concentrations are required and for the other substances concentration ranges are allowed. In most of these countries (8/10), special forms are used for notification and in two countries the format is free as long as the requirements are met. Various routes of electronic notification and processing have been developed. *Discussion:* Because European Directive No. 1999/45/EC does not define which information should be notified and in what way, this has resulted in a huge variety of country specific requirements, formats and methods of notification. The lack of understanding by companies introducing products on the European market can be imagined. The willingness to provide adequate product information could be improved if the MSDS would serve as a starting point and European PICs and competent authorities reach consensus on which additional information is essential to perform their task. A next step in European harmonisation would be a common electronic format. Remarkably, guidelines on the requirements concerning the composition and concentration were already presented by an informal EAPCCT working group in 1989 and again published in the EAPCCT newsletter in 1996. It was proposed that all ingredients should be mentioned, the actual concentrations on (very) toxic and corrosive ingredients and specified concentration ranges for the others. When comparing these guidelines with the various requirements of the responding countries, this proposal still seems a reasonable compromise. It should be discussed if a revision is necessary to reach consensus between countries. Topics for special attention are the use of (low) concentration thresholds above which substances should be mentioned as an alternative for the exact composition and the use of exact concentrations and/or ranges. If there ever was a proper moment to start the discussion to reach harmonisation on product notification and to legally enforce the requirements on a European level, it is now. With REACH and GHS initiatives changing the relevant European legislation we should clearly present our needs for an adequate product notification for medical purposes.

14. Toxicovigilance of German Poisons Centers. An Epidemic of Serious Intoxications Caused by New Sealing Sprays Based on Nanotechnology

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Objective: Toxicovigilance represents the detection, validation, assessment, and adequate reaction to poisonings that could threaten the public. Due to their numerous contacts with both the public and health professionals, poisons control centers play a key role in the detection of newly emerging poisonings. In this case series, two new household products based on nanotechnology were withdrawn from the market 31 hours after their launch. *Methods:* On the basis of this incident the process of toxicovigilance with its consequences is described. *Results:* On March 27, 2006, a leading department-store chain in Germany introduced two new sealing sprays for glass and ceramics, and for hygienic facilities, respectively. GIZ-Nord Poisons Centre registered a poisoning case, a woman had developed severe dyspnea after having used one of the sprays in the proper way, at 1:30 p.m. that day. She was admitted to the hospital. GIZ-Nord

informed the manufacturer and received very incomplete product data. During the same day and the following night, four more intoxications were registered. German Poisons Centres' Toxicovigilance Network was activated. All poisons centers in Germany and the centers in Vienna, Zurich, and Strasbourg were contacted by "Giftforum" mailing list and telephone, where seven more intoxications had been registered. The next day hospitals reported four cases with pulmonary edema or toxic alveolitis. The GIZ-Nord Poisons Centre informed the competent ministries of the federal states, the Federal Institute for Risk Assessment (BfR), and the head office of the supermarket chain that had introduced these products. The ministries and GIZ-Nord Poisons Centre released press releases warning about the use of these sprays. On March 28 at 3:00 PM, these products were taken from all 2,500 shops in Germany. In summary, more than 120 intoxications occurred and one third of them had to be treated in hospitals, although these sprays were on sale for only 31 hours. *Conclusion:* According to the Chemical Act in Germany, poisons centers have a duty to report on important poisonings to the ministries in order to detect and prevent public poisoning threats. This task was carried out. This epidemic of poisonings with novel household products illustrates the fast and concerted action of poisons centers and authorities in charge. As a result of action a lot of additional intoxications could be prevented. This case demonstrates that the poisons centers' sentinel role in national as well as in international toxicovigilance systems is rising.

15. The Problematic Practice of Toxicology in an Emerging Country

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Objective: The practice of toxicology differs globally. This is due to various conditions by which patients are poisoned and managed clinically. The availability of and access to certain poisons varies. For instance, in Asia a large number of pesticide poisonings occur and there are great opportunities to undertake research on the clinical management of such intoxications (1). There are also opportunities to develop new antidotes (2). However, there are challenges within the context of clinical management of poisoned patients that are not within the purview of research. Diagnostic facilities to document and confirm the type and amount of toxicity can also vary depending on the area (urban or rural) of practice. The access to known and effective antidotes is very difficult. *Methods:* Consultation with fellow clinical toxicologists was undertaken on commonly encountered problems in practice. *Results:* Many of the issues in the medical practice of clinical toxicology can be both difficult and problematic in an emerging nation like the Philippines. *Human Resource:* The development of toxicological human resource is not fast enough for the country's needs. The specialty field of toxicology is not an attractive discipline from an economic perspective when compared to other medicine specialties. Due to the low priority given to toxicology and the lack of attractiveness of toxicology to young doctors, problems of toxicology are addressed in a reactive manner. *Supportive Facilities:* Analytical laboratory systems are poorly developed. Laboratories are spread in different parts of the city. There is low return of investment commercially in having a toxicology laboratory. There is lack of scientific and technical resources to deal with environmental contamination. *New Forms of Poisoning:* Capacity limitations within the drug regulatory agency have allowed the entry of smuggled pharmaceutical goods which are suspect counterfeit drugs that do not have pharmacological or toxicological effect during overdoses, yet there are no real-time ways to test this, leading to inefficient clinical management, longer hospital stays and inefficient use of resources. *Medico-legal Issues:* While it is necessary to assist in court activities, doctors in general and toxicologists in particular have a reluctance to be engaged as court expert witnesses. The reasons for these include lack of training, time invested to provide testimony is often wasted, and the expert witness is often treated like the accused in the witness box. *Misuse of Health Technology:* The growth of "detox" spas and youth rejuvenation clinics using chelating agents inappropriately is observed and these are not adequately regulated. An example is the use of chelating agents for autistic children secondary to immunization which has no scientific basis (3). *Epidemiology and Economics:* Lack of hospital resources and patients having to pay out of pocket for their medical consultations and hospitalizations also restricts the number of toxicology cases attended to and hence real statistics on poisoning cases are extremely inaccurate. Access to antidotes is low partly due to the small number of toxicology cases, resulting in the pharmaceutical industry's reluctance to invest in service item orphan drugs. Because of the meagre health budget, there is also low government priority to invest in medical conditions that compete with the public health needs of a resource-poor country. A foreseeable consequence of lack of funds is the demise of good research and publications, experience and human resource. Following detoxification, there are few substance abuse rehabilitation centers to refer patients to and these plus psychiatric counselling are of considerable expense. *Conclusion:* Incentive is a remote concept for the toxicology practitioner. Perhaps to be appreciated and to be relevant, the solutions to these problems might be a more targeted advocacy on the role of toxicology in our everyday lives. Toxicologists need to be communicators in their community and should not be afraid to provide their services when called to rise to the occasion. Engaging the science of toxicology with public health education at a much earlier age (while children are in school, perhaps) may pave a longer and sustainable way to promoting the general awareness of safety and the prevention of chemical harm. More global networking, twinning arrangements and sharing of resources can be a start. Clinical toxicology practice attempts to bridge the gap between science, engineering and public health in the Philippines. *References:* 1. Eddleston M. Pesticide poisoning in Asia. 5th Asia-Pacific Association of Medical Toxicology, (Abstract 2006) Sri Lanka. 2. Hewawasam RP, Jayatilaka KAPW, Pathirana C. A study on the antioxidative effect as the mechanism of hepatoprotection by vetiveria zizanioides in paracetamol-induced hepatotoxicity. 5th Asia-Pacific Association of Medical Toxicology, (Abstract 2006) Sri Lanka. 3. Fombonne E, Zakarian R, Bennett A, et al. 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16. Foodborne Botulism in Italy: The Pavia Poison Centre Cases in 2005

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Introduction: Botulism (Bo) can be a medical and public health emergency, and prompt diagnosis and early treatment are essential. In Italy, foodborne botulism (FBo) is the most frequent form; from 1984 to 2005, 267 cases of FBo (eleven of which fatal) have been laboratory confirmed at the National Reference Centre for Botulism (NRCB), Istituto Superiore di Sanità, Rome. *Objective:* To analyze all cases of Bo referred to Pavia Poison Control Centre (PCC). *Methods:* A retrospective analysis of all cases of Bo referred to PCC in the year 2005 was performed to evaluate (i) incidence of Bo, (ii) concordance between symptoms and typical syndrome, and (iii) indication, use, efficacy and safety of the antidote treatment. *Results:* In 37 cases, a possible contaminated food was ingested; in 12 of these (12/37; 32.5%), the clinical diagnosis of FBo was made by the toxicologist, and were included in this study. Three outbreaks were observed, and in 9 cases (9/12) the contaminated food was identified by epidemiological criteria and/or laboratory analysis. Time of hospital presentation and clinical course of poisoned patient (age: 9 months - 65 years) were different in all cases. Dry mouth, diplopia, bilateral ptosis, and dysarthria were the most common symptoms at presentation; seven cases (7/12) evolved with a typical descendent paralysis and needed prolonged mechanical ventilation; in nine cases (9/12) antidote (trivalent antitoxin ABE) was administered, without adverse reactions; and in six cases (6/12) laboratory analysis performed by NRCB confirmed clinical diagnosis. For the first time in Italy, two cases resulted of type F botulism and were unresponsive to antidotal treatment with trivalent antitoxin started before the identification of the toxin-type. Eleven cases (11/12) recovered completely in a variable time (1–8 months): one fatal case was reported. *Conclusion:* Bo is a rare disease in which early and accurate diagnosis is difficult and may require a toxicological consultation. The poison centre represents a clinical and epidemiological point of reference for Bo: the cases of this study represent the 80% of the all assessed Italian cases in 2005. So, the PCC support is essential for the diagnosis and the management of poisoned patients (e.g., specific laboratory tests, antidotal treatment), and in the identification and surveillance of possible outbreaks. To ameliorate the diagnosis of Bo a rapid test should be necessary. The optimal antitoxin dose needs to be established in the single case.

17. Post-mortem Toxicology of Drugs of Abuse

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Introduction: In most jurisdictions violent, sudden, or unexplained deaths are referred for investigation by police or by judicial authorities. In Luxembourg, toxicological analyses are requested in all autopsy cases. In more than 50% of the cases toxicology plays an important part. If a death certificate is amended it is most commonly the result of toxicological investigation. The breadth of cases the forensic toxicologist may be called upon to investigate includes not only deaths associated with the use of common drugs of abuse, but also hallucinogen production by prisoners by tampering with legal medicinal drugs; inadequate supervision of use of methadone in prison; drug trafficking by body packers; use of magic mushrooms; and possible use of date rape drugs (drug facilitated sexual assault, DFSA). *Challenges Facing Forensic Toxicology:* As in clinical analytical toxicology, expectations (detecting the undetectable), continue apace and are coupled with requirements for decreased turnaround time, improved accuracy and selectivity, reduced sample analysis time, and of course reduced cost/test. The development of chromatographic techniques linked with mass spectrometry (MS) can offer improved specificity and sensitivity. Moreover, recent innovations such as solid-phase microextraction (SPME) and ultra-performance liquid chromatography (UPLC) coupled to MS have in some cases improved analytical methodology still further with significant gains in resolution and a marked reduction in the overall analysis time. Nevertheless, to help the forensic toxicologist to decide the appropriate test(s) to perform in possible fatal poisoning cases, information on the circumstances of the suspected exposure such as any information on ante-mortem features, clinical history, etc. is vital, but all too often little information is transmitted other than screen for common drugs of abuse. Adequate sampling at autopsy is also of great importance (1–3), yet is again often neglected. Collection of specimens other than (ideally) peripheral blood should be undertaken, for example, in cases needed to confirm that a death was drug abuse-related, and to help elucidate route(s) of drug administration if this is important. Paraphernalia found at the scene may indicate which drugs to look for in biological samples. The interpretation of analytical toxicology results in samples obtained post-mortem is especially complex and is absolutely dependent on the context in which the analysis is undertaken (4). Amongst the factors to be considered are tolerance; the likelihood of post-mortem change in blood composition, possibly including diffusion of unabsorbed drug from the gastrointestinal tract; *in vivo* and *in vitro* cocaine degradation, for example; artefacts introduced by putrefaction; and the possibilities of (i) genetic variations in cytochrome P450 isozyme, UDP-GT, and transport protein activities, and (ii) the occurrence of drug-drug interactions in life. Finally, more emphasis on chain-of-custody procedures is needed to ensure the integrity of results. When someone has died quantitative measurements in a particular fluid or tissue are only available at the time of necropsy. Thus, even the sparse pharmacokinetic data available as regards many illicit drugs are not easily applicable to dead people, especially when the likelihood of post-mortem change in blood composition is considered. A relatively recent innovation is hair testing, which can give semi-quantitative information on prior exposure the drugs and other poisons that is not available from other sources and can be especially useful in assessing tolerance. Enantioselective separations of amphetamine-type stimulants and methadone have also been developed to allow proper interpretation of analytical results. *Conclusion:* Modern post-mortem forensic toxicology of drugs of abuse is characterized by complex scientific investigation including the use of expensive and technically complex analytical equipment. Assessment of exposure is made by careful study of pharmacodynamic, pharmacokinetic, and pharmacogenetic data. In spite of all this apparent progress, interpretation of results to elucidate the cause of an individual death often remains a difficult task. In some cases comparative information from casework data may be all that is available to aid interpretation, thus emphasizing the need to share knowledge by publishing novel case reports of possible forensic value. The forensic toxicologist can only operate effectively as part of a team in partnership with law enforcement officials and forensic pathologists on the one hand, and with the wider toxicological community on the other. *References:* 1. Tracqui A, Ludes B. De l'autopsie au prélèvement. In: Kintz P, ed. Toxicologie et pharmacologie médicolégales. Paris: Elsevier, 1998:15–26. 2. Skopp G. Preanalytical aspects in post-mortem toxicology. Forensic Sci Int 2004; 142:75–100. 3. Flanagan RJ, Connally G, Evans JM. Analytical toxicology: guidelines for sample collection post mortem. Toxicol Rev 2005; 24:63–71. 4. Flanagan RJ, Conally G, Interpretation of analytical toxicology results in life and at postmortem. Toxicol Rev 2005; 24:51–62.

18. Generation and use of Post-mortem Toxicology Data

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Introduction: The results of a single forensic toxicological investigation are normally used for the case in question, and after due process the case and file are closed. With time, however, single cases form a greater entity that can provide information that goes far beyond the original purpose of the basic investigation. This information is both useful and valuable to society, and is often otherwise difficult or impossible to obtain (1). *Background:* If the results of forensic case work are to be used reliably for epidemiological purposes certain requirements must be fulfilled. First of all, the size and structure of the population studied must be known. The analytical practices of the laboratory, such as the scope and sensitivity of drug screening procedures and the care given to the interpretation of the analytical results (2,3), should also be known and should remain stable over time. If several laboratories are involved in one area or country the detection limits, analytical principles, and scope of these laboratories should be compatible and known. Of course epidemiological research is much easier if the data are computerized and laboratories have information management systems. In prospective studies the questions and parameters to be studied can be set beforehand, but in retrospective studies the questions must fit with the existing data. *Fatal Poisoning:* In most cases epidemiological reports from toxicology laboratories or from national databases give the number of fatal poisonings caused by a single drug or category of drugs in a year, and in the best cases the figures are monitored annually to reveal trends (see http://www.cdc.gov/nchs/about/otheract/ice/projects.htm#Poisoning). However, this kind of examination does not allow true comparison of the toxicity in overdose of different drugs or other drug safety considerations since the degree of consumption or the route of administration, for example, is not taken into consideration. A much more informative picture of fatal poisoning may be obtained if it is possible to relate fatalities to the overall consumption of a particular drug. For drugs that may be purchased over-the-counter and illicit drugs this is of course largely an unknown quantity, and for certain prescribed drugs such as methadone, other considerations such as subject tolerance, diversion of supply, or uncertainties as to mode of administration may be more important in determining outcome than quantity prescribed. *Fatal Toxicity:* There are several ways that can be used to evaluate consumption of prescribed drugs. In the best case the number of prescriptions is known and it is possible to calculate a fatal toxicity index, where the number of deaths associated with a drug is divided by the number of prescriptions. These indexes allow drugs to be compared and ranked. This in turn can indicate if one drug differs from other drugs in the same category, information which can indicate abuse potential or some other abnormality. However, the number of prescriptions is not always available, and in these cases consumption can be estimated using either sales in kilograms, or using the concept of defined daily doses (DDD) per 1000 population per day. All these three methods have been used to rank and compare antidepressants in terms of their incidence in post-mortem toxicology reports, and all three rank these drugs in a similar order (4–6). The biggest application in relating fatal poisoning to consumption concerns not only antidepressants, but also antipsychotics (1,7). Within both categories individual drugs can show vastly different risks: in Finland, for example, the antipsychotics melperone and levomepromazine are much more often associated with fatal poisoning than newer drugs like olanzapine. Likewise for antidepressants, tricyclics such as trimipramine, doxepin, and amitriptyline carry a bigger risk in overdose than the newer selective serotonin reuptake inhibitors (SSRIs), for example citalopram and fluoxetine. In addition to intrinsic toxicity, this kind of examination can give other information. In Finland, zopiclone and temazepam are both classified as hypnotics and, although they are not related chemically, they share a common receptor and their toxicity indexes are of the same order of magnitude. However, with oxazepam, which is chemically and pharmacologically closely related to temazepam, but is classified as an anxiolytic and not a hypnotic, the risk is much lower, suggesting use in a different population. *Conclusion:* The primary role of the forensic toxicological examination when someone has died is to help establish the cause of death. However, by careful, systematic examination of the data produced, invaluable information can be obtained to help in the evaluation not only of trends in fatal poisoning with illicit and over-the-counter drugs, but also of the relative safety in overdose of certain prescribed drugs. *References:* 1. Lahti RA. From findings to statistics: an assessment of Finnish medical cause-of-death information in relation to underlying-cause coding. Thesis, University of Helsinki 2005. ISBN 952-10-2754-1 (pdf). 2. Flanagan RJ, Connally G. Interpretation of analytical toxicology results in life and at post mortem. Toxicol Rev 2005; 24:51–62. 3. Koski A. 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19. Pharmacological and Forensic Toxicological aspects of Classical and New Designer Drugs

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Introduction: Designer drugs based on amfetamine such as MDMA, MDEA, MDA, DOB, MTA, and TMA-2 are the most popular and most extensively studied group of rave drugs. They are used recreationally despite many studies showing toxic effects to the serotonin (5-HT) and/or dopamine (DA) systems at the doses taken. Neurotoxicity can lead to motor and cognitive impairment. Unfortunately, amongst users these drugs are still thought of as safe, even though, for example, there are many reports of deaths associated with these compounds (1). *New Developments:* In the last few years other types of designer drugs have entered the market, such as the benzyl- or phenyl-piperazine analogues (BZP, MDBP, mCPP, TFMPP, MeOPP), the pyrrolidinophenone-type (PPP, MOPPP, MDPPP, MPPP, MPHP, MPBP), the phenethylamine-type (2C-T-2, 2C-T-7, 2C-B, 2C-I, 2D-D, 2C-E), and the phencyclidine-type (PCPr, PCMPA, PCMEA, PCEEA, PCEPA). All these drugs produce feelings of euphoria, disinhibition, increased energy, and a desire to socialize. However, a range of adverse effects have been associated with the recreational use of these classes of drugs in humans, including serotonin syndrome, hepatotoxicity, neurotoxicity, and psychopathology, all of which may be life-threatening. There is also the risk of acute, overdose toxicity, in children in the homes of users for example, and as a result of dose-escalation during normal use. In many cases metabolites are thought to contribute at least in part to the toxic effects observed. Therefore, knowledge of the metabolism of these compounds is a prerequisite for toxicological risk assessment (2,3). Some principal metabolic pathways involving cytochrome P450 (CYP) or monoamine oxidase (MAO) isoenzymes have been well described, whilst with some compounds the metabolic pathways are still under investigation. On the other hand, the toxic effects of some compounds, most obviously MDMA, seem in many cases not to be clearly related to dose hence conventional toxicological assessment is clearly less useful, and of course formal post-marketing surveillance is not an option! *Forensic Implications:* All the drugs discussed are poisonous to varying degrees. Exposure may not only lead to clinically-apparent toxicity, but there are also issues as regards driving impairment, reduction in responsibility for a criminal act whilst 'under the influence', and indeed other crimes such as theft and robbery in order to finance supply. Screening and quantification procedures for use with biological specimens, which may include alternative matrices such as oral fluid and hair, are thus needed in both clinical and forensic toxicology. Unusually, this requirement also includes methods for enantiomer separation (4). *References:* 1. Schifano F, Corkery J, Deluca P, Oyefeso A, Ghodse AH. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994–2003). J Psychopharmacol 2006; 20:456–63. 2. Kraemer T, Maurer HH. Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. Ther Drug Monit 2002; 24:277–89. 3. Maurer HH, Kraemer T, Springer D, Staack RF. Chemistry, pharmacology, toxicology, and hepatic metabolism of designer drugs of the amphetamine (ecstasy), piperazine, and pyrrolidinophenone types: a synopsis. Ther Drug Monit 2004; 26:127–31. 4. Peters FT, Samyn N, Lamers CT, Riedel WJ, Kraemer T, de Boeck G, Maurer HH. Drug testing in blood: validated negative-ion chemical ionization gas chromatographic-mass spectrometric assay for enantioselective measurement of the designer drugs MDEA, MDMA, and MDA and its application to samples from a controlled study with MDMA. Clin Chem 2005; 51:1811–22.

20. A New Rapid Alert System for Poison Centres in Europe - Testing of EU-RAS-CHEM

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Objective: Poisons centers (PCs) in Europe play an increasingly important role in detecting epidemics of poisoning. A number of recent outbreaks have been detected at an early stage by poisons centers' toxicovigilance. This role is appreciated by the European Union's public health administration, especially with respect to poisoning risks that arise from deliberate release of chemicals. A research project "Alerting System and the Criteria for Development of a Health Surveillance System, for the Deliberate Release of Chemicals by Terrorists" (ASHT) started in October 2005 with substantial active contribution from European poisons centres, the board of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT), World Health Organization (Geneva) and Health Protection Agency (Centre for Radiation, Chemical and Environmental Hazards, Chilton, UK). The first main objective of the ASHT project is the design and testing of a web-based rapid alert system for communication between PCs and European public health institutions in Europe (Rapid Alert System for Covert Chemical Release by Terrorists = EU-RAS-CHEM). *Method:* A detailed technical description of the PC alert system was developed through a 10-month process of discussion through email, meetings and teleconferences. Careful analysis of two prototype simulations of EU-RAS-CHEM was performed and three test reports were prepared and submitted to the programmers. A group of PCs throughout Europe, in addition to the ASHT partners, will test EU-RAS-CHEM. *Results:* A pilot version of EU-RAS-CHEM has been developed. A detailed work plan for testing EU-RAS-CHEM has been defined, involving a two-stage process with an increasing number of active users in the system. Due to unexpected IT security problems EU-RAS-CHEM was not available in 2006, but shall be available in January 2007. Thus, the test phase is delayed for 9 months. *Conclusion:* EU-RAS-CHEM may become an important platform for poisons centre communication between scientific congresses. EAPCCT will play an essential role in evaluating the system and defining its role in future cooperation of poisons centres in Europe.

21. Sodium Bicarbonate in Acute Organophosphorous Poisoning

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Introduction: Organophosphorous (OP) compounds are widely used as pesticides and were also applied as chemical warfare nerve agents during the Iraq-Iran war between 1983 and 1988 (1), and in the terrorist attacks in Japan in 1994 and 1955 (2,3). The very well known antidotes of OP poisoning are atropine sulfate and oximes. Atropine counteracts the muscarinic effects of OP poisoning, but the therapeutic effects of oximes are controversial. In addition, the high cost of pralidoxime and the hepatotoxicity of obidoxime particularly with high doses (1), have spurred clinicians and scientists to search for more effective treatments. Following an experimental study (4) a clinical trial on the effects of continuous low dose sodium bicarbonate in OP poisoning was carried out during 1997–1999 in Mashhad. It did not alkalinize the blood significantly (5) and thus higher doses of sodium bicarbonate were studied in patients with moderate to severe acute OP pesticide poisoning (6). *Treatment Regimen:* In addition of the standard treatment of OP poisoning (atropine and oxime), sodium bicarbonate (5 mEq/kg over one hour, followed by 5–6 mEq/kg daily until recovery/death) was infused. Arterial blood gases and pH were performed on admission and at certain intervals to maintain pH between 7.45 and 7.55. To avoid hypokalemia, for each 50 mEq of sodium bicarbonate, 20 mEq of potassium chloride was added. *Results*: The study was performed on 53 patients (30 M and 23F), aged 24.9 ± 9.3 years. Most of the patients (94.4%) were suicidal and only 3 patients (5.6%) were poisoned accidentally. Intensive care therapy, mechanical ventilation and mortality rate were non-significantly lower but hospitalization days were significantly ($p = 0.037$) lower in the patients received sodium bicarbonate than in the controls. There were no statistically significant differences on acetylcholinestrase (AchE) activities, arterial blood pH and the other biochemical and hematological investigations on admission between the two groups. However, arterial blood pH increased following sodium bicarbonate infusion and the pH of this group (7.48 ± 0.02) was much higher ($p < 0.0001$) than the controls (7.36 ± 0.02). AchE activities were similar during treatment in both groups, ranging from 0.01 to 1.8 U/ml (Normal > 4.2 U/ml). Serum electrolytes and other biochemical tests did not change significantly during treatment except for the

severely intoxicated patients who died in ICU due to organ failure. Initial transient leukocytosis and neutrophylia were observed in some patients of both groups with no significant differences. There were no statistically significant differences in the atropine doses which were infused either on admission or during the first 24 hr of admission between the two groups, but the total atropine doses used for the sodium bicarbonate group (93.4 ± 59.1 mg) were significantly ($p = 0.048$) lower than in the control group (129.45 ± 61 mg). *Discussion:* Blood alkalinization has already been used for the treatment of tricyclic antidepressant overdose. We have applied the same regimen for OP poisoning. Following Palacio (4), Cordoba et al. (7) in 1983 also reported the effects of sodium bicarbonate in 13 dogs poisoned by an OP (DDVP) with a survival of 84.6% and recommended its use as an aid in OP poisoning. In our study, morbidity was significantly reduced in patients who received high doses of sodium bicarbonate as judged by reduced hospitalization days. The significant lower total atropine dose of the treated group is probably a reflection of the shorter duration of hospitalization. The needs for intensive care therapy, particularly resuscitation and mechanical ventilation were also less in the bicarbonate group, although they were not statistically significant due to the very low number of patients in each sub-group. The same argument is true for the mortality that was double in the controls (two patients) compared with the sodium bicarbonate group. AchE activities were similar in both groups. It means that sodium bicarbonate does not effect on the enzyme. OP compounds are esters of phosphoric acid and thus hydrolysis of the molecules may increase with increase in pH. Hydrolysis of OP is usually a route of detoxification. In addition, blood alkalinization to pH 7.5 with sodium bicarbonate may facilitate destruction of OP molecule (7,8). *Conclusion:* Infusion of high doses of sodium bicarbonate (5 mEq/kg in 60 min. followed by 5–6 mEq/kg/day to obtain arterial blood pH of around 7.50) appeared to be effective in treatment of patients with OP pesticide poisoning. It may thus be an aid and could be added to the treatment regime of OP poisoning. However, further study is recommended of the effects of sodium bicarbonate in different OP poisonings (including the chemical warfare nerve agents) experimentally in varieties of animal species to find out the true mechanisms of action and to carry out multicenter clinical trials on patients with acute OP pesticide poisonings to obtain more precise results on each OP poisoning and optimum dosing of sodium bicarbonate. *References:* 1. Balali-Mood M, Shariat M. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. J Physiology (Paris) 1998; 92:375–378. 2. Morita H, Yanagisawa N, Nakajima T, et al., Sarin poisoning in Matsumoto, Japan. Lancet 1995; 346:290–293. 3. Ohbu S, Yamashina A, Takasu N, et al., Sarin poisoning on Tokyo subway. Southern Med J 1997; 90:587–593. 4. Palacio DC. New approach to treatment of OP poisoning, Ant Med Medelin (Col,) 1982; 31:1–2. 5. Balali-Mood M, Salimifar R, Shahab-Ahmadi A. Effects of sodium bicarbonate in human organophosphates poisoning in Iran. Proceedings of CBMTS, Switzerland, 7–12 May 2000, pp. 12–19. 6. Balali-Mood, M, Ayati MH, Ali-Akbarian. Effects of High Doses of Sodium Bicarbonate in Acute Organophosphate Pesticide Poisoning. J Toxicol Clin Toxicol 2003; 41:456–457. 7. Cordoba D, et al. Organophosphate poisoning – Modification of acid-base equilibrium and use of sodium bicarbonate as an aid in the treatment of toxicity in dogs. Vet Human Toxicology 1983; 25:1. 8. Garcia-Repetto R, Martinez D, Repetto M. The influence of pH on the degredation kinetics of some organophosphorous pesticides in aqueous solution. Vet Human Toxicology 1994; 36:202–204.

22. Acute Chloroquine Poisoning: Toxicokinetic/Toxicodynamic Relationships for Blood and Plasma Chloroquine Concentrations

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Objective: Chloroquine is responsible for severe poisonings with membrane stabilizing effects. Early management is mandatory to allow patient survival. Bad prognostic factors include an elevated supposed ingested dose (SID) >4 g, a systolic blood pressure (SBP) <100 mmHg, and a QRS duration >100 ms. The interest in chloroquine concentration measurement in plasma is unknown. Only the prognostic value of chloroquine concentration in the whole hemolyzed blood has been established. *Methods:* Prospective study of all the patients admitted in an ICU in 2003–2006 for chloroquine poisoning; study of the correlations (Pearson tests) between the chloroquine concentrations in blood and plasma (using UV spectrometry) and different pertinent clinical and electrocardiogram parameters; modelling of the toxicokinetic/toxicodynamic (TK/TD) relationships between the epinephrine infusion rate and the chloroquine concentrations (Win-Nonlin software); presentation of the results as median [25–75%-percentiles]. *Results:* Forty-four patients (29F/15M, 33 years [25–41], SAPS II: 50 [30–68]) were included. The chloroquine SID was 4.6 g [2.8–7.5] and the poisoning a multidrug ingestion in 59% of the cases. On admission, the SBP was 100 mmHg [70–120], the heart rate 80/min [66–96], and the QRS length 120 ms [101–143]. Fifteen patients (34%) presented with cardiac arrest (10 pre- and 5 intra-hospital arrests). The plasma lactate concentration was 5.9 mmol/l [3.7–9.9], the potassium concentration 2.4 mmol/l [1.9–3.1], the creatinine concentration 88 µmol/l [70–114], and the $PaO2/FiO_2$ 290 mmHg [211–410]. The chloroquine concentration was 16.1 µmol/l [9.6–31.2] (therapeutic range: 1–6 µmol/l) in blood and 3.7 µmol/l [2.8–6.9] in plasma. Patient management included mechanical ventilation (80%), 8.4% sodium bicarbonate (66%), epinephrine (73%, maximal infusion rate: 2.8 mg/h [0.8–5.0]), norepinephrine (13%) and activated charcoal (45%). Seven patients were treated with extracorporeal life support. Seven patients died (3 following brain death, 2 cerebral anoxia, and 3 multiorgan failure). Chloroquine concentrations in blood and plasma were correlated ($R = 0.78$). The coefficient of variation of the TK area under the curve (AUC) supported the existence of a huge inter-individual variability. On admission, correlations of chloroquine concentrations with the SID ($R = 0.70$ regarding blood versus 0.50 regarding plasma), QRS duration ($R = 0.50$ versus 0.54), lactate concentration ($R = 0.52$ versus 0.58), and epinephrine infusion rate ($R = 0.52$ versus 0.44) were comparable. Concentrations were significantly different between the groups with and without a cardiac arrest ($p = 0.0002$ versus 0.02). On the other hand, during the poisoning course, the TK/TD relationships clearly demonstrated a better prognostic value regarding the severity of shock, for the blood chloroquine concentrations (sigmoïdal Emax TK/TD relationships) than the plasma concentrations (anarchic TK/TD relationships). *Conclusion:* While in pharmacology, blood and plasma concentrations decrease in parallel, they may vary independently in toxicology. Only blood chloroquine concentration, a better marker of tissue distribution, is useful to evaluate the prognosis on admission as well as during the poisoning time course.

23. Flumazenil as a Differential Diagnostic Tool in Coma of Unclear Aetiology

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Background: The benzodiazepines and the benzodiazepine-related pharmaceuticals are among the most common drugs used for self-poisoning. Flumazenil, a specific benzodiazepine antagonist, was introduced in the late 1980s and its use in acute drug poisoning is well documented (1,2). This antidote effectively reverses CNS depression caused by these drugs. *Literature Scrutiny:* Most experts agree that flumazenil is a valuable therapeutic tool in selected cases of severe, pure benzodiazepine overdose (especially in children, the elderly and patients with chronic pulmonary disease) and that its use in this setting is acceptably safe. However, well-justified concern has been raised about the safety of flumazenil in suspected mixed drug poisoning and in coma of unclear aetiology (3–5). The concern has nothing to do with any adverse effects of flumazenil itself, but is based on the risk of undesired negative effects due to the abrupt benzodiazepine blockade. On the other hand, the potential clinical advantage of flumazenil as a differential diagnostic tool is obviously most important in such cases and several authors have advocated its use on this indication in selected cases (6–8). It is well known also that other potent antidotes, such as naloxone and physostigmine, occasionally provoke severe undesirable reactions, especially if they are given incautiously or in inappropriate situations. The main risks involved with administration of flumazenil in patients with mixed drug poisoning or coma of unclear aetiology include the possible provocation of convulsions or a benzodiazepine withdrawal syndrome. Seizures are a recognised hazard (4) and are most feared, as they may lead to hypoxia, acidosis and aspiration unless promptly controlled (5). Patients at risk of developing seizures in this situation include those with epilepsy or long-standing benzodiazepine abuse and those who have overdosed with a mixture of a benzodiazepine and a convulsant drug, such as an antidepressant, cocaine, amphetamine, chloroquine or aminophylline. In severe poisoning with one of these drugs, benzodiazepine administration is an important part of the treatment, and the use of flumazenil is therefore inappropriate for many reasons. The main potential advantages of administration of flumazenil in patients with coma of unclear aetiology may be summarised from the results of a double-blind randomised controlled trial addressing these questions (9). In that study, 105 comatose patients were evaluated concerning the need for different diagnostic and therapeutic interventions before and after administration of flumazenil or placebo. A standardised interview was also conducted with each patient within 10 minutes after the blind injection. The results showed that gastrointestinal decontamination, orotracheal intubation and urinary catheterisation were rendered unnecessary in a significant number of patients after injection of flumazenil. Further, in some cases artificial ventilation, CT-scan of the brain, EEG, lumbar puncture and blood cultures were no longer required after flumazenil administration. Twenty-one of the patients in the flumazenil group (40%) were able to give important information about their ingested drugs shortly after the injection, although only four of the 53 patients in this group had taken benzodiazepine alone. One severe adverse reaction was recorded; this occurred in a young woman with a mixed overdose of benzodiazepine and maprotiline, and consisted of a transient fall in blood pressure shortly after the flumazenil injection. No arrhythmia or seizure was noted in the study. In a similar but smaller randomised controlled trial (10) a trend toward lower resource utilisation and decreased ICU admission rates was apparent in the flumazenil group. In that study no major drug related complication was recorded. When flumazenil treatment is considered in patients with coma of unclear origin or in suspected poisoning, it is of utmost importance that attention be paid to its contraindications and to the mandatory precautionary administration routines outlined in the following. The contraindications include 1) known epilepsy, 2) known benzodiazepine addiction, 3) suspected mixed poisoning with a benzodiazepine and a convulsant drug, and 4) pathologically wide QRS complexes on ECG. Administration routines for flumazenil are a) physical examination (must show clinical signs typical for a benzodiazepine-induced coma, i.e., preserved cranial nerve function, lack of focality, a generally decreased muscle tone and absence of high fever); b) electrocardiogram (a diagnostic ECG should be recorded before injection); c) administration procedure (measures to prevent aspiration in the event of provoked vomiting or seizure, i.e., drainage position and access to suction, oxygen and propofol; the flumazenil dose should be carefully titrated to obtain the desired level of consciousness and not given as an abrupt bolus); and d) supervision (frequent re-sedation necessitates careful observation and occasionally repeated flumazenil administration). *Conclusion:* In the light of available data and assuming that flumazenil is used appropriately as described above, this antidote seems to be a valuable tool in the management of selected patients with coma of unclear aetiology. However, routine use as part of a "coma cocktail" is not recommended. *References:* 1. Weinbroum A, Halpern P, Geller E. The use of flumazenil in the management of acute drug poisoning – a review. Intensive Care Med 1991; 17:32–8. 2. Höjer J. Management of benzodiazepine overdose. CNS Drugs 1994; 2:7–17. 3. Seger DL. Flumazenil: antidote or toxin? J Toxicol Clin Toxicol 2003; 41:400. 4. Spivey WH. Flumazenil and seizures: analysis of 43 cases. Clin Ther 1992; 14:292–305. 5. Burr W, Sandham P, Judd A. Death after flumazenil. BMJ 1989; 298:1713. 6. Winkler E, Almog S, Kriger D, et al. Use of flumazenil in the diagnosis and treatment of patients with coma of unknown etiology. Critical Care Med 1993; 21:538–42. 7. Ritz R, Zuber M, Elasser S, Scollo-Lavizzari G. Use of flumazenil in intoxicated patients with coma. A double-blind placebo-controlled study in ICU. Intensive Care Med 1990; 16:242–7. 8. Park GR, Navapurkar V, Ferenci P. The role of flumazenil in the critically ill. 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24. Sodium Thiosulfate in Sodium Hypoclorite Poisoning

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Objective: Accidental or voluntary poisoning from domestic products occurs frequently. Caustic agents such as bleach cause tissue damage by altering the structure of the derma or mucous membrane, which affects the ionized state and disrupts covalent bonds. In water solutions, the hydroxide ion (OH^-) is responsible for the toxic effects of alkali substances: a liquefactive necrosis is typical of intentional alkali exposure. Sodium thiosulfate ($Na_2S_2O_3$), a thiol group donor, reacts with sodium hypochlorite (NaClO) inactivating the mechanism that leads to colliquative necrosis caused by alkali. The purpose of this study was to evaluate the use of sodium thiosulfate as an antidote in hypochlorite poisoning. *Methods:* We report a series of 53 sodium

hypochlorite poisonings observed between 1st January 2002 and 15th November 2006. Thirty-eight patients ingested hypochlorite accidentally (quantity range about 10–30 ml, 5% sodium hypochlorite concentration); 15 ingested 50–100 ml of sodium hypochlorite for a suicidal purpose: 2 of these 15 patients ingested an industrial product, with a higher concentration of sodium hypochlorite (15%). All patients, independent of the lesions initially observed, underwent supportive therapy and endoscopy upon admission and 12 hours after ingestion. *Results:* Patients presented with a wide variety of symptoms, from mild discomfort, sialorrhea and lacrimation to severe oropharyngeal and esophageal pain and swelling. 23 patients received supportive therapy only, because of the small amount of sodium hypochlorite ingested. Of these, 12 had severe gastric and esophageal burning, 8 developed significant edema and esophageal stenosis that required endoscopic dilation, and 3 patients required emergency surgery. 30 patients received also sodium thiosulfate within 30–90 minutes from ingestion. None of the 16 patients who received sodium thiosulfate within 30 minutes following the ingestion of up to 80 ml of sodium hypochlorite had severe sequelae. Of the 14 patients who received sodium thiosulfate between 30 and 90 minutes after ingestion, 12 suffered mild oropharyngeal and esophageal burns or mild edema of the upper esophageal tract that required only medical therapy, while the other 2 patients who had ingested up to 100 ml of industrial products underwent endoscopic dilation, despite the administration of sodium thiosulfate within 90 minutes. *Conclusion:* This experience suggests that the administration of sodium thiosulfate, associated with appropriate supportive therapy, considerably improves the outcome of alkali oral ingestion.

25. In Search of Optimizing the Dose for Antidigitalis Fab (ADFAB)

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Objective: Since ADFab became available in the early 80s patients with severe digitalis intoxication could be saved. At the same time the incidence of digitalis intoxications declined making clinical studies difficult. ADFab are expensive costing around 4000 € per treatment leading to considerations of using a smaller dose than so far suggested. *Patients and Methods:* Since 1982 we treated in our department 44 cases of digitalis intoxications with ADFab, 39 were digoxin and 5 digitoxin poisonings (all survived). Digoxin or digitoxin was measured by RIA or by other immunoassays. In 6 cases we were able to measure free digoxin after the administration of ADFab, separating the free digoxin from the antibody bound digoxin by dialysis. *Pharmacokinetic Considerations:* The Vd is 5.6 l/kg for digoxin and 0.56 l/kg for digitoxin. The serum half life is 35 hours for digoxin and 160 hours for digitoxin. The volume of distribution is 0.5 – 1 l/kg for ADFab and the half life is 10–20 hours. In the circulation blood is only 1% of digoxin. The dissociation half time of digoxin from its cardiac receptor is 50 minutes. *Results:* The digoxin levels of our patients were between 3.9 and 19.5 µg/ml before treatment. The digitoxin levels between 70 and 210 µg/ml. In the beginning we used the ADFab as advised in the producer's instruction giving the whole calculated dose in a short infusion over half an hour (5 cases). In these cases the free digoxin went down to zero but started rising again after 5 hours. Later on we used 160 mg ADFab as starting dose and infused the rest of the calculated dose over 7–24 hours. Again the free digoxin came down to zero immediately after the starting dose but rose again during or after the continued infusion (3.2–7.5 µg/ml free digoxin). *Conclusion:* Giving the total dose of ADFab in one go is a waste because there is very little digoxin in the central compartment and the half life of ADFab is much shorter than that of digoxin/digitoxin. Probably 40 mg of ADFab would be enough as a starting dose. A continuous infusion of the rest or of parts of the calculated dose over 24 hours (longer for digitoxin) may save the amount of antiserum needed and thereby money. EAPCCT should do an international multi centre study in this field. *References:* Schaumann W, et al. Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxications. Eur J Clin Parmacol 1986; 30:527–533.

26. Foxface Rabbitfish Toxic Spine-induced Hand Injury

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Objective: To describe a local envenomation by a common exotic salt water trade fish with little reported information regarding the toxin or its mechanism of action. *Case Report:* We report the case of an avid young male aquarist with accidental distal phalanyx contact with a dorsal spine of the Foxface Rabbitfish, *Siganus (Lo) vulpinus*. Examination of the right index finger revealed a small punctate wound on the volar pad and subungual region with distal erythema. Proximal pallor of the digit was noted. Capillary pulse refill was normal. Range of motion of the digit was intact. Even with hot water immersion, the usual treatment of choice for fish envenomation, severe local pain persisted. Delayed relief did occur with parental narcotics. No systemic symptoms developed or long term disability. The Foxface Rabbitfish, *Siganus (Lo) vulpinus*, an exotic fish from the Indo-Pacific region, is popular among salt water aquarists because of brilliant colours and low maintenance. Despite their mild temperament, included among its defence mechanism is reported toxin secretion from its dorsal, pelvic and anal spine. A review of the medical and marine science literature produced little information on the type of venom or mechanism of action. Of interest, the *Siganus (Lo) vulpinus* appears to selectively alter its feeding based on its environment. Thus, selective feeding behaviour may be a potential mechanism of various toxin bioaccumulation and exploitation which may explain the lack of response to hot water in our patient. Additionally, as with other non-native environments, specific toxins from fish may change in regard to new feeding environments. The potential toxin accumulation or change may alter its response to traditional therapeutic interventions. Further molecular biologic studies are needed to identify the specific toxic compounds and sites of action. *Conclusion:* With the increase in the exotic fish trade, the clinical importance of this case emphases the need for the practitioner to recognize the potential non-endemic marine toxins pertaining to the health of the public.

27. Neostigmine after Coral Snake Bite (*Micrurus spp*). A Case

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Objectives: Some Brazilian coral snakes from genus Micrurus, have neurotoxin with postsynaptic action, affecting acetylcholine receptors on the muscle fibers, the effects of which closely mimic myasthenic features (1,2), the objective here is to present a case of *Micrurus ssp* bite treated with atropine and neostigmine, highlighting the muscle recovery rate evaluated using a Hg manometer. *Case report:* A 19-year-old man, 53 kg in weight who was bitten by a coral snake at 12h on the 08/9/2006, in the rural area of Andradas City, Minas Gerais State. The reptile was not captured. After being bitten he had intense pain on the affected region for 10 to 15 minutes, followed by a numb sensation involving the whole limb. He needed to walk about one km to reach a house, but 200 m before, he was forced to stop because his vision was blurred. In addition, he experienced intense weakness, proving difficult for him to arrive at his destination. The patient was taken to the Community Hospital, on arriving at 12:30h he presented with blurred vision, palpebral ptosis, ophitalmoplegy, generalized weakness, incapacity to maintain the cervical posture, inability to stand, walk and somnolence. At 15:00h he was treated with 10 vials of antielapidic serum (Butanta Institute) intravenously and transferred to the University Hospital. On arriving at 17:00h, he presented with the same neuroparalytic signs. Atropine sulphate 0.5 mg was given intravenously (in bolus), duration 2 minutes, being given immediately, neostigmine 1 mg intravenously (in bolus), duration 2 minutes. During the atropine administration the pulse increased from 78 beats/minutes to 128 and during the neostigmine administration decreased from 128 to 71. Fifteen minutes after the neostigmine the neuroparalytic picture began to improve. It was possible for the patient to open and move the eyes, to read and to walk. He remained in good condition during the night but in the morning he was not able to keep the eyes open for more than 30 seconds, he felt weakness, however was able to walk. At 9:30h a second dose of atropine/prostigmine was administrated. Using Hg manometer for measuring the leg strength, we had before-50 mmHg; after atropine+prostigmine. 11 minutes – 110 mmHg, 16'-150, 20'-165, 22'-215, 27'-220, 36'-280, with right leg. After the second prostigmine injection he remained in good condition and was discharged two days later. *Conclusion:* We presented a case of Micrurus bite successfully treated with neostigmine and antivenom. *References:* 1. Vital Brazil O, Vieira RJ. Neostigmine in the treatment of snake accidents caused by Micrurus frontalis: report of two cases. Rev Inst Med Trop. S. Paulo 1996; 38:61–67. 2. Sharan R. Neostigmine in the management of snakebite. J Indian MA 1982; 78:61–63.

28. Antivenom for Viper Snakebite: When and How Much - A Case Report

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Objective: The use of snake-antivenoms is limited in Italy by their shortage on the market and the restricted hospital use. In case of uncertain snake-bite or when the victim is admitted to the emergency department (ED) many hours after the bite, the dose of antivenom that needs to be administered is controversial. *Case Report:* A 68-year-old man was admitted to ED two hours after a bite by an unidentified animal in the finger while he was picking up vegetables. The man complained of a small sting and there were no local or general signs on first examination: he was discharged from hospital without treatment. Twelve hours later, the man was readmitted to ED showing a large oedema on the bitten arm, and complaining of severe pain and paresthesia. Vital signs were normal and laboratory analysis revealed only D-Dimer alterations (12.94 mcg/ml). After a consultation with the Poison Centre, the administration of nadroparin calcium (5700 U.I. subcutaneously) and European Viper Venom Antiserum (Fab-antivenom, 1 vial in normal saline solution, intravenously) were started; the patient was admitted to the intensive care unit (ICU) for further monitoring and treatment. In ICU the patient was submitted to hourly checks of the circumference of hand, forearm, thorax and neck of the affected body side. During the first six hours the patient's vital signs remained stable and there was a slight reduction of angioedema and pain of the arm. A subsequent increase in local swelling and angioedema forced the second dose of Fab-antivenom, with consequent stabilization of the lesions. Next morning, the hemithorax and the neck of the same side became oedematous and the patient required oxygen by face-mask to maintain a normal saturation rate and a third dose of Fab-antivenom with stopping of progression of the oedema. An echo-doppler exam of the bitten arm revealed no obstruction of arterial and venous vasculature. The D-Dimer value returned to normal in two days and, on the third day, the patient was transferred to a medical ward. *Conclusion:* The report of severe anaphylactic reactions to viper antivenom and the shortage on the Italian market has restricted its indications to severe cases. In this case, a late diagnosis required several doses at different times of antivenom. When the animal is unknown, clinical and laboratory monitoring is essential to precise timing and dosing of antivenom.

29. Evaluation of the Safety of Antivipmyn® in Humans

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Antivipmyn® is an anti-venom used in Mexico in case of poisonings by venomous snakes. *Objective:* In the present study we evaluated the safety of Antivipmyn® in humans. *Methods:* Experimental protocol was approved by the Human Subjects Ethical Committee of our institution. Written informed consent was obtained from 14 (18–25 years) healthy volunteers. Clinical history, physical examination, vital signs, laboratory analyses (blood chemistry, hematology, urinalysis, HIV and hepatitis B), chest X-ray and EKG were carried out in all the cases before the study. The subjects received Antivipmyn® by a 30 minutes intravenous infusion period (1 ampoule Antivipmyn® dissolved in 100 ml of isotonic NaCl solution). Physical examination, vital signs and evaluation of systemic symptoms were carried out throughout the period of infusion and after 3, 6, 12 and 24-h. Three weeks after the first dose the subjects received a second dose of Antivipmyn® and the same clinical parameters were evaluated. Laboratory analyses were made after the evaluation period. *Results:* Repeated physical examination performed during the study disclosed no abnormalities in any subject. Antivipmyn® had no significant effect on blood pressure, temperature, pulse and respiration and all

clinical laboratory results were normal in all the cases. *Conclusion:* During the testing period no clinical drug-related symptoms were found in any subject after Antivipmyn® intravenous administration.

30. Evaluation of Animal Poisoning Exposure Inquiries to the New Zealand National Poisons Centre During 2005

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Objective: In New Zealand there is no dedicated veterinary poison information service. However, the National Poisons Centre (NPC) receives calls from both the public and veterinarians concerning animal poisoning exposures. The aim of this study was to evaluate the role of the Centre in the context of responding to animal poisoning. *Method:* A retrospective analysis of all animal related poisoning inquiries to the NPC was undertaken for the year 2005. *Results:* Total animal poisoning related calls to the Centre was 1416, representing 4.6% of total inquiries to the Centre (31037). Of these calls 54.4% (771) emanated from veterinarians with the balance 45.6% (645) from the public. The majority of calls involved canines (1001, 70.7%) and felines (279, 19.7%). Other calls included inquiries about cattle, deer, sheep, horses, goats, pigs, alpacas, rats and other rodents, turtles, fish and birds. Calls for canines most frequently involved fertilizer, followed by glyphosate, pindone, ibuprofen, pyrethroids and theobromine. For calls involving felines, the most common agents were imidacloprid, quaternary ammonium compounds, glyphosate, fertilizer, paint and alphachloralose. *Conclusion:* Animal poisoning exposure calls to the NPC represent a significant percentage of total calls and present the opportunity to initiate a formalized veterinary poison information service. Following the lead demonstrated by the London Veterinary Poison Information Service (1) the NPC has recently commenced discussions with Veterinary Science staff at Massey University to advance this objective. *Reference:* 1. Campbell A. Should poisons centres provide veterinary advice? EAPCCT XXVI Congress 2006, abstract number 30.

31. D-Dimer as Prognostic Factor and Therapeutic Indication for Antivenom Treatment in Viper Bite Envenomations

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Objective: To define D-dimer as prognostic factor and therapeutic indication for Fab antivenom treatment in viper bites. While deaths due to viper bites are relatively rare, the reports of acute exposures to Viperides in Italy have increased in the recent years, with an average of 250 cases/year in the last 5 years and a high incidence of disability and long-term sequelae. We report a case in which D-dimer was successfully used as a therapeutic indicator and prognostic factor in a patient with viper bite envenomation. *Case Report:* One male patient (age 41) was bitten on the right thumb, quickly developing swelling in the bitten extremity and complaining of nausea and minimal visual disturbances 30 minutes after the bite. After 2 hours abdominal pain, vomiting, weakness and hypotension were present. *Results:* Laboratory data revealed a D-dimer value of 845 ng/ml, rapidly increasing during observation. However, despite severe signs of systemic envenomation in the first 12 hours (pain, oedema, lymphangitis, muscle weakness, nausea), no significant alteration of the coagulation profile was observed. Since D-dimer constantly increased (up to 5890 ng/ml) and fibrinolysis signs (platelets 6500/mm3) appeared, we administered Fab antivenom with rapid patient improvement. The patient was discharged on the fourth day in good condition. *Conclusion:* In the management of snakebite envenomations, coagulation disturbances are widely accepted as a definitive indication to antivenom administration. We reviewed a case of viper bite considering D-dimer alteration as a prognostic factor and indicator for antivenom treatment, following its values during the observation and recommending Fab administration only in case of fast and constant increase of its value.

32. How Frequent are Accidents with Venomous Animals and Especially with Exotic Venomous Animals in Baden-Wuerttemberg?

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Objective: Keeping exotic animals became rather popular in Germany in recent years. So accidents due to exotic venomous animals are considered an emerging issue in the German public. To support this assumption we analyzed the cases documented in our poisons centre's database for accidents with venomous animals. *Results:* The Freiburg Poisons Centre serves approximately 10.5 million people in Baden-Wuerttemberg/Germany. From 2000 to 2005 the center received 82,538 calls concerning actual or suspected poisonings. 545 cases (0.7%) concerned venomous animals. In 65 of these cases the animals in question were not native to Germany (exotic). Major groups of these exotic venomous animals were fishes (15 cases), scorpions (14), and spiders (13). The number of calls concerning exotic animals rose from 4 in 2000 to 16 in 2005 (from 8 to 14% of all accidents with venomous animals). 44 contacts with venomous animals resulted in moderate or severe symptoms. 5 of these cases were due to exotic animals. The fraction of severe or moderate cases was 8% for exotic as for non-exotic animals. The significance of these findings is limited because of the small number of cases with exotic animals. *Conclusion:* Calls concerning accidents with venomous animals are a minor part of our centre's work. Accidents with exotic animals are rare but their number is increasing. Severity of accidents with exotic animals was not different from that of accidents with native animals. Considering the fact that people are more likely to call if they are not used to dealing with the causative agent of an accident, minor accidents with exotic animals may be overrepresented compared to envenomations by native animals.

33. Tranference from a Loxosceles Spider-bite Dermal Lesion to Normal Skin by Contact - Stamp-like Lesion

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Objectives: The clinical spectrum of the wounds caused by Loxosceles-bite ranges from minimal local itching and erythema, blebes, ecchymoses to a full-thickness skin necrosis (1,2). The objective is to present cases with evidence of transference from a Loxosceles bite dermal lesion to normal skin by contact. *Case Reports:* 1. A man was bitten on the upper part of the right axilla. The lesion had two central points of necrosis surrounded by erythema of irregular shape. He had another less severe lesion on the posterior part of the axilla exactly as a mirror image of the first lesion. A third injury was less pronounced and located in the antero-inferior axilla and also in a mirror fashion of the first. 2. A woman was bitten on the inner right thigh, presented with a small necrotic area with erythema like a "V" pointed forward. On the left thigh there was a specular image of the right lesion, although more atenuated. 3. A woman was bitten on the anterior to inner side of the left thigh, where she presented a large (6×2 cm) bleb surrounded by erythema. On the left thigh there was a specular erythematous lesion, but without bleb. 4. A man was bitten on the proximal part of the anterior face of the right thigh, about 10 cm from the inguinal pleant, where, he presented a 2×3 cm erytemato-violacous lesion. He had a similar lesion on the abdominal wall in the right inguinal region, in the exact local contact when the thigh is bent over the abdomen. *Conclusion:* The position of two points of skin necrosis and the morphology of the erythema in three lesions of the first man; the angular opening and position of the "V" erythema in the first woman, the shape and the location of the lesions in the cases 3 and 4, could not be explained by multiple bites. The only way to reproduce the lesions would be that the inoculated spider venom was able to damage the healthy skin throughout contact. The inoculated Loxosceles venom or the lesion mechanism is transferred to healthy skin by contact, giving a stamp-like new lesion. Further research may contribute to a better understanding of the mechanisms involved. *References:* 1. Wright SW, Wrenn KD, Murray L, et al. Clinical presentation and outcome of brown recluse spider bite. Ann Emerg Med 1997; 30:28–32. 2. Tambourgi DV, Morgan BP, De Andrade RMG, et al. Loxosceles intermedia spider envenomation induces activation of an endogenous metalloproteinase, resulting in cleavage of glycophorins from the erythrocyte surface and facilitating complement-mediated lysis. Blood 2000; 95:683–91.

34. Temporary Loss of Taste, Caused by the Suction of a South American Rattlesnake (*Crotalus Durissus Terrificus*) Bite - A Case

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Objectives: The venom of these snakes has a well known neurotoxicity, acting at neuromuscular junctions to produce neuromuscular blockade, a myotoxicity resulting in rhabdomyolysis and a thrombin-like component that results in coagulopathy (1,2), but the objective here is to present a case of *Crotalus durissus terrificus* accident with loss of taste after sucking the site of the bite, on his own foot, immediately after being bitten. *Case Report:* A 30-year-old man, was bitten by a South American Rattlesnake (*Crotalus durissus terrificus*) on the left foot at 19:30 h on February 26, 2006. Immediately after being bitten, the patient pressed the affected area with his hand and sucked with his mouth in an attempt to remove the venom. On arriving at the Community Hospital, the patient complained of paretic sensation in his lips with formication and numbness. He was referred to the University Hospital where he arrived at 22:45h presenting a decrease in visual acuity, diplopia, bilateral palpebral ptosis, ophthalmoplegia. The dorsal surface of the left foot presented two pointform fang marks lesion, mild edema and erythema. The offending snake was brought and identified as *Crotalus durissus terrificus*. The patient was treated with anticrotalus serum, (Butanta Institute), sufficient to neutralize 200 mg of the venom, intravenously. During the serum administration, the patient presented urticaria and generalized erythema, treated with 500 mg of hydrocortisone and 1mg of adrenaline by intravenous route (in bolus). The patient didn't eat anything during the night, but when he had breakfast 12 h after the accident perceived that he had completely lost his sense of taste. Only three days after the accident did he recover the taste sweet, four days the taste salty, five days the taste sour and six days, the taste bitter. *Conclusion:* We presented a case of a patient who had temporally lost his sense of taste caused by the venom of *Crotalus durissus terrificus* sucked by the mouth from the bitten area of his own foot. The taste recuperation occurred from 3 to 7 days after the accident beginning from the anterior the posterior part of the tongue, that is, sweet, salty, sour and bitter. *References:* 1. Azevedo-Marques MM, Cupo P, Coimbra TM, et al. Myonecrosis, myoglobinuria and acute renal failure induced by South American rattlesnake (Crotalus durissus terrificus) envenomation in Brazil. Toxicon 1985; 23:631–36. 2. Bucaretchi F, Herrera SRF, Hyslop S, Baracat ECE, Vieira RJ. Snakebites by Crotalus durissus ssp in children in Campinas, São Paulo, Brazil. Rev Inst Med Trop S. Paulo 2002; 44:133–38.

35. Incidence of Stonefish Envenomation Presented to a Singapore Hospital

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Objective: Stonefish are commonly found in the shallow waters of the Indo-Pacific region and are considered the most dangerous and venomous of the scorpionfish family. However, little is known regarding the epidemiology of stonefish envenomations in general. The aim of this study was to describe the incidence of stonefish envenomation and treatment outcome in patients presenting to Singapore General Hospital. *Methods:* Data involving stonefish stings was retrospectively retrieved from the Accident & Emergency (A & E) Emerge Version 3.7.6 database from October 2004 – September 2006. *Results:* A total of 30 cases were identified. The average age was 27.7 years (Range: 9–52 yrs). The majority were male (24/30, 80%) and 47% of cases (14/30) were foreign nationals. Most incidences occurred on weekends/public holidays (23/30, 77%). November had the highest number of cases (7 cases). The majority of cases (24/30, 80%) arrived at the hospital within 2 hours of envenomation. The most common complaints were extreme pain, swelling and redness of the affected limbs. The average pain score upon arrival was 7.4 (with 10 being most extreme pain). 19 cases presented with swollen limbs and 15 cases had erythema. 24 (80%) cases received hot water soak treatment and tetanus jab upon arrival. 27 (90%) patients received analgesia. 9 patients (9/27, 33%) required additional analgesics. 5 (16%) received anti-histamines and 1 (3.3%) case received steroid. 17 cases (58%) were treated and discharged, 8 (26%) were referred to a specialist for follow-up and 5 (16%) were warded. The average pain score upon discharge was 1.4. 13 patients (13/25, 52%) were discharged with antibiotics. The average number of days warded is 3 (Range 1–7). All reported improvement of symptoms upon discharge. One case had persistent pain and hyperalgesia 5 months post-envenomation. No deaths and systemic symptoms were reported. *Conclusion:* Stonefish envenomation presenting to our hospital showed that the majority of patients were young male adults. As more people visit beaches on weekends and public holidays, it is consistent

with the increase in occurrence of envenomations. Stonefish envenomation, though rarely fatal, can still cause significant morbidity such as extreme pain, swelling and erythema. Standardized guidelines for treatment of stonefish envenomation would optimize management and treatment outcome for such patients.

36. *Phoneutria Nigriventer* Spider Bite: An Unusual Case Report

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Background: Spiders of the genus *Phoneutria* account for 19% of the ~7,500 bites by venomous spiders notified each year in Brazil. Most bites by *Phoneutria spp*. cause mild envenoming, with only 0.5–1% being severe, mainly in children. *Case Report:* A previously healthy, 52-year-old male was cleaning a public garden when he leant against a tree and was bitten on the right side of the neck by an 8-cm-long female *P. nigriventer*. Immediately after the bite, there was moderate to intense, non-radiating pain, followed by blurred yellow vision, profuse sweating, tremors and an episode of vomiting. At the first medical service where he was attended, 1–2 h after the bite, the patient showed agitation and severe arterial hypertension (200 × 130 mmHg) and received sublingual captopril (25 mg) and meperidine (50 mg, IV). Upon admission at UNICAMP 4 h after the bite (T0), blood pressure was 130 × 80 mmHg, with tachycardia (150 beats/min), mild tachypnea, local erythema at the bite site, agitation, cold extremities, profuse sweating, generalized tremors and priapism. The case was classified as moderate/severe and the patient received 5 vials of undiluted antiarachnid antivenom [AV, F(ab)2, 5 mL/vial, equine origin] infused IV over 15–20 min; local anesthesia with 2% lidocaine and Ringer lactate 500 mL IV infusion were also initiated. All the systemic manifestations disappeared within 1 h after antivenom, and residual local pain was treated with additional lidocaine. Laboratory analyses showed increased glycemia at T0 (163 mg/dL) and normal serum potassium, sodium, creatinine and urea. At the studied times (T0, T1, T6, T12, T24, T48 and T113), circulating venom was detected by ELISA only at T0 (47.5 ng/mL), before AV infusion; IL8 and TGFβ2 serum levels were unaltered but IL6 was significantly increased at T0 (18.5 pg/mL) and T1 (29.8 pg/mL). The patient was discharged on the 2nd day with a normal blood pressure; a follow-up three days after discharge revealed no sequelae. *Conclusion:* Systemic envenoming by *P. nigriventer* in adults is very unusual and the rapid onset and severity of the symptoms seen here probably resulted from rapid venom absorption from the bite site close to major neck vessels. *P. nigriventer* venom stimulates the release of catecholamines and venom peptides that can cause vascular smooth muscle contracture, as well as nitric oxide formation via the tissue kallikrein system. These mediators may have contributed to the autonomic manifestations, hypertension and priapism in this case. This is the first communication of a confirmed, moderate/severe bite by *P. nigriventer* with the quantification of circulating venom and some cytokines in an adult.

37. Cerebellar Symptoms after Consumption of Edible Morels (*Morchella Conica, Morchella Esculenta*)

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Morchella esculenta and *morchella conica* are edible morels, well known for their delicious taste. They are frequently picked by mushroom hunters. However, we observed 6 persons who developed neurologic disturbances after meals with these mushrooms. From our poison control centre we have knowledge of 10 other persons with the same toxidrome. All had eaten relatively great amounts (250 – 600 g) of freshly self collected and prepared morels (13 *morchella esculenta*, 1 *m. conica*, 2 not specified), before they developed cerebellar symptoms after a latency of 6–12 hours. The toxidrome consisted in ataxia and dizziness (all patients), miosis (2 patients) or mydriasis (1 patient). Two persons had diarrhoea. The symptoms resolved within one day with no specific therapy. In all 6 cases, we had seen, the mushrooms were identified by ourselves. This mild toxidrome is not known in the medical literature. However, some mycologists mention similar cases. The intoxication occurs sporadically, but in some cases, all persons sharing the meal were affected. The intoxication occurs inconsistently: in one occasion one of the authors ate morchella esculenta, with no adverse effect. He had collected the morels from the same place, where two of the patients had found them. The toxin is not known. Possibly, it is a volatile toxin causing intoxications when great amounts of morels are cooked not long enough.

38. Mushroom Poisoning: Outcome Improvement with Interdisciplinary Approach

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Objective: To define the organization of a "Mycological Unit" in the treatment of mushroom poisoning. Although most mushroom exposures are benign, some can be life threatening, especially if mushrooms containing amatoxins are involved. Efforts must be concentrated on good supportive care and in obtaining a detailed history of the exposure (time of first ingestion, symptoms onset, how the mushrooms were prepared). Although identifying mushrooms from their physical characteristics is challenging, it is mandatory in the decision to administer invasive therapy except when concentrating on identification of the mushroom would delay supportive care. Mushroom poisoning needs an interdisciplinary effort in order to determine whether the ingested species are potentially life-threatening, to provide timely supportive therapy and to detect if the patient is definitely poisoned by amatoxins. *Methods:* The authors report their experience on 56 cases of mushroom ingestion, treated in cooperation with a mycology unit and the ED laboratory, trying to identify the mushroom species and to detect urinary amatoxin within 3 hours from ingestion. In our ED we recently introduced emergency dosage of urinary amanitine; at the same time we activate a mycologist 24 hours/day to identify the various mushroom species even from ingested material. In this way, administering intensive care since admission, it is possible to suspend such therapy when both assessments (laboratory and mycologic) are negative. *Results:* We treated 56 patients by administering intensive care and antidotal treatment with N-acetylcysteine. Poisoning from mushrooms containing amanitine was confirmed in 3 cases (2 amanita and 1 lepiota). In the other 53 cases the invasive and antidotal therapy was suspended, with optimal patient outcome. *Conclusion:* The cooperation with the mycological unit and the possibility of rapid amanitine dosage are undoubtedly an advantage for the patient and a considerable saving of resources.

39. Hyponatremia Associated with Oleander Toxicity

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Background: Oleander species contain cardiac glycosides: oleandrin and nerioside. Ingestions of significant amounts of oleander can result in vomiting and cardiac glycoside toxicity: conduction blocks, arrhythmias and hyperkalemia. Hyponatremia is not typically associated with oleander poisoning. We report a case of hyponatremia associated with oleander ingestion. *Case report:* A 66-year-old female presented to the Emergency Department two hours after intentionally ingesting an unknown amount of oleander leaves. She denied any medical conditions and was not taking any medications. Initial vital signs (VS) were: HR = 64 in sinus rhythm, BP = 155/78. The Poison Control Center (PCC) recommended single-dose activated charcoal (AC), electrolytes, cardiovascular monitoring and a digoxin level. On follow up 2.5 hours after ingestion the patient remained alert and oriented but vomited several times. Vital signs were HR = 51 sinus bradycardia, BP = 167/67. The digoxin level was 2.7 ng/mL, calcium 9.0 meq/L, sodium = 115 meq/L, potassium = 6.5 meq/L, blood urea nitrogen (BUN) = 16 mg/dL, creatinine = 0.9 mg/dL. The PCC recommended digoxin-specific immune Fab (Digibind®), intravenous hydration, and serial electrolytes. Two hours post administration of ten vials of Digibind® HR = 80–90 and potassium = 4.2 meq/L. Ten hours post ingestion the patient continued to vomit, HR = 50 in second degree atrialventricular (AV) block and systolic BP = 90–100. She was receiving 3% sodium chloride. A repeat dose of AC was recommended. Twelve hours post ingestion HR = 61, BP= 88/28, sodium = 122 meq/L, potassium = 4.9 meq/L, BUN = 13 mg/dL, creatinine = 1.0 mg/dL. Twenty hours post ingestion the patient developed third degree AV block with a rate of 30–40, BP= 90s/30s on 7 mcg/kg/min of dopamine and five additional vials of Digibind® were administered. Twenty-seven hours post ingestion HR = 50–60 in first degree AV block, BP = 133/60, sodium = 128 meq/L, potassium = 3.4 meq/L, BUN = 12 mg/dL, creatinine = 0.9 mg/dL. Thirty six hours post ingestion vitals were: HR= 69 in sinus rhythm, BP = 145/47, sodium = 138 meq/L, potassium = 3.4 meq/L, BUN= 15 mg/dL, creatinine = 0.8 mg/dL. The patient remained clinically stable and was discharged four days post ingestion. *Conclusion:* We report a case of significant and prolonged hyponatremia as well as cardiac glycoside poisoning after ingestion of oleander leaves. With aggressive supportive care including AC, Digibind®, hypertonic saline and dopamine hyponatremia resolved and the patient recovered without complications.

40. *Clitocybe Amoenolens* Poisoning: 10 Years of Investigation

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Background: In 1996, a new mushroom poisoning resulting in erythromelalgia was identified. First symptoms appeared more than 24 hours after ingestion. They consisted of painful paraesthesia of the toes and fingers, followed by paroxysmal burning pain associated with heat sensations, and sometimes numbness, oedema, and erythema. Symptoms were enhanced by heat, movement and contact, and relieved by cold water. They resolved within 1 to 4 months (1). *Results:* The responsible species was identified as *Clitocybe amoenolens*. Its toxicity appears to be similar to that induced by *Clitocybe acromelalga* in Japan. The two species belong to the same taxonomic section. Several toxins have been identified in *C. acromelalga*, acromelic acids and beta-cyanoalanine (B-CA) principally. The publication of the French cases made it possible to recognise other cases in the Abruzzi (Italy) in 2003. Acromelic acid A (AAA) was detected and measured in *C. amoenolens* using the LC-MS method. It was not detected in taxonomically close species. B-CA was detected using the GC-MS method. AAA, a powerful member of the non-NDMA glutamate agonist family, exhibits neuroexcitatory properties. It induces characteristic behavioural changes, as well as selective damage to the interneurons of the lower spinal cord in rats. Increasing mushroom doses were administered randomly in rats in order to assess the toxicity of *C. amoenolens*. Doses ranged from 1 to 25 fold the dose ingested by the most severely poisoned patient. Rats that received the two highest doses presented with locomotor disabilities and erythema of the toes. Electron microscopic examination of the sciatic nerves showed a reduction in axon density and the alteration of neuronal fibres. Rats also experienced skin disorders, as described after oral administration of *C. acromelalga*. Whether erythromelalgia is related to acromelic acids or not remains to be determined. An animal model of nociceptive peripheral neuropathy (tail immersion test) was used on rats who had previously ingested powdered *C. amoenolens*. The general toxicity was assessed by measurements of body weights and of motor activity (using an actimetre). A significant reduction in motor activity, body weight gain, and tail withdrawal latencies was observed. But the administration of concentrated extracts of AAA – obtained after specific extraction and purification procedures – failed to reproduce these effects. *Conclusion:* Acromelic acids might not be the only causative agents for motor and nociceptive peripheral neuropathy. *Reference:* 1. Saviuc P, et al. J Toxicol Clin Toxicol 2001; 39:403–7.

41. Plant Thorn Injuries as Reported to the National Poisons Information Service (Cardiff)

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Background: Plant thorn synovitis is a well documented if relatively unusual complication of mechanical injury from plant and cactus spikes and thorns. Symptoms of chronic arthritis can arise when fine fragments of plant material become incorporated into the synovium producing hypertrophic synovitis with granulomata containing foreign body giant cells (1). This can occur even if attempts have been made to remove plant fragments (2). Synovitis, granulomas, cysts

and foreign body reactions can be caused by thorns from a number of plants including cactus, blackthorn, hawthorn, roses and date palm. Symptoms may continue for months or years and total synovectomy may be required before a full recovery is made (2). *Objective:* To identify whether calls to NPIS (Cardiff) are made involving penetrating plant injury. *Case Series:* During the 12 months between November 2005 and November 2006, the Cardiff Unit of the National Poisons Information Service received five calls requesting advice on mechanical thorn injuries. Four of these involved blackthorn and one involved a date palm thorn. Four of the five patients developed symptoms prior to the call, whilst one (involving blackthorn) was asymptomatic. Symptoms reported included swelling, redness, inflammation and ischemia. Three enquiries related to fingers, one to a thumb and one to a knee injury. The patients were between 32 and 42 years of age. *Conclusion:* Although not common, calls involving penetrating plant injury are made to NPIS (Cardiff). *Discussion:* Several common poisons information databases do not list thorn injuries as potential sources of complications. Indeed they are not mentioned at all in some poisonous plant books. However, a detailed search elicits the potential adverse effects that can follow exposure to spiny plant material. Although the NPIS (Cardiff) received only a small number of calls involving this type of exposure, due to the potential for long-term sequelae it is essential that specialists in poisons information and emergency staff are aware of the need for correct care and follow up required to avoid plant thorn synovitis. Whilst being relatively unusual, it is a potentially serious complication which can follow a seemingly minor incident. *References:* 1. Sugarman M, Stobie DG, Quismorio F, et al. Plant thorn synovitis. Arthritis Rheum 1977; 20:1125–8. 2. Doig SG, Cole WG. Plant thorn synovitis, resolution following total synovectomy. J Bone Joint Surg (Br) 1990; 72(B):514–515.

42. Acute Renal Failure Induced by *Amanita Proxima* Poisoning: Three New Case Reports in Southern France

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Objective: Amanita proxima is a rare mushroom which grows in Southern France. This species can be the origin of poisonings with severe acute renal failure and moderate hepatic cytolysis. The first case series of this new kind of poisoning was reported in 1998 by the Poison Centre of Marseille (1), describing 53 observations mainly due to the confusion with the edible *Amanita ovoidea* (83% of the cases). Since this study, sporadic poisonings with *Amanita proxima* ingestions are still observed in Provence. *Case Series:* Three new cases were recently collected. The first one concerned a 53-year-old woman who ate in October 2005 mushrooms identified as *Amanita ovoidea*. She had digestive troubles 15 hours after the meal which persisted 2 days, and biological disturbances then appeared with oliguria and renal insufficiency. She improved after the 7th day and did not need dialysis. The second case concerned a couple (67-year-old man, 68-year-old woman) who ate in November 2005 unidentified white mushrooms. They both presented a classical *Amanita proxima* poisoning clinical feature with initial digestive troubles and development at the third day of renal failure and transitory hepatic cytolysis. They did not require dialysis and recovered after 10 days of hospital management. Finally, the third case concerned a 67-year-old man who ate in October 2006 *Amanita proxima* identified as *Amanita ovoidea*. He had also a similar clinical feature and stayed at the hospital for 9 days with no necessity of dialysis treatment. *Discussion: Amanita proxima* is a toxic mushroom which can induce in the very limited geographical area where it grows severe human poisonings. The three new cases were characterized by the development of a typical clinical feature but none of the patients needed dialysis, while 11 patients of 53 in the previous case series were treated with dialysis (1). *Reference:* 1. de Haro L, Jouglard J, Arditti J, et al. Insuffisance rénale aiguë lors d'intoxication par Amanita proxima: expérience du Centre Anti-Poisons de Marseille. Néphrologie 1998; 19:21–4.

43. Ingestion of Mescal Beans (*Sophora secundiflora*) Causing Agitation in an adolescent - A New Intoxicant

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Objective: Mescal beans from *Sophora secundiflora* have historically been used by Indians of the southwest and Central and South America during ritualistic ceremonies to obtain divinatory states. Toxicity, however, limited extensive use and upon the discovery of the hallucinogenic properties of mescaline found in *Lophophora williamsii* (peyote) use of *Sophora secundiflora* waned. Although detailed studies are lacking, the mescal bean is known to contain the alkaloid cystine which is similar in action to nicotine and has activity at both nicotinic and muscarinic receptors. This case is the first clinical description of intoxication from *Sophora secundiflora*. Additionally, it illustrates use of the internet for finding new or natural psychoactive drugs. *Case Report:* A 20-year-old young man became agitated shortly after being arrested by police. During a search of his person "red beans" described as similar size and shape as pistachio nuts were discovered. The patient was brought to the Emergency Department for evaluation and was noted to be mumbling that he took mescaline. In the Emergency Department the patient responded to verbal stimulation but only with single words. He had a fluctuating level of consciousness with intermittent agitation and was noted to be diaphoretic. His initial vital signs included: temperature 100.4 (rectal), heart rate 130 beats/minute and blood pressure 150/88 mmHg. On physical exam he had marked mydriasis. The patient's agitated delirium was treated with benzodiazepines and his mental status was significantly improved after three hours. Urine screen for drugs of abuse was positive for 1THC, otherwise laboratory tests were unremarkable. The patient subsequently clarified that he hadn't taken "mescaline" rather he'd eaten "mescal beans", after reading on the internet that they were hallucinogenic. *Conclusion:* There is limited information in the medical literature describing *Sophora secundiflora* as an intoxicant yet it is listed in the website Erowid as a hallucinogenic plant. Despite its inclusion as a hallucinogenic plant on various informational websites (Erowid) and other than historical references there are no reports of human toxicity from the mescal bean. This report is the first documented case of intoxication from mescal bean ingestion. It also serves as a reminder that while internet web sites such as Erowid serve as sources of information for rare and/or emerging drugs of abuse, for some individuals this information is used for finding new or alternative intoxicants.

44. Mass Poisoning by Datura Stramonium

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Objective: To describe a mass poisoning by the plant *Datura stramonium* (DS) which had grown as a pest in a culture of edible vegetables (*Amaranthus blitum*). Emphasis is given to the necessity of timely cooperation of the responsible services and the effectiveness of the information and vigilance of the public. *Case Series:* Three groups of 9 adults (5 males and 4 females) proceeded late at night and the next day to different hospitals of Athens with symptoms including nausea, vomiting, dry mouth, mydriasis, blurred vision, flushed skin, hypotension, tachycardia, confusion, and sleepiness. The first diagnosis varied from food poisoning to stroke attack. CT was performed in two patients; one had been admitted to an intensive care unit. Subsequent communication with the Poison Information Centre led to the diagnosis of anticholinergic poisoning by alkaloids. Administration of physostigmine as an antidote resulted in immediate recovery from most of the symptoms. Supportive treatment lasted from 24h to 72h. All patients had consumed vegetables (*Amaranthus blitum*) 90 min to 6 hours before the symptoms occurred. The second report to PIC about patients having consumed vegetables from the same supermarket, as the patients of the 1st report, rendered us sensitive to the possibility that we were not facing a random incident rather, but a massive poisoning with vegetables. The same night the PIC in cooperation with Hellenic Food Authority withdrew the specific lot of vegetables (grown on a specific farm) from the market and the public was informed through the Media in less than 24 hours after the first incident. Thus only two more incidents were reported during the next few days. Benaki Phytopathological Institute identified the pest *Datura stramonium* to have contaminated the culture of *Amaranthus blitum*. *Conclusion:* Clinicians have to be aware and report to PIC patients who present with uncommon symptoms. The close cooperation with PIC assists in the immediate diagnosis of this kind of poisoning. The prompt cooperation of the responsible services can prevent the expansion of such imminent mass poisonings.

45. Acute Poisoning with *Tricholoma equestre* as α Consequence of Simvastatin-Mushroom Interaction

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Objective: The incidence of myopathy and/or rhabdomyolysis is less than 0.1% among patients treated with simvastatin. On the other hand, rhabdomyolysis was described as a life-threatening consequence after repeated ingestion of *Tricholoma equestre* in 12 patients in France (1) and in two patients in Poland (2). We report a case after consumption of these mushrooms under simvastatin treatment. *Case Report:* A 71-year-old male patient suffering from diabetes type II, hyperlipaemia, hypertension, and chronic ischaemic heart disease had been treated with simvastatin for six months. Occasionally, he had reported muscular pain. In the past he had eaten *T. equestre* in large quantities without problems. He developed myalgia, fatigue, muscle weakness, and profuse sweating after ingestion of mushroom meals twice daily on six consecutive days. Creatine phosphokinase (maximum 4,934 U/L) and myoglobin (maximum 3,976 ng/ml) as well as aspartate aminotransferase (330 U/L) and alanine aminotransferase (209 U/L) were increased. Simvastatin treatment was discontinued immediately. Alkaline diuresis was administered to prevent myoglobin precipitation in renal tubules. Symptoms disappeared and pathological laboratory findings decreased but were not fully normalised under this treatment within ten days. *Conclusion:* The underlying mechanism of toxic interaction still remains unknown. Possibly, an increased simvastatin plasma level may be the result of increased absorption and/or of inhibition of cytochrome P450 3A4-mediated metabolism resembling the interaction of simvastatin and grapefruit. Otherwise, a direct combined cytotoxic action may be targeted on muscle fibres and liver cells. Although a recent study could not demonstrate toxic effects in patients treated with different statins and fibrates consuming large quantities of *T. equestre* (between 300 g and 1200 g for four consecutive days) simultaneously (3), we discourage from ingestion of *T. equestre* patients receiving HMG-CoA-reductase inhibitors. *References:* 1. Bedry R, Baudrimont I, Deffieux G, Creppy EE, et al. Wild-mushroom intoxication as a cause of rhabdomyolysis. N Engl J Med 2001; 345: 798–802. 2. Chodorowski Z, Waldman W, Sein Anand J. Acute poisoning with Tricholoma equestre. Przegl Lek 2002; 59:386–387. 3. Chodorowski Z, Sein Anand J, Madalinski M, Rutkowski B, et al. Enzymatic examination of potential interaction between statins or fibrates and consumed Tricholoma equestre. Przegl Lek 2005; 62:468–470.

46. Poisoning by *Solanum torvum*, The Normally Edible Susumber Berry

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Objective: We describe a case series of neurological and gastrointestinal poisoning by susumber berries (*Solanum torvum*) and the detection of alkaloids not present in the non-toxic berry. Consumption of immature, environmentally stressed, or other *Solanum species (*particularly the potato) has caused gastrointestinal and neurological symptoms (1). *Case Series:* Three family members ate a traditional evening meal of codfish, ackee, and susumber berries harvested in Jamaica. All were symptomatic the following morning. An adult woman who did not seek medical attention consumed a minute amount of berries due to their significant "bitterness" and experienced transient diarrhea. A 55-year-old man with moderate consumption sought care because of dizziness, slurred speech, expressive aphasia, left sided facial droop, facial numbness, and unsteady gait confirmed by emergency medical services personnel. Upon ED arrival, all findings had resolved. Extensive cardiac and neurological workup was negative. A 64-year-old woman, who ate "a lot" of berries, awoke with facial droop, dysarthria, blurry vision, dry mouth, gastric discomfort, and facial numbness. Diagnosed with a mild ischemic CVA, she required intensive therapy for persistent hypertension. Brain imaging, CSF analysis, echocardiogram, and carotid dopplers were normal. The following day, her facial weakness had resolved, but CK and bilirubin rose to 9471 U/L and 48 micromol/L. She developed confusion and mild proximal upper extremity weakness and was intubated for hypercapnic respiratory failure. Nerve conduction studies demonstrated normal conduction, normal repetitive stimulation in the hand and face, and normal needle EMG. Extremity weakness resolved within 24 hours, but she repeatedly failed ventilatory weaning, and required tracheostomy. She was discharged after a prolonged hospitalization on day 27. Ingested berries were analyzed along with those implicated in a previous geographically and temporally disparate outbreak (2). Both samples

contained alkaloids not present in "normal" berries. The first had a UV spectrum identical to chaconine/solanine, with a shortened HPLC column retention time. Two additional products eluted immediately after expected solanine retention but displayed non-chaconine/solanine UV spectra. *Conclusion:* We confirm that susumber berry poisoning can produce a variety of neurological and gastrointestinal effects seen in a prior outbreak (2). These may be mediated by solanaceous alkaloids present in the berries. *References:* 1. Morris S, Lee T. The toxicity and teratogenicity of Solanaceae glycoalkaloids, particularly those of the potato (*Solanum tuberosum*): A review. Food Technol Aust 1984; 36:118–124. 2. Thompson M, Thornton M, Verjee Z. Poisoning by susumber berries. J Toxicol Clin Toxicol 2003; 41:729.

47. *Amanita phalloides* Poisoning: A 5-Year Survey of the Czech Toxicological Information Centre

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Objective: To evaluate the severity of hepatic and kidney damage with the focus on their reversibility, and to analyse the prognostic factors following *Amanita phalloides* poisoning. *Methods:* Data concerning the clinical course of patients with *Amanita phalloides* poisoning confirmed by microscopic analysis reported to the Czech Toxicological Information Centre between 2000 and 2004 were analyzed. A variety of clinical and laboratory parameters was collected. Student's t-test, Fisher's test and the calculation of linear correlation coefficients were used for the statistical analysis. *Results:* Five out of the 33 patients were children and 29 were adults (the mean age 41 years). The mean interval from ingestion to the onset of gastrointestinal symptoms was 12 hours; the mean interval from ingestion to hospitalization was 27 hours. Therapy was based on multiple dose activated charcoal (82%), antidotes (benzylpenicillin 70%, N-acetylcysteine 3%), extracorporeal elimination methods (haemoperfusion 39%, forced diuresis 24%, haemodialysis 15%). Reported symptoms included vomiting (76%), diarrhoea (62%), abdominal cramping (22%), weakness (4%), hepatic failure (24%), and renal failure (18%). Two patients died on the fifth day after mushroom poisoning. Serum alanine aminotransferase (ALT) as well as serum aspartate aminotranferase (AST) levels peaked 2 to 6 days after mushroom consumption (the mean peak ALT level 47.96 microkat/l, the mean peak AST level 42.71 microkat/l). The prothrombin index (PI) decreased to a mean value of 52.4%. The mean minimum prothrombin index in adults who did not recover until discharge was significantly lower than in patients who recovered ($p=0.00$). The mean peak serum transaminases levels in adults who did not recover until discharge was significantly higher than in patients who recovered ($p < 0.04$ for ALT and $p < 0.10$ for AST). In 18 patients serum levels normalised until discharge; in 8 patients serum levels normalised up to 4.5 months (range 1 – 18 months) on average after discharge. One 69-year-old patient with a solitary kidney died due to persistent renal damage (serum creatinine 137 micromol/l) 19 months after discharge. Five patients were not interested in further follow-up. *Conclusion:* The recovery of the hepatic and kidney damage until discharge depended mostly on decrease of PI and increase of serum AST, ALT levels. Most of the patients (95%) who survived the acute stage recovered in a few months after discharge from a hospital. *Acknowledgement:* This study was supported by Research Project No. MSM 0021620807 of the Ministry of Education of the Czech Republic.

48. Isolation of Novel Neurotoxins from the Venom of the Australian Rough-scaled Snake (*Tropidechis Carinatus)*

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Background: T. carinatus is an Australian elapid snake whose venom possesses significant neurotoxic effects. These have been observed clinically and demonstrated *in vivo*. To date, specific neurotoxins have not been isolated from the venom. *Objectives*: To isolate and characterize neurotoxic components *T. carinatus* venom to better understand the clinical features of neurotoxicity from this species. *Methods:* Whole *T. carinatus* venom was separated into protein fractions utilizing size-exclusion liquid chromatography (LC), and C2/C18 reverse-phase LC. Purity and mass of isolated proteins was assessed by MALDI-mass spectrometry. At each separation phase, fractions were tested for neurotoxicity utilizing the indirectly-stimulated chick biventer cervicis nerve-muscle preparation (CBCNMP). Pre- or post-synaptic neurotoxicity were determined. N-terminal protein sequences of isolated toxins were determined by Edman degradation and compared to existing neurotoxins using a Blastp search of the Swiss-Prot/trEMBL database. *Results:* Size-exclusion LC produced two distinct fractions, Fraction-A containing proteins with mass around 43 kDa and Fraction-B containing proteins with masses 6–13 kDa. *Invitro* CBCNMP bioassay demonstrated Fraction-A having significant presynaptic neurotoxic activity and Fraction-B postsynaptic neurotoxicity. As presynaptic neurotoxins have not been previously isolated from the venom of *T. carinatus*, Fraction-A was characterized further. C2/C18 LC of Fraction-A revealed four major components (A.4, A.6, A.8, A.9). Bioassay of these revealed significant presynaptic neurotoxic activity in fraction-A.8, weak pre-synaptic neurotoxicity in fraction-A.9, and no neurotoxic activity in the remaining two fractions. Fraction-A.8 (13717 Da) showed sequence homology with the alpha-chain of the pre-synaptic Australian elapid neurotoxin, taipoxin from *Oxyuranus s. scutellatus*. This was named tropidexin-alpha. Fraction-A.4 (13370 Da) showed homology to non-toxic elapid phospholipase A2 enzymes and named tropidexin-beta. Fraction-A.6, 16264 Da, appeared to be glycosylated and was tentatively named tropidexin-gamma. The combined mass of these three proteins is consistent with the weight of protein initially collected in Fraction-A (43 kDa) suggesting that these three proteins are subunits of a trimeric toxin similar to other elapid presynaptic neurotoxins such as taipoxin. Monovalent tiger snake antivenom prevented, but did not reverse, neurotoxicity from whole venom and the isolated tropidexin alpha-chain. *Conclusion: T. carinatus* venom contains a trimeric presynaptic neurotoxin tropidexin similar to other elapid venoms and at least one postsynaptic neurotoxin that requires further isolation. This information may lead to a better understanding of the course of clinical envenoming by *T. carinatus*.

49. Treatment of a Potentially Fatal Dose of Methyl Salicylate Utilizing High Volume Fluid Administration

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Objective: To report an intentional ingestion of a potentially fatal dose of methyl salicylate and the use of large volume fluid administration with vasopressors to maintain adequate perfusion and to counter the insensible fluid losses. *Case Report:* A patient presented to the Emergency Department an hour after ingesting 60 mL of pure methyl salicylate (equivalent to 84 grams of salicylate). Initial symptoms were tinnitus and a respiratory rate of 38 per minute. A salicylate level at 1.5 hours post-ingestion was 87 mg/dL. Urinary alkalinization was instituted with a sodium bicarbonate infusion at 150 mL/h, and a renal consult for hemodialysis was obtained. At 2 hours post-ingestion, the patient seized and was intubated. Serum pH went from 7.47 at initial presentation to 7.18 at 3 hours post-ingestion, with a pCO_2 of 22%. Hydration fluid administration rate was increased to 1000 mL/h, and the bicarbonate infusion was increased to 500 mL/h. At five hours after presentation, the patients temperature rose to 102.2F, and she was started on vasopressors. Hemodialysis was started and the patient was dialyzed for 3 hours, and by 8 hours post-ingestion she had received 9 liters of IV fluids. A post-dialysis salicylate level was 26 mg/dL. The patient was more responsive, and the IV fluid rate was decreased to 250 mL/h. Intermittently, she required saline fluid boluses to maintain her blood pressure. In light of the large volume of fluid administration, close monitoring of the cardiovascular status was instituted by CVP placement, echocardiogram and meticulously monitoring the urine output. At 18 hours post-ingestion, the patient was alert and oriented, and was extubated. At 22 hours post-ingestion, the patient's vital signs had normalized, and the salicylate level was 18 mg/dL. She had received a total of more than 16 liters of intravenous hydration and urinary alkalinization fluid. Her CPK peaked at 4 hours post ingestion to 5948 U/L. The lowest serum sodium was 140 mEq/L at almost 24 hours after the ingestion. Throughout the hospital course, the patient's urine output remained adequate with no symptoms of fluid overload. *Conclusion:* Healthcare professionals caring for a salicylate-intoxicated patient should weigh the benefits and risks of large volume fluid administration to counter the insensible losses seen. More trials are needed to confirm the benefit of such large volume fluid administration before routine recommendations can be made. Close monitoring for the development of pulmonary edema secondary to salicylate-induced increased pulmonary tissue permeability and fluid overload must be exercised.

50. An Approach to the Diagnosis and Management of Acute Poisonings of Unknown Aetiologies in a Developing Country, Based on Experience with Arsenic and Strychnine Poisoning

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Objective: When dealing with an acute poisoning of unknown aetiology, poisons with a high inherent toxicity should be identified as soon as possible in order to prevent permanent organ damage. In a country with sparse resources, laboratories should at least be able to speedily identify these poisons, where determinable. The objective, therefore, was to compile a short list of poisons with high inherent toxicity. *Methods:* Two cases of near fatal arsenic poisoning, leading to permanent organ damage, were compared to 10 cases of strychnine poisoning, one of whom died on his way to hospital. Differences in mechanisms of action, clinical profiles, management and outcome of arsenic and strychnine poisonings were studied and compared. Using arsenic as a typical example, a short list of poisons with a high inherent toxicity were identified from a pool of approximately forty thousand acute poisoning exposures dealt with by the Tygerberg Poison Information Centre over a period of 20 years. *Results and Discussion:* Arsenic irreversibly affects mitochondrial enzymes, leading to permanent cell damage. It is, therefore, classified as a poison with a high inherent toxicity. Poisons with a high inherent toxicity are defined as those which cause irreversible or slowly reversible direct structural or functional tissue damage. Strychnine, on the other hand, reversibly blocks glycine receptors in the brain, causing transient central nervous system stimulation with seizure-like activities. It does not cause direct tissue damage and its toxic effects are completely reversible. Although strychnine is a potentially deadly poison, a patient will survive without permanent sequelae if given symptomatic and supportive treatment only. Strychnine is, therefore, classified as a poison with a low inherent toxicity. Other examples in this category include the opiates, benzodiazepines, and neurotoxic cobras. Using arsenic as a typical example, a short list of 15 poisons with high inherent toxicity is identified, and includes: carbon monoxide, cytotoxic snake bite, cyanide, digoxin, ethylene glycol, isoniazid, lithium, heavy metals, methanol, cyclopeptide mushrooms, organophosphates, paracetamol, paraquat, salicylates and theophylline. *Conclusion:* When dealing with a suspected or unknown poison, a priority should be to identify, or at least consider, poisons with a high inherent toxicity as soon as possible, so that timely antidotal or special decontamination procedures can be instituted to prevent permanent cell damage. Laboratories should be equipped to identify the above listed poisons rapidly, where determinable. Fortunately, the vast majority of potential poisons have a low inherent toxicity and patients will usually survive acute poisonings without permanent sequelae if they are given symptomatic and supportive care only.

51. Availability of Antidotes and Sufficiency of their Deposits in Greek Hospitals

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Background: The particular geographical disposition of Greece - number of isolated communities and occasionally inaccessible islands - sets the necessity for a promptly available stock of antidotes for use by the local health care units. *Objective:* To define the sufficient amount of antidotes to fulfil the local necessities, establish a feedback system of exchanging information and improve the existing system. *Method:* Of 125 local health-care units, 92 had records of availability of 21 antidotes which have been categorized in three groups based on their emergency use: 1st group: prompt (atropine, flumazenil, naloxone, sodium nitrite, sodium thiosulphate, methylene blue, protamine sulphate); 2nd: in the first 12 hours (biperiden, Viper Venom Antiserum, dimercaprol, bentonite, calcium edetate, pralidoxime,

desferioxamine, Digoxin Immune Fab, dicobalt edetate, silibinin, N-acetylcysteine, physostigmine; and 3rd: in the first 24 hours (vitamin K1, protamine sulphate). The hospitals have also been divided into three groups according to their geographical location: A) urban areas, B) difficult access areas, and C) remaining areas. *Results:* The average sufficiency of antidotes of the 1st group was found to be 48.87% in A, 45.71% in B and 45.18% in C areas; of the 2nd group 32.45% in A, 27.5% in B and 29.25% in C; whereas of the 3rd group it was 50% in A, 55% in B and 50% in C areas respectively. It is interesting to underline the difference in sufficiency of sodium nitrite (55.7%) in contrast with sodium thiosulphate (18.6%) despite the fact that they are administered together. Furthermore, the low percentage of adequacy of antidotes such as Digoxin Immune Fab (2.1%), Viper Venom Antiserum (14.4%) and pralidoxime (5.2%), which are crucial for the treatment of the respective poisonings, has to be emphasized. *Conclusions:* Taking into account that many areas are not easily accessible either because of their geographical position or due to difficult weather conditions, the deficiency of antidotes may prove fatal. The data collected indicate that the supplying of antidotes is not based on their necessity for therapies, but mainly on the frequency of incidents. This is why the operation of a Poison Information Centre, as well as its main function, is also important for the surveillance and the satisfactory availability of antidotes for the local health services.

52. Antidote Administration in Cases of Poison-related Fatality

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Objective: Antidote indications, timing, and compliance are critical to the management of many poisonings. However, the timing and compliance with antidote administration in fatal poisonings is not well described. We aimed to determine whether antidotes were administered in cases of poison-related fatality in which initial cardiac arrest occurred after hospital arrival. *Methods:* We studied consecutive cases resulting in fatality referred to a regional poison control center over the seven-year period from 2000 to 2006. Data were collected prospectively as part of standard patient care and analyzed retrospectively. Comprehensive clinical data including patient demographics, laboratory information, poisoning information, timing of antidote administration, and free text clinical details were reviewed using an electronic database. For a large number of cases, medical examiner data had been entered into the database and this was used to help determine cause of death. Timing of initial cardiac arrest, defined as loss of pulse, was recorded as either pre-hospital or in-hospital. Poison centre recommendations for antidote administration and compliance with recommendations were recorded. Simple descriptive statistics were used to analyze the study population. IRB approval was obtained at the study institution. *Results:* 447 deaths were reviewed during the study period, of which 266 were excluded (96 pre-hospital cardiac arrests, 66 were unlikely poison-related, 59 were unknown if poison-related, 30 veterinary cases, 15 coding errors), yielding 181 poison-related fatalities (52% males, mean age 44.4) with initial cardiac arrest after hospital arrival. Of these, antidotes were not recommended in 65 (36%) patients and recommendations were unclear in 2 (1%) patients. Antidotes were recommended in 114 (64%) patients, of whom 14 (12%) had already received the antidote prior to calling the poison centre. Of the remaining 100 cases, 91 (91%) had the antidote administered and 9 (9%) patients were not given the recommended antidote. Antidotes not given in 9 fatal cases included the following: fomepizole (2), alkalinization (2), high-dose insulin euglycemia (2), digoxin-specific Fab (1), N-acetylcysteine (1), and hyperbaric oxygen (1). *Conclusions:* In this large cohort of reported poison-related fatalities, the majority of patients received antidotes. Non-compliance with recommendations for antidote administration was rare. Among cases involving non-compliance with antidote recommendations, potentially life-saving treatments and interventions were not administered.

53. Comparison of Charcoal Hemoperfusion and Hemodialysis in Treatment of Severe Carbamazepine Intoxications

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Objective: Effective drug elimination in severe carbamazepine toxicity is expected to decrease morbidity and mortality. Management of carbamazepine overdoses utilizes gut clearance techniques and multiple doses of activated charcoal. Unfortunately, its efficacy is reduced when given more than 1 hour after ingestion. Because of absorption capacity of activated charcoal for carbamazepine, many authors recommend charcoal hemoperfusion (HP) for enhanced clearance, but its clinical benefit is often insufficient because of a moderately large volume of distribution, reequilibration after detoxification and rebound of drug level in plasma. Furthermore, it is uncertain if the highly protein bound carbamazepine is effectively removed by hemodialysis (HD). Recently there have been reports of successful treatment with both conventional, albumin enhanced and high-flux HD. Therefore we decided to examine the clinical and toxicometric efficacy in severe carbamazepine intoxication. *Methods:* Eight patients with severe carbamazepine intoxication underwent HP on charcoal hemosorbent (350 ml) with blood flow 100 ml/min for 1 hour. Four patients were treated by HD (Gambro, S 1.4 m2, dialysis fluid flow rate 500 ml/min 6–12 hours). Two patients after HP underwent HD. Additionally, we performed experimental plasmadialysis on plasma, obtained from plasmapheresis. Previously carbamazepine 1 mg/ml was added to the plasma. The serum concentration carbamazepine was measured by fluorescent polarizing immunoassay (TDx-FLx, Abbott Laboratories). *Results:* Carbamazepine clearance in experimental plasmadialysis was 93.9+14.0 ml/min. The plasma level of carbamazepine 1 hour after the procedure decreased to 28%. A similar clearance (96.9+1.0 ml/min) was obtained for charcoal HP. Carbamazepine concentration before HP was 20.4+4.5 mcg/ml and decreased to 16% after HP. In five of eight patients there was clinical improvement, but three remained comatose. These latter three patients underwent HD. Two of them were successfully weaned from ventilator support and fully recovered. One patient died, despite a dramatically decreased level of carbamazepine from 40 to 9 mcg/ml. Two patients, initially treated only by HD, recovered consciousness. Their carbamazepine level before HD was very high – 36.7 and 31.5 mcg/ml and decreased to 43.0 and 32.5%, respectively. Carbamazepine clearance obtained in HD was 50.4 ml/min. *Conclusion:* HD may be an effective component of decontaminating measures in severe carbamazepine intoxications. It seems to be promising to investigate albumin enhanced and high-flux versus conventional HD.

54. Use of Hemodialysis (HD) and Charcoal Hemoperfusion (HP) for Toxin Removal: A 21-year American Experience

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Objective: We examined trends and indications for use of HD and HP in treatment of poisoning from 1985–2005 as recorded by the Toxic Exposure Surveillance System (TESS). *Methods:* The TESS database was queried for single-substance exposures. Combination exposures (e.g., salicylate plus an opioid) were assumed to have been dialyzed for the known dialyzable toxin (e.g., salicylate). To examine the use of HD for less accepted indications, we excluded cases with substances having accepted indications for HD, and cases that had clinical effects which might explain the indications for HD unrelated to the exposure. *Results:* Total number of cases reported to have received HD or HP per million exposures were: 1985–1989 (HD 205, HP 80), 1990–1995 (HD 264, HP 45), 1996–2000 (HD 320, HP 14), and 2001–2005 (HD 421, HP 9). The most common reasons for HD were ethylene glycol (2,950), lithium (2,563), salicylate (1,493), methanol (860), and aminophylline/theophylline (549). Since 1989, acetaminophen was the sixth most common exposure in cases receiving HD, and in 2001 it became the fifth most common exposure, replacing aminophylline/theophylline. The most common reasons for HP were aminophylline/theophylline (385), long-acting barbiturates (57), carbamazepine (49), acetaminophen (47), and salicylate (30). The leading indication for HP was aminophylline/theophylline until the year 2000, when its prevalence as a cause of poisoning began to drop. In 2005, there were no reported cases of HP performed for aminophylline/theophylline. Substances dialyzed for less accepted indications were acetaminophen (392), cardiac glycosides (168), unknown drugs (153), long-acting barbiturates (138), and ethanol (136). *Conclusion:* The number of cases receiving HP has decreased over the past two decades, while those receiving HD has increased. The consistent prevalence of acetaminophen exposures treated with HD may be explained by documentation bias or failure to recognize renal toxicity associated with severe acetaminophen poisoning. The decreased use of HP and HD for aminophylline/theophylline may be due to decreased availability of HP or more likely, decreased clinical use of this drug. Cardiac glycosides were a common reason for HD among exposures with less accepted indications. It is unclear if this represents poorly documented renal dysfunction as a cause for cardiac glycoside toxicity or a misguided attempt to remove the toxin. Further evaluation of exposures receiving HD for less accepted indications may illuminate unrecognized uses within the US.

55. Antidote Usage in California During 2004

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Objective: To analyze cases reported to a statewide system, the California Poison Control System (CPCS), in which select antidotes were administered to poisoned patients. *Methods:* A cross-sectional study of cases reported to the CPCS involving the administration of selected antidotes was conducted over a 12-month period (January 1 to December 31, 2004). Antidotes were selected based on a range of utilization rates and the presence of specific indications or contraindications for their use. CPCS charts were identified in which patients had received one of the following: naloxone, pyridoxine, fomepizole, deferoxamine, methylene blue, flumazenil, glucagon, digoxin-specific antibodies, or octreotide. These charts were evaluated for demographic and clinical data including age, gender, co-ingestants, symptoms, reason for exposure, treatment, disposition, and outcome. Cases were also identified by the frequency of CPCS recommendations for their use. *Results:* During this 12-month period, CPCS charted approximately 222,660 human exposure calls. A total of 1114 CPCS charts were reviewed in this study. Fifty-one percent of these cases (567) ingested multiple substances. While the majority of exposures were intentional (75%), the methylene blue and digoxin-specific antibody groups involved predominately unintentional exposures, 100% and 79.5% of cases, respectively. More females (56%) than males received an antidote. Ages of patients ranged from 0.2 to 94 years of age. The frequencies of antidote administration were: naloxone (741), flumazenil (123), glucagon (75), pyridoxine (53), fomepizole (51), digoxin-specific antibodies (39), octreotide (15), deferoxamine (9), and methylene blue (8). The CPCS recommended their use in 24% (267) of cases. Frequencies of antidotes administered without CPCS advice were: naloxone (91%), flumazenil (86%), deferoxamine (44%), digoxin-specific antibodies (33%), methylene blue (25%), pyridoxine (21%), fomepizole (18%), glucagon (16%), and octreotide (13%). Eleven deaths occurred, five in the naloxone group, three in the digoxin-specific antibody group, and one in each of the glucagon, fomepizole, and deferoxamine groups. *Conclusion:* A substantial proportion of cases reported to the CPCS were administered antidotes without the recommendations of the CPCS. It will be important to assess why antidotes were administered to poisoned patients without poison center advice and whether they are at higher risk for inappropriate use leading to unnecessary complications and expense. *References:* Kearney TK. Therapeutic Drugs and Antidotes. In: Olson KR, ed. Poisoning and Drug Overdose. 4th ed. New York: McGraw-Hill, 2004:404–509.

56. Acetylcysteine for Early Presenting Overdoses of Acetaminophen Combination Products

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Objective: Acetaminophen products with other active ingredients that decrease GI motility may alter absorption kinetics of acetaminophen which may impact on interpretation of acetaminophen levels and duration of acetylcysteine therapy. The purpose of this study was to evaluate acetaminophen levels, duration of intravenous acetylcysteine therapy and hepatotoxicity following overdoses of acetaminophen combination products in early presenters and determine risk factors for poor outcomes. *Methods:* A retrospective chart review from January 1, 2005 through July 31, 2006 of a regional poison center's cases involving acute overdoses of acetaminophen combination products presenting at <10 hours was conducted. Inclusion criteria included toxic acetaminophen concentrations on the Rumack-Matthew nomogram and treatment with intravenous acetylcysteine. Severe hepatotoxicity was defined as AST &/or ALT > 1000 U/L. Acetylcysteine administration for more than 21 hours was considered extended

therapy. *Results:* Of 28 cases meeting inclusion criteria, 21 involved acetaminophen/diphenhydramine. The median age was 34 years (range, 15 to 74) with 57% female. All but two cases were suicide attempts. Time of presentation ranged from 0.5 to 9 hours (mean, 3.3 ± 2.3). High initial acetaminophen levels (293–793 µg/mL) occurred in seven cases; three other patients had subsequent levels higher than the initial 4–5 hour level. Severe hepatotoxicity occurred in four (14.3%) cases, three of which had markedly elevated repeat acetaminophen levels. In one case, the 4.5 hour post-ingestion level of 194 µg/mL rose to 351 µg/mL at 14 hours, followed by levels of 279, 213 and 13 µg/mL at 28, 42 & 79 hours, respectively. In the second case, a 4–5 hour level of 697 µg/mL was followed by levels of 498, 141, and 4 µg/mL at 10, 21 and 46 hours, respectively. The third patient had 5.5 and 28 hour levels of 293 µg/mL and 112 µg/mL, respectively, and required a liver transplant. The fourth patient had 6 and 8 hour levels of 162 and 115 µg/mL, respectively. Extended acetylcysteine therapy was administered to eight (28.6%) patients; four of these patients had markedly elevated initial acetaminophen levels, and five had persistently high subsequent levels measured at 21–48 hours. Total duration of extended therapy ranged from 26–144 hours; however, therapy was stopped and re-instituted in some patients. *Conclusions:* Markedly elevated initial acetaminophen levels, rising and/or persistently elevated acetaminophen levels are risk factors for hepatotoxicity associated with acetaminophen combination products that affect GI motility. Therefore, current dosing guidelines for intravenous acetylcysteine may be ineffective in some early presenting acetaminophen combination product overdoses.

57. Patterns of Whole Bowel Irrigation use in Single Drug Ingestions

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Objective: To describe the patterns of Whole Bowel Irrigation (WBI) use in poisoned patients with single drug ingestions referred to the California Poison Control System (CPCS) from the year 2000 to 2005. *Methods:* This was a retrospective review of all cases of single drug ingestions referred to the CPCS in which WBI was recommended by poison center staff or performed by the consulting physician, as recorded in the Visual Dot Lab (VDL) database. We obtained approval from the CPCS research committee and the University of California, San Francisco committee on human research. *Results:* From 2000 to 2005 there were a total of 1,718 single drug ingestions in which WBI was coded as performed. There was a trend towards increasing WBI use that peaked in 2003 and then declined over the duration of the study period. Figure 1 illustrates WBI use classified by drug type. Drugs of abuse accounted for the greatest percentage of WBI usage (27%), followed by valproic acid (13%) lithium (13%), aspirin (10%), iron (9%), calcium channel blockers (7%), bupropion (7%), and venlafaxine (2%). There was a trend toward increased WBI use in cases involving drugs of abuse and aspirin. Figure 2 illustrates WBI use classified by indication. Extended release drugs accounted for the greatest percentage of WBI usage (30%), followed by body stuffers (27%), substance not binding to charcoal (22%) and others (12%). There was a trend toward increased WBI use in cases involving body stuffers. Other indications for which WBI was performed included ingestions of foreign bodies, batteries and medicinal patches among others. *Conclusions:* The use of WBI as a decontamination method may be increasing over time. In our patient population WBI was most commonly used in patients having ingested illicit drugs and in those ingesting extended release preparations.

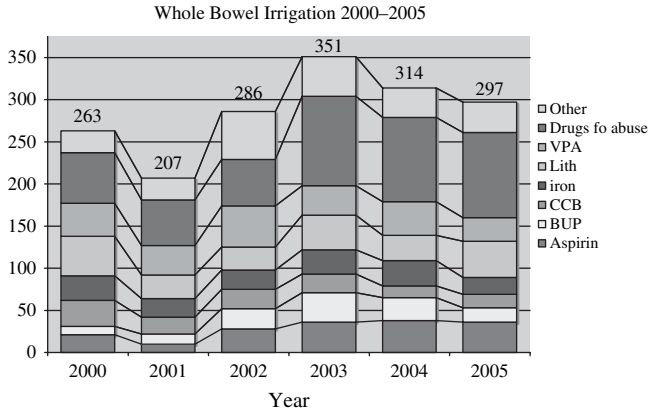

Fig. 1. Drugs of abuse.

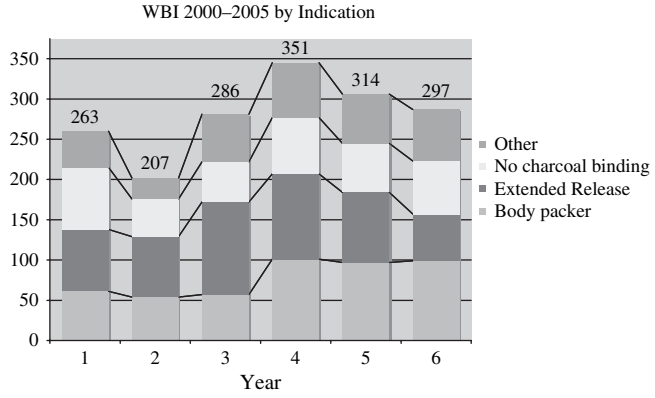

Fig. 2.

58. The Relationship between Naloxone Dose in the Treatment of a Non-fatal Heroin Overdose

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Objectives: To examine the relationship between patient variables and variation in naloxone dose (from standard dose of 2 mg IV) administered in the hospital management of heroin overdose. *Methods:* A retrospective analysis of 185 patients' records of non-fatal heroin overdose cases collected in the University hospital. The main outcome measure was the dose of intravenous naloxone required to increase the level of consciousness and the respiratory rate in patients presenting with suspected heroin overdose. The patient variables influencing the dose that were recorded included: age, sex, initial patient presentation and reported concurrent alcohol use. *Results:* Patients with higher levels of consciousness and respiratory rates on arrival in the emergency department were more likely to receive a less than standard dose of naloxone. Conversely, patients with lower level of consciousness and low respiratory rates received greater than standard doses of naloxone for resuscitation. Patients who received greater than the standard dose of naloxone were 95%CI times more likely to have been under the influence of alcohol when consuming the heroin that resulted in overdose. *Conclusions:* The concurrent use of alcohol with heroin resulted in the use of greater than standard doses of naloxone in resuscitating overdose patients. It is possible that the higher dose of naloxone is required to reverse the combined effects of alcohol and heroin. There was also a link between initial patient presentation and the dose of naloxone required for resuscitation. In light of these findings, it would appear that initial patient presentation and evidence of alcohol use might be useful guides in providing the most effective dose of naloxone in the Emergency Department. *Reference:* Cantwell K, Dietze P, Flander L. Resuscitation 2005; 65:315–9.

59. Rhabdomyolysis and Acute Renal Failure in a Carbon Monoxide Poisoning

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Introduction: Carbon monoxide (CO) is the leading cause of accidental poisoning in our country and worldwide. CO causes tissue hypoxia and produces various systemic and neurological complications. Rhabdomyolysis is one of the major complications of acute carbon monoxide poisoning. Myoglobin has a CO affinity constant approximately eight times lower than that of haemoglobin. The combination of this affinity and the lower dissociation constant for CO favors retention of CO in muscular tissue, and thus a considerable amount of CO can be potentially stored in the skeletal muscle (1). Rhabdomyolysis can also be due to prolonged coma status or seizures. *Case Report:* We present the case of a young patient transferred to our department 18 hours after accidental CO exposure. Initial treatment was carried out in another hospital where the medical record describes a patient with GCS8, with dyspnoea, tachypnoea and oligoanuria. The status improved under oxygen administration, the patient became conscious, but amnesic. The oligoanuria persisted, the tests of azotate retention raised and the patient was transferred to our department. On admittance: severe general status, conscious but confused, bradylalia, spontaneous and normal breathing, normal lung auscultation, BP 120/90 mmHg, 110 beats/min, sinus rhythm, oligoanuria. Neurological examination diagnosed hypoxic encephalopathy and proximal myopathy. Laboratory tests lead to a diagnosis of acute renal failure with anuria, hepatic and pancreatic dysfunction, and secondary anemia. These show elevated values for CK, CK-Mb, LDH, liver and pancreatic enzymes, BUN and creatinine. The patient received supportive care and haemodialysis. Haemodialysis was performed over 5 days and then the patient became polyuric and the BUN and creatinine began to decrease. All system and organ dysfunction improved. He was discharged after 20 days with normal mental status, without neurological sequelae, with normal renal, liver and pancreas function. *Conclusion:* In this case, rhabdomyolysis and consequent acute renal failure was due to the direct myotoxic effect of CO. The patient was not in a deep coma and his neurological status improved shortly after he began the oxygen therapy. There was no history of seizures. No evidence of muscle swelling was found. The muscle enzymes rose soon after the exposure. Renal failure due to myoglobin effects developed rapidly. In CO poisoning it is important to monitor the muscle enzyme levels in order to prevent myoglobinuric acute renal failure. Most cases of CO poisoning may be associated with rhabdomyolysis. Its recognition and diagnosis, therefore, depend on a high index of clinical suspicion. *Reference:* 1. Finley J, VanBeek A, Glover JL. Myonecrosis complicating carbon monoxide poisoning. J Trauma 1977; 17:536–540.

60. Criminal Clozapine Poisoning

Luzhnikov EA[1], Ilyashenko KK[1], Ostapenko YuN[3], Sliundin DG[2], Livanov AS[2], Ermokhina TV[1], Zimina LN[1]. *[1]Sklifosovsky Clinical and Research Institute for Emergency Medicine*; *[2]Moscow City Clinical Hospital No 33*; *[3]Research and Applied Toxicology Center of Federal Agency for Health and Social Development*, *Moscow, Russia.*

Objective: For recent years criminal poisoning with clozapine in Moscow has come top, replacing clonidine which prevailed before. Hence, the objective of this study was to investigate clinical symptoms and treatment of criminal poisoning with clozapine. *Methods:* The study included 611 patients with criminal clozapine poisoning aged from 16 to 55 years. They had consumed various drinks with persons little known to them and within 5–15 minutes developed a sudden weakness with loss of consciousness. All of them were robbed. The time from toxic substance exposure to hospital admission varied from 1.5 to 3 hours. Forensic chemical and organ morphology investigations were made in 22 men aged 30–35 years who died at a pre-hospital stage from criminal clozapine poisoning. Clozapine was identified in the urine and in the organs of the dead, ethanol was found in the blood and urine in concentrations corresponding to

intoxication of moderate to severe degree. *Results:* On patients' admission the level of consciousness scored 7.9 ± 0.6 on the Glasgow Coma Scale with periods of non-pronounced psychomotor agitation similar to neuroleptic syndrome. Patients also showed marked dysarthria, decrease in muscle tone, prolonged miosis for 4–6 hours and skin pallor. In 60% of cases we observed moderately pronounced hypersalivation. Tachycardia with normal arterial blood pressure was a typical symptom. Nine patients (1.5%) showed severe respiratory impairment that required mechanical lung ventilation for 3–8 hours. Clozapine urine concentration averaged 4.7±3.1 mcg/ml, and ethanol blood and urine concentrations 2.2±1.4 g/l and 3.0±1.5 g/l respectively. Consciousness was restored within 8–16 hours. The process was accompanied by psychomotor agitation and consequent transition to asthenia persisting for 14–22 hours. Detoxification therapy included forced diuresis, gastric lavage followed by activated charcoal and laxatives. 2–3 mg intravenous aminostigmine or galantamine (Nivalin) were used as antidotes and were followed by rapid (within 15–20 minutes) restoration of consciousness. In 21% of cases a repeated administration of antidote was required. The length of hospital stay was 36±4.3 hours. All patients recovered. The most prominent postmortem organ abnormalities were found in the liver as predominant droplet, both focal and diffuse, fatty hepatocytes degeneration. *Conclusion:* Criminal clozapine poisoning has been a topical problem for Moscow region and characterized by a milder course compared to suicidal cases, hence the main treatment approach includes antidote therapy with Nivalin. However, the hepatocyte damage means that liver protective therapy is needed in patients with severe poisoning.

61. Driving with Excess Alcohol: The Forensic Pharmacology of Legal Defences in 100 Cases

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Introduction: In the United Kingdom the maximal permitted alcohol concentration for driving is 80 milligrams of alcohol per 100 ml blood, 35 micrograms alcohol per 100 ml breath or 107 milligrams alcohol per 100 ml urine. On average 3,000 people a year are killed or seriously injured in the UK in drink-drive collisions. Penalties are severe, and those accused are often anxious to avoid them, either by acquittal or by putting forward 'special reasons' why they should not be disqualified from driving (1,2). *Objective:* We wished to see what defences had been proposed in drink-driving cases referred to us, and what forensic pharmacology was invoked. *Method:* We examined retrospectively a consecutive series of 100 drink-driving cases referred by lawyers to two clinical pharmacologists. *Results:* Of 100 cases reviewed, 45 cases related to co-ingestion of other substances, of which 36 were drugs potentially altering alcohol metabolism; two involved mouthwashes containing alcohol; and seven concerned inhalers and solvent inhalation interfering with breath alcohol analysis. Thirty-six cases required pharmacokinetic calculations with reference to the pre-absorptive state when driving (2); drinking after the driving offense has occurred (the "hip-flask defence") (12); further alcohol added to the drink without the drinker's knowledge (the "lacing defence") (11); or being in charge of a vehicle with no intention of driving, sleeping off the effects of the alcohol and only intending to drive a number of hours later (11). Nine cases related to disease processes either in the provision of a sample or the disease altering alcohol metabolism such as liver disease; three cases relating to post mortem alcohol concentration and its interpretation; two cases relating to the alcohol concentration being so high that defendant would have been in coma; in two cases, blood and breath readings being inconsistent; and there were three miscellaneous cases: sample deterioration, discrepancy in breath reading, and auto-production of alcohol. *Summary:* The public's perception on the ingestion and metabolism of alcohol is often erroneous. The forensic pharmacologist can help to provide a useful scientific perspective in the evaluation of drink drive cases. *References:* 1. Ferner RE. Chapter 7 Ethanol. In: Forensic pharmacology: medicines, mayhem, and malpractice. Oxford, England: Oxford University Press, 1996:113–139. 2. Jones AW. Top ten defence challenges among drivers in Sweden. Medicine, Science and the Law 1991; 21:229–238.

62. Reliability of Toxicological Analysis in Acute Poisonings In Childhood

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Objective: To study the reliability of toxicological analysis in acute poisonings in childhood in the emergency setting and to verify the usefulness of these methods in some difficult to diagnose cases. *Methods:* We have analyzed toxicological tests performed in Children Toxicological Department of the Emergency Medicine Institute 'Pirogov' for 2004 and evaluated the role of toxicological analysis in the diagnostic-treatment process in acute poisonings in childhood. We present two case reports of children admitted to the hospital in which the toxicological analysis turned out to be crucial for diagnosing severe acute poisoning. *Results:* A total of 1,040 toxicological examinations on 525 biological materials (2 analyses per sample on average) have been performed in 2004. In 237 of them quantitative methods were used and in 803 - qualitative methods were used. Analysis of the structure of toxicological analyses for 2004 showed that in 70% of the tests various medicinal products are detected (19% - sedatives/neuroleptics; 10% - cardiovascular), in 8% - narcotics and in 22% ethyl alcohol are detected. *Case Report: 1*. Three children for a period of two months (when there was an epidemiological outbreak of viral encephalitis in the country) were admitted to the hospital in a comatose condition with convulsions. The express toxicological analysis detected the presence of glibenclamide and a severe poisoning with oral antidiabetics has been diagnosed. Owing to the performed toxicological test appropriate treatment with glucose substitution was started immediately and the children were discharged healthy without any sequelae. *Case Report 2:* A 13-month-old baby was admitted to the antishock room with severe pulmonary insufficiency and bradypnoea (3 breaths/minute) of unknown origin. On admission the child was conscious but with severe bradypnoea, cyanotic and with myotic pupils. Various examinations were done (including brain CT) and all of them were negative. The condition of the patient did not approve despite the oxygen treatment. At that point a toxicological exam was done and it turned out to be positive for heroin. Antidote treatment was started and the child improved within several minutes and was discharged healthy after a one day hospital stay. *Conclusion:* The presented case reports confirm the important role of timely toxic-chemical analyses in children, particularly in cases of uncertain diagnosis, when application of antidotes is discussed, or in cases in which elimination therapy is taken in consideration. Thus, we recommend the performance of toxicological analysis in all cases of unclear diagnosis in childhood even in the absence of history for poisoning.

63. Emergency Toxicology Laboratory Service - Experience of Greek Poison Information Service (PIC)

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Objective: To present part of the function of the Greek PIC's laboratory. Many acute poisonings need clinical toxicology laboratory tests for diagnosis and/or for the proper treatment of patients. Since 1993 our PIC has produced some serum toxicology tests to provide emergency clinical toxicology services (24-hour availability), that could influence immediate patient management, not only in the Emergency Department (ED) of our hospital, but also in other hospitals around Athens. The PIC also provides therapeutic drug monitoring (TDM) services. *Methods:* PIC determines serum levels of acetaminophen, digoxin, benzodiazepines, tricyclic antidepressants, valproic acid, carbamazepine, phenytoin, phenobarbital, ethosuximide, netilmycin, amikacin, tobramycin, gentamycin, and vancomycin by Fluorescence Polarization Immunoassay Technology. From 2000 to 2006 the laboratory of pharmacokinetics performed 18,472 screenings in the serum of patients treated in our hospital or other general hospitals in Athens. Toxicological determinations were only available for diagnostic and treatment purposes in ED on an urgent basis. Routine TDM services were provided for pediatric patients, especially neonates, and for the intensive care unit of our hospital. Additionally, advice is offered to other hospitals, which have the capability of providing this service themselves. *Results:* 18,472 screening tests were performed during the last seven years by the Greek PIC, either as routine TDM service or for emergency purposes. Determination of carbamazepine is responsible for 6.51% of tests, valproic acid 19.02%, phenytoin 3.048%, phenobarbital 5.42%, ethosuximide 0.08%, amikacine 12.97%, tobramycine 7.46%, gentamycin 5.33%, netilmycin 15.68%, digoxin 2.17%, acetaminophen 2.84%, benzodiazepines 0.70%, tricyclic antidepressants 0.7%, 42.34% of acetaminophen, and 58.40% of benzodiazepines assays were performed for internal patients, 56.65% and 20.35%, respectively, concerned patients treated in other hospitals of Athens. *Conclusion:* Emergency toxicology services should offer 24-hour availability, especially for suspected poisonings with acetaminophen, salicylates, digoxin, lithium, iron, methanol and drugs of abuse, when treatment is dependent on the serum level of the drug. The cost of maintaining such a service, even for a large hospital, is very high. It could be mediated with the establishment of a regional toxicology service. More complex methods (chromatography, spectrophotometry) or detection of heavy metals could be provided on a less urgent basis from a specific toxicology laboratory. The PIC's laboratory could especially help smaller general hospitals, but the lack of staff to provide monitoring in an emergency all around the clock restricts this goal. Improvements are needed to perform more assays including drugs of abuse and also some additional tests (paraquat, amatoxine screening test) in order that more requests are satisfied.

64. Total Organic Carbon (TOC) in Parenteral Solutions Currently used in Brazil

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Objective: Human contamination due to the leaching of plasticizers used in PVC bags in parenteral solutions, specially di-(2-ethylhexyl)phthalate (DEHP) is well know in medical hospital procedures (1–4). Health risks associated to DEHP exposure like hepatotoxicity, endocrine disruption and reproductive toxicity has been addressed in recent literature. To evaluate the amount of exogenous organic carbon compounds in parenteral solutions used in Brazil, TOC analysis was used as a rapid and reliable screening tool. *Methods:* From a total of 150 low density polyethylene (LDPE) and PVC bags containing water for injection and cristalloide parenteral solution used in the University's Clinical Hospital (UNICAMP), 75 bags were analyzed for TOC by high temperature combustion followed by gas chromatography coupled mass spectroscopy (GC/MS) for confirmatory qualitative analysis. Chromatographic determinations were used for DEHP and possible metabolites in 2 samples with TOC values above 25 mgC/L. *Results:* TOC levels varied from 0.53 up to 54.4 mgC/L. Higher TOC values were obtained for PVC bags, whereas LDPE showed consistent lower values, independent of the fluid type held. Small volume containers presented higher TOC values most likely due to the area/volume ratio. GC/MS analysis showed the presence of 2-ethylhexanol, cyclohexanone and phthalates. *Conclusion:* Despite the fact that there are no TOC guidelines for parenteral solutions in Brazil, both US and European Pharmacopeia establish the maximum of 0.5 mgC/L of TOC in water for parenteral use. Values above 0.5 mgC/L are likely to be due to leaching of sample walls as well as the printing ink used in the PVC bags. Recent work found plasticizers contamination in PVC bags from Australia, Europe and North America (5). Despite the fact that DEHP toxicity is not established, the tolerable daily intake (TDI) recommended by the European Union is 20–48 g/kg/day. Quantitative analysis of these plasticizers is currently under investigation. *References:* 1. Latini G. Monitoring phthalate exposure in humans. Clinica Chimica Acta 2005; 361:20–29. 2. Koo HJ, Lee BM. Human monitoring of phthalates and risk assessment. J Toxicol Environ Health A 2005; 68:1379–92. 3. Koch HM, Bolt HM, Peuss R. Intravenous exposure to di(2-ethylhexyl) phtalate (DEHP): metabolites of DEHP in urine after voluntary platelet donation. Arch Toxicol 2005; 79:689–93. 4. Duty SM, Silva MJ, Barr DB, et al. Phthalate Exposure and Human Semen Parameters. Epidemiology 2003; 14:269–77. 5. Story DA, Leeder J, Cullis P, Bellomo R. Biologically active contaminants of intravenous saline in PVC packaging: Australasian, European, and North American samples. Anaesth Intensive Care 2005; 33:78–81.

65. Evaluation of a Urinary Acetaminophen (APAP) Point-of-care Test (POCT)

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Objective: Investigate the performance of the qualitative APAP POCT marketed by BIOSITE. *Hypothesis:* An APAP POCT will reliably detect a recent APAP ingestion. *Methods:* Unblinded volunteer experimental trial. *Setting:* Hospital Based Clinical Research Center. IRB approval and informed consent obtained. *Subjects:* Five healthy male volunteers. Following an APAP 37.5 mg/kg dose serial samples were collected at established times over a 24 hour period. Ten urine samples were collected from each volunteer. *Results:* Gold standard = urinary threshold of 5mg/l. POCT had a sensitivity = 100%, specificity = 87.5%, positive predictive value = 97.7% and a negative predictive value = 100%. The BIOSITE POCT identified several specimens as positive

when the [APAP] ranged from 3–5 mg/L. *Conclusions:* A negative BIOSITE urinary APAP POCT can reliably exclude recent, large ingestions of APAP. The limit of detection of the POCT suggests that large (greater or equal to 37.5 mg/kg) ingestions within the previous 24 hours will be detected. The clinical utility of this POCT requires further testing in an overdose population.

66. Gas Chromatographic - Mass Spectrometric Method for Quantitative Determination of Methadone and Methadone Metabolite 2-Ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in Urine Samples

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Objective: A validated method for determination of methadone and methadone metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in urine from patients undergoing treatment for heroin addiction is presented. *Methods:* Methadone is a potent analgesic and sedative. It is widely used in the treatment of heroin addiction and is often encountered in forensic specimens. Quantitative determination by gas chromatography with mass spectrometry detection (GC-MS) was performed. Midazolam has been used as an internal standard. *Results:* In electron impact (EI) gas chromatography/mass spectrometry (GC/MS) mode, methadone produces predominantly a m/z 72 ion and methadone metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) produces predominantly a m/z 276 ion. Different amounts of EDDP were detected by GC-MS during confirmation analysis. We observed EDDP concentration in urine samples from 13.8 microg/l to 45 microg/l and the methadone concentration from 44.5 microg/l at 53 microg/l for one case. We obtained results from 10 patients in treatment for heroin addiction at different times. *Conclusion:* Measuring levels of methadone and methadone metabolite 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) in the urine in microg/l is helpful in determining how much of the medication is eliminating from the patient's system. Urinary levels are interpreted in the context of the patient's clinical presentation.

67. Comparison of Psychological Profiles Between Intentional and Accidental Opioid Overdose Patients in Mashhad, Iran

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Background: Intentional and accidental opioid poisonings are common in northeast Iran (1,2). However, the psychological profiles of these patients has not been previously studied in detail. The psychological profiles of intentional and accidental opioid overdose patients hospitalized in the Toxicology Ward of our centre were therefore investigated. *Methods:* All cases with intentional and accidental opium overdose were studied prospectively between March 2006 and October 2006. As a second control group, cyclic antidepressant intentional overdose patients were also interviewed by a Psychiatrist (KT). All patients were visited at the last day of hospital stay when intoxication was at its lowest. SCL-90 test, which has previously been validated for a Persian population, was used (3). Analysis of variance (ANOVA) was applied for statistical analysis. *Results:* Overall 55 overdose cases were interviewed (20 opium intentional, 15 opium accidental, and 20 cyclic intentional). The differences in depression (P = 0.004), anxiety (P = 0.044) and other features (0.020) were significantly different from each other (see table). Opioid intentional overdose were significantly different from opioid accidental overdoses in obsession (P = 0.043), depression axis (P = 0.016), anxiety (0.031), paranoia (P = 0.039), and others (P = 0.027). Opium accidental overdose and cyclic intentional overdose were significantly different in depression (P = 0.001), Anxiety (0.022) and other psychiatric disorders (P = 0.007). Opium Intentional Overdose and cyclic intentional overdose were not different in any axes. *Conclusions:* Patients with intentional opium overdose are psychologically different from those with accidental overdose. This difference is significant in terms of obsession, depression, anxiety, paranoia and others using a validated SCL-90 test. As expected opioid and cyclic antidepressant intentional overdoses were not different psychologically. Cases of intentional opium overdose should be psychologically evaluated and managed differently from accidental opium overdose. *References:* 1. Afshari R, Majdzadeh R, Balali-Mood M. Pattern of acute poisoning in Mashhad, Iran 1993–2000. J Toxicol Clin Toxicol 2004; 42:965–75. 2. Afshari, R. Descriptive epidemiology of intoxication in Mashhad, Iran. 56111. 2001. Tehran University of Medical Sciences (M.P.H. Thesis). 3. Kaviani H, Musavi A, Mohit A. Interview and psychological tests in Tehran, Sana Publishers, Tehran, Iran, 1380.

	ANOVA	OIO[1] & OAO[2] (T-test)	OAO & CIO[3] (T-test)	OIO &CIO (T-test)
Somatization	0.147	1470	0560	570
Obsession	0.106	0430	0920	730
Inter	0.986	9050	9790	870
Depression	0.004	0160	0010	290
Anxiety	0.044	0310	0220	850
Hostility	8940	6560	8880	730
Phobia	0.689	5050	4050	840
Paranoia	0.99	0390	4330	150
Psychosis	0.605	9530	0.447	0.350
Others	0.020	0.027	0.007	0.556

Differences in P-values between psychological profiles of the three groups: [1]OIO: opium intentional overdose; [2]OAO: opium accidental overdose; [3]CIO: cyclic intentional overdose.

68. Repeated Supratherapeutic Acetaminophen Use Resulting in a Fatality

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Objective: In the United States, acetaminophen is the most commonly used non prescription analgesic. In addition to its non prescription use, acetaminophen is also a common component of prescription opioid combination products. One such product is the combination of hydrocodone and acetaminophen, which is the most frequently prescribed generic drug product in the United States. Typically, these products contain hydrocodone 2.5–10 mg and acetaminophen 325–750 mg per dosage unit. This case report describes an acetaminophen-related fatality that occurred as a consequence of an unintentional overdose of a prescribed hydrocodone/acetaminophen product. *Case Report:* A 38-year-old female received a prescription for a combination product that contained hydrocodone 7.5 mg and acetaminophen 750 mg/tablet. The recommended dose is one tablet every four to six hours as needed for pain with a maximum of five tablets every 24 hours. She was instructed to use the product for pain control after orthopedic surgery. The prescription directed the patient to take one to two tablets every four to six hours as needed. The hydrocodone/acetaminophen prescription was interpreted by the patient to mean that she could take up to two tablets every four hours. The surgery was uneventful and the patient was discharged to home where she took two tablets every four hours (20 tablets total), except during a brief period of time during which she experienced some hydrocodone intolerance and the combination product propoxyphene napsylate 100 mg and acetaminophen 650 mg was substituted (five to six tablets total). Over a 48-hour period she ingested 18.25–18.9 gm of acetaminophen and an additional 750 mg four to eight hours later. Over the ensuing three days she developed fulminant hepatic encephalopathy (AST 12,915; ALT 8,579; INR 4.2), renal failure and had an acetaminophen concentration of 20.8 mcg/mL at 28–32 hours after the last acetaminophen dose. She died four days after the final dose of acetaminophen. The autopsy revealed hepatic necrosis consistent with acetaminophen overdosage. *Conclusion:* Fatalities are uncommon after supratherapeutic acetaminophen use, but significant elevations in liver function tests have been reported in volunteers who ingested as little as 9.6 gm/day over 48 hours. A randomized controlled trial of volunteers who ingested acetaminophen 4 gm/day, with and without hydrocodone, for 14 days revealed that 31–44% of the subjects had ALTs in excess of three times the normal ALT. Patients must be counselled to not exceed doses of hydrocodone/acetaminophen products that contain in excess of acetaminophen 4 gm/day. This patient developed hepatic necrosis after the ingestion of acetaminophen in excess of 9 gm/day by interpreting the prescription literally.

69. Clinical Value of Estimated Half-life in Paracetamol Poisoning as a Complement to Rumack's Nomogram

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Objective: The aim of this study was to determine the incidence and clinical profile of patients with paracetamol poisoning in our study and to determine the usefulness of estimated paracetamol half-life in relation to the development of hepatotoxicity. *Methods:* Twenty-one patients with paracetamol overdose were admitted to Son Dureta Hospital (Palma de Mallorca) and Clinic Hospital (Barcelona) over 12 months. Hepatotoxicity is defined as AST or ALT >1000 IU/L. The estimated half-life is calculated using the quotient between two plasma paracetamol concentrations separated by 2 or more hours. If the quotient is less than (positive quotient) or greater than (negative quotient) a predefined value based on paracetamol pharmacokinetics, the half life is over or under four hours, respectively. We consider a paracetamol half-life of over 4 hours to be a predictive marker for hepatotoxicity. We also calculated the half-life using standard equations for first order kinetics. Paracetamol concentration was measured by fluorescent polarization immunoassay. *Results:* Patients (age-years): 39±18, sex (n, % female): 12 (57%), overdose type: unique ingestion 15 (71%), multiple ingestion 6 (29%), intentional 17 (81%), unintentional 3 (14%) and unknown 1 (5 %), paracetamol dose (n, gr): 18, 16 ± 11. We found a significant difference ($p < 0.005$) between the group with hepatotoxicity (n = 3), half-life=8.5 [3.6 – 8.7] hours, and without hepatotoxicity (n = 18) half-life = 2.4 [1.6 – 4.3] hours. We have observed an agreement between positive ratio and a half-life >4 hours and negative ratio with half-life < 4 hours. We detected a false positive case (half-life > 4 hours without toxicity) and a false negative case (half-life < 4 hours with hepatotoxicity) with half-life values of 4.3 and 3.6 hours, respectively. *Conclusion:* We propose that Rumack's nomogram should be complemented with half-life estimation in all cases of paracetamol poisoning, especially with those patients for whom we are not able to determine the time of ingestion at presentation or if there has been a multiple-timepoint ingestion.

70. Determination of Acetaminophen Urinary Kinetics following Supratherapeutic Non-toxic Ingestion

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Objective: More than 80% of acetaminophen (APAP) measurements are negative (1). *Hypothesis:* A urinary APAP threshold (UAT) of 5 mg/L is sufficient to detect a supratherapeutic APAP ingestion in the past 24 hours. *Methods:* Unblinded volunteer experimental trial. *Setting:* Hospital Based Clinical Research Center. *Subjects:* Five healthy adult male volunteers. Serial serum and urine samples were collected at established times over the next 24 hours following a dose of APAP (37.5 mg/kg). *Results:* Serum determinations became negative by 16–20 hours. Urinary [APAP] were significantly higher than serum values at any given time. A UAT of 5 mg/L would have detected every volunteer at 16 hours and one volunteer at 24 hours. *Conclusion:* An [APAP] of 5 mg/L is not sufficient to eliminate the possibility of a supratherapeutic APAP ingestion 24 hours post-ingestion, although a potentially toxic ingestion (150 mg/kg) would likely be detected. *Reference:* 1. Wu AHB, McKay C, Broussard LA, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. Clin Chem 2003; 49:357–379.

71. Poisonings with Paracetamol among Adolescents in Sweden

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Objective: The Swedish Poisons Information Centre has observed a continuously increasing number of inquiries related to paracetamol overdose in adolescents. The aim of this study was to elucidate the current situation of paracetamol poisoning in this age group. *Methods:* All inquiries to the PC regarding analgesics during six months (January-June 2006) were analyzed. In

addition, case records from Swedish hospitals concerning paracetamol overdose among adolescents (age 10–19 years) during the same period were studied retrospectively. Epidemiological data were documented and the cases were graded according to the Poisoning Severity Score (PSS). *Results:* Analgesics were involved in 24% of all inquiries concerning overdose with pharmaceuticals in adults and adolescents (n = 7727). About one third of all inquiries concerning paracetamol overdose (n = 838) were related to adolescents. Based on observations in the first six months of 2006, the number of paracetamol inquiries regarding adolescents is expected to increase by 14% this year compared to 2005. A total number of 90 hospital case records concerning paracetamol overdose among adolescents were received by the PC, allowing a more detailed study of the clinical course. Females dominated (n = 85). Most patients were in their late teens, but 15 were between 10–14 years old. The majority of the patients had minor or no symptoms. Intravenous N-acetylcysteine was given to 71% of the patients. Severe poisoning (PSS 3) with liver failure occurred in 7% of the patients and one had a fatal outcome. All of these patients arrived at hospital at a late stage. *Conclusion:* Paracetamol was the drug most frequently taken in overdose by female adolescents. There is a continuous increase of inquiries to the PC about these poisonings. The situation is difficult to tackle since paracetamol is a widely used and easily available pharmaceutical. Discussions regarding package size, warning labels, and age limit for purchase are ongoing in Sweden between authorities, the pharmaceutical industry and the PC.

72. Paracetamol-induced Renal Failure in Severe Paracetamol Poisoning

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Introduction: Liver failure following acute paracetamol overdose is well recognised. Some patients develop renal failure following overdose (1). Most cases of renal failure occur in association with liver failure; however isolated renal failure in the absence of liver damage has been reported (2). The overall incidence of paracetamol-induced renal failure has been reported to be less than 2%, but it reaches 10% in severely poisoned patients (1). *Objective:* to explore the frequency of paracetamol-induced renal injury, in patients with liver injury, in severe paracetamol poisoning. *Method:* This was a retrospective study on data collected from patients with paracetamol overdose who were referred to SLTU (Scottish Liver Transplant Unit) at the Royal Infirmary of Edinburgh from referral hospitals in Scotland between 1992 and 2004. Liver failure was defined as PT> = 25 seconds (INR>2.5). Moderate renal injury was defined as creatinine > =160 µmol/l to < 300 µmol/l, and severe renal failure as creatinine > = 300 µmol/l. *Results:* Over the period of 1992–2004, 523 patients with paracetamol overdose were referred to SLTU. 49.1% of patients were male and 50.9% female with mean (± SD) age of 35.6 ± 12.6y. In the referral hospital, 67.6% of subjects had liver failure with or without renal damage. 16.4% had moderate renal impairment and 9.5% severe, with or without liver failure. In the SLTU 90% of patients had liver failure. 27.2% had moderate renal impairment and 16.2% severe. 34% of all cases with renal dysfunction required dialysis. All cases with renal dysfunction had developed liver failure. There was a significant correlation between delay in initial presentation to hospital and serum creatinine at presentation ($r = 0.41$, $p<0.01$). *Conclusion:* Renal failure after severe paracetamol overdose is common. The onset of renal damage is later than liver injury. Most cases of paracetamol-induced renal damage are in association with hepatic injury, but hepatic injury is not always associated with renal damage. Thus the processes underlying renal and hepatic injury in man following severe paracetamol overdose appear different. *References:* 1. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. J Am Soc Nephrol 1995; 6:48–53. 2. Kher K, Makker S. Acute renal failure due to acetaminophen ingestion without concurrent hepatotoxicity. Am J Med 1987; 82:1280–1.

73. Very Late Second Peak in Acetaminophen Concentration Following Tylenol™ Extended Relief Overdose

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Objective: The presence of a second increase in APAP concentration is extremely unusual, although overdose of anticholinergic and opioid coingestants may delay the peak APAP concentration. Tylenol™ Extended Relief (TER) contains 650 mg acetaminophen (APAP), half of which is released immediately and half is released after a brief delay. One previous report of a late increase in acetaminophen concentration was also attributed to a TER overdose. We report a case with a dramatically late second rise in serum APAP. *Case Report:* A 78-year-old woman presented the ED after an intentional overdose at an unknown time. According to her husband, only TER was available to her. Initial vital signs were normal. Initial laboratories were significant for APAP concentration of 3855.72 µmol/L (584.2 µg/mL), ALT 12 U/L, and AST 19 U/L. Urine toxicologic screen was negative for opioids. She was obtunded, but her physical examination was otherwise unremarkable. Gastrointestinal decontamination was not performed. N-acetylcysteine (NAC) was administered using the standard infusion regimen. The patient was admitted to the ICU with constant one-to-one observation to prevent self-harm. On the second hospital day, she was intubated for respiratory distress thought to be caused by aspiration. Serial APAP concentrations are shown in the table. Despite continuous NAC (6.25 mg/kg/h), the aminotransferases peaked at 85 hours with an ALT of 2903 and AST of 2954. Although her hepatotoxicity began to improve, on hospital day 8 she expired. Her cause of death was listed as sepsis. *Conclusion:* TER may be associated with a substantial and delayed secondary rise in acetaminophen concentration. In the previously reported case, the concentration was approximately 1059.2 µmol/L at 14 hours (1). Our patient's second peak in APAP concentration occurred at 36 hours. In contrast, a series of 41 patients presenting after TER overdose found no patients with delayed increase in APAP (2). In supratherapeutic doses, TER has an apparent serum t1/2 of 4.02 hours (compared with 2.56 hours for regular release APAP) but does not demonstrate a second peak (3). *References:* 1. Bizovi KE, et al. Late increase in acetaminophen concentration after overdose of Tylenol™ Extended Relief. Ann Emerg Med 1996; 28:549–551. 2. Cetaruk EW, et al. Tylenol™ Extended Relief overdose. Ann Emerg Med 1997; 30:104–108. 3. Stork CM, et al. Pharmacokinetics of Extended Relief versus regular release Tylenol™ in simulated human overdose. J Toxicol Clin Toxicol 1996; 34:157–161.

Time following presentation (h)	0	14	25	29	36	37	49	61	85	96
Serum APAP (µmol/L)	3855.7	1852	1865.5	3310	3711.8	3673.4	2778.6	1343.8	431.6	<66.2

74. Poisoning by Analgesics - A Ten-year Perspective

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Objective: To document the current pattern of poisonings by analgesics in Sweden (8.9 million inhabitants) and to compare with the situation ten years earlier. *Methods:* Case records obtained from hospitals concerning overdoses with analgesics among adults and adolescents (age >10 years) during a three-year period (2000–2002) were studied retrospectively. The Poison Centre receives case records concerning about one third of all poisoning cases, so a collection over three years would numerically correspond to approximately one year's material. Epidemiological data were documented and the cases were graded according to the Poisoning Severity Score (PSS). The results were compared with those of a corresponding study from 1991–1993. Also data from the National Cause of Death Register (2002) and the Hospital Discharge Register (2002) were included. *Results:* A total number of 1,455 case records were received during the study period. Most of the poisonings were intentional and 75% of the patients were females. Paracetamol had been taken in nearly half of the cases (n = 649). Severe poisoning (PSS 3) with liver failure occurred in 7% of these patients, and there were five deaths. None of those who had overdosed NSAID (n = 174) developed severe symptoms. Among patients aged 10–19 years (n = 345) nearly 75% of the poisonings involved non-prescription analgesics, mainly paracetamol. Intoxication with dextropropoxyphene occurred in about one quarter of the cases (n = 394). Severe and life-threatening respiratory depression (PSS 3) was observed in 15% of these patients, six of whom died after arrival to hospital and two of whom had neurological sequelae. Poisonings with tramadol (n = 123) were graded as severe (PSS 3) in 10% of the cases, mainly due to convulsions and deep unconsciousness. A comparison with corresponding data from 10 years earlier showed that the number of paracetamol poisonings is relatively unchanged, whereas dextropropoxyphene overdose nowadays is less common. According to national hospital statistics in 2002, poisoning by analgesics (n = 1804) was the main diagnosis in 25% of all drug poisonings. In the National Cause of Death Register, 40% of the drug-related deaths were referred to nonopioid analgesics (n = 21) and narcotics, including dextropropoxyphene, (n = 226). Most deaths occur outside hospital and are due to opioids. *Conclusion:* Analgesics are involved in approximately 25% of all drug poisonings treated in Swedish hospitals. Mortality is high in opioid overdose. However, the number of dextropropoxyphene poisonings has been reduced since more restricted prescription rules recently were implemented. Tramadol, with lower acute toxicity, has to some extent replaced dextropropoxyphene. Paracetamol poisoning still remains an unchanged, large problem. The patients require extensive diagnostic and treatment interventions. Young girls are overrepresented. All this is a matter of concern.

75. Co-drugs and Tramadol – Changes in Legislation for Co-proxamol

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Objective: To examine changes in prescribing patterns, admissions to one hospital and accesses to an Internet database for co-drugs and tramadol. *Methods:* Due to fears about the safety of co-proxamol (paracetamol/dextropropoxyphene), particularly in overdose (1) the UK Medicines Health and Regulatory Authority announced a phased withdrawal on 21/01/2005. For the period 1/1/2003 to 30/6/2006 Scottish quarterly prescription data for the top four prescribed opioid preparations at Q1/2003 [co-proxamol, co-codamol (paracetamol/codeine), co-dydramol (paracetamol/dihydrocodeine) and tramadol] were analysed, together with Scottish accesses to TOXBASE (Internet database of the UK National Poisons Information Service). Admissions to the Royal Infirmary of Edinburgh for self-poisoning with the same preparations were compared with prescription data for Lothian, the area served by the Infirmary. *Results:* Scottish prescriptions for co-proxamol averaged 304,726/quarter until the end of Q4 2004 and then fell to 67,997 in Q2 2006 (77.7% decrease). Co-codamol prescriptions increased by about 25% from an average of 440,818/quarter to 551,307/quarter. Co-dydramol (122,337 at Q1 2003) and tramadol (104,832) showed rising prescription levels throughout the period (19.6% and 37.9%, respectively). TOXBASE Scottish accesses showed a similar but slightly delayed pattern for co-proxamol with a decrease from Q2/2005 (average to Q2 184 accesses/quarter falling to 80 at Q2 2006). TOXBASE accesses for co-dydramol rose to a peak of 410 in Q3 2005 then fell slightly. Co-dydramol remained fairly steady at 98 accesses/month. Tramadol accesses almost doubled over the period. A ratio of TOXBASE accesses/100,000 prescriptions was calculated for each quarter. The average for co-codamol was 71 accesses/100,000 prescriptions/quarter before the change in licensing and 70 after. For co-dydramol the average ratios were 76 and 70, for co-proxamol 61 and 109 and for tramadol 108 and 130, respectively. Lothian prescriptions showed a similar pattern to those for the whole of Scotland, except that the proportion of tramadol prescriptions was lower. There are 1,800–2,000 admissions/year for self-poisoning to the Royal Infirmary of Edinburgh. Numbers of admissions for poisoning with co-drugs and tramadol are small but in each quarter co-codamol predominated (average 41.5/quarter). Co-dydramol and tramadol had fewer than 10 in most quarters. For co-proxamol a decreasing trend was seen throughout the period from around 40/quarter in 2003 to around 8/quarter in 2005–6. *Conclusion:* Changes to the prescribing regulations for co-proxamol produced a rapid decrease in prescriptions issued for this preparation in 2005. This was reflected more slowly in admissions for poisoning which fell throughout the period. Tramadol was responsible for proportionately more TOXBASE accesses throughout the period and co-proxamol accesses increased in proportion to prescribing after the prescription change, suggesting increased awareness

of toxic risk. *References:* 1. Afshari R, Good AM, Maxwell SR, Bateman DN. Co-proxamol overdose is associated with a 10-fold excess mortality compared with other paracetamol combination analgesics. Br J Clin Pharmacol 2005; 60:444–7.

76. Idiopathic Intracranial Hypertension Associated with Short-duration Minocycline for Acne Vulgaris

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Objective: Idiopathic intracranial hypertension (IIH) is a syndrome of elevated intracranial pressure without clinical, laboratory or radiologic evidence of intracranial pathology. The most significant consequence of untreated IIH is permanent visual defects. While often described in relation to obesity, IIH has also been reported in association with medication exposures, such as the tetracycline family and retinoids (1). There are several case reports documenting minocycline-associated IIH after several weeks to months of treatment (2). We report a case of IIH in which symptoms began on the ninth day of minocycline therapy. *Case Report:* A 12-year-old non-obese boy presented to the emergency department (ED) with a chief complaint of distance diplopia. Two weeks prior to presentation, he had been started on a course of minocycline therapy for acne vulgaris. Six days prior to presentation (day 9 of therapy), he had stopped taking the minocycline due to headache. Three days prior to presentation he developed distance diplopia. In the ED, the patient's vitals signs included a blood pressure of 116/68 mm Hg, heart rate 117 beats/minute, respirations 20 breaths/minute, and temperature 37.4 degrees Celsius. Ophthalmologic evaluation revealed bilateral papilledema. Non-contrast brain computed tomography was normal. Blood and urine laboratory tests were unremarkable. Lumbar puncture was performed in the flexed left lateral decubitus position. Cerebrospinal fluid (CSF) opening pressure was 44 cm H20 (normal < 20 cm H_20). CSF was obtained for analysis and was drained therapeutically to achieve a closing pressure of 18 cm H20. CSF leukocyte count was 1 cell/microliter. CSF red blood cell count was zero. CSF protein and glucose were 23 mg/dL (normal 15 – 45 mg/dL) and 56 mg/dL (normal 60 – 80 mg/dL), respectively. CSF analysis for Lyme antibodies was negative. CSF gram stain and bacterial culture were negative. The patient was discharged home from the ED on acetazolamide 250 mg twice daily with neurology and ophthalmology follow-up. *Conclusion:* IIH may occur in association with daily minocycline therapy of short duration. Although classically described in obese patients, the occurrence of medication-associated IIH with certain therapeutics should prompt physician awareness of this complication, and promote vigilant screening. *References:* 1. Skau M, Brennum J, Gjerris F, Jensen R. What is new about idiopathic intracranial hypertension? An updated review of mechanism and treatment. Cephalgia 2006; 26:384–399. 2. Ang ERG, Zimmerman JCC, Malkin E. Pseudotumor cerebri secondary to minocycline intake. J Am Board Fam Pract 2002; 15:229–233.

77. Analytical Identification of Oral Antidiabetic Misuse in an Emergency Setting

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Objective: Sulphonylureas and biguanides (phenformin and metformin) are the two classes of oral antidiabetic drugs usually prescribed in diabetic patients. Sulphonylureas act as hypoglycaemic agents stimulating endogenous insulin production; biguanides are antihyperglycaemics that enhance the action of insulin. In Italy, chlorpropamide or glibenclamide are associated with biguanides in pharmaceutical preparations. Analytical identification and quantification can be useful in cases of oral antidiabetic misuse in the emergency setting. *Methods:* Cases of antidiabetic misuse in patients admitted during a 36 months period to the emergency department (ED) for hypoglycaemic crisis of undetermined origin were retrospectively studied. Antidiabetic analysis was performed in biological fluids: serum screening for sulphonylureas was made with a method based on liquid/liquid extraction and HPLC-UV separation/detection. Phenformin was analysed using HPLC-UV: the serum was deproteinized, while urine was directly injected. Metformin was first derivatized in serum and urine, then submitted to liquid/liquid extraction and GC-MS examination. *Results:* Five cases of suspected oral antidiabetic misuse were included. All the patients were admitted for hypoglycaemic crisis (glycaemia range: 17–30 mg/dl). Clinical examinations never revealed pathological causes, so toxicological analysis, in particular sulphonylurea screening, was requested of the analytical toxicology laboratory. Only one patient had a history of diabetes, but no one was known to be on therapy with oral antidiabetics; in two cases a psychiatric disease was present in the history. Three cases resulted positive for glibenclamide in serum: one of them was positive also for metformin and another one for phenformin in serum and urine. Two cases tested negative for sulphonylureas and biguanides in blood, but positive for metformin in urine. Therapeutic or subtherapeutic concentrations were always detected. *Conclusion:* The suspected antidiabetics misuse has been confirmed by the toxicology laboratory analysis in all the patients. The presence of glibenclamide clearly correlates to the hypoglycemic crisis in three patients. The presence of biguanides in the urine of two patients can be likely interpreted as an assumption of an associated pharmaceutical preparation since biguanides alone normally don't cause an important decrement in blood glucose. The analytical methods adopted are suitable to reveal sub-therapeutic concentrations of sulfonylureas. If the misuse is related to associated preparations, the analysis of metformin and phenformin is a useful diagnostic tool in case of delay between drug consumption/hypoglycemic crisis and sample collection, since the extensive metabolism of most sulphonylureas makes their evaluation difficult in biological samples collected several days after drug ingestion.

78. Relevance of Analytical Identification of Biguanide Poisonings in Emergency Settings

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Objective: Metformin and phenformin are prescribed in Italy as monotherapy or associated with sulphonylureas. Cases of biguanide poisoning can be suspected in the emergency setting, but analytical confirmation is not always accessible because of the unavailability of simple and rapid analytical methods. *Methods:* The analytical results of eight cases of biguanide poisoning obtained in the emergency setting have been evaluated. The serum quantification of the drugs was performed with a method based on protein precipitation and HPLC-UV. *Results:* At admission, serum metformin concentration was 10.4 mcg/ml (therapeutic: 0.18–1 mcg/ml) in one case of intentional overdose, whereas higher serum levels (between 60 and 100 mcg/ml) were detected in 6 of the 7 cases of poisoning secondary to accumulation as a consequence of renal impairment during chronic therapy. The seventh case of accumulation was related to phenformin, with a serum level of 0.38 mcg/ml (therapeutic: 0.16–0.24 mcg/ml). In four cases sulphonylureas were also present. All patients presented with significant lactic acidosis (lactate range 18–33 mmol/l, pH 6.62–7.24). In the case of attempted suicide the renal function was normal, the patient was treated with sodium bicarbonate and the drug was eliminated over 36 hours. The patients with metformin accumulation during treatment underwent dialysis, and the one with a serum level of 100 mcg/ml died. The phenformin-poisoned patient was treated with sodium bicarbonate and the metabolic acidosis resolved in 12 hours. *Conclusion:* In our cases metformin levels above 10 mcg/ml were related to important toxic effects, and the appearance of renal impairment during chronic therapy was the most relevant cause of severe biguanide toxicity. Serum phenformin level of 1.5 times greater than the normal range is related to severe lactic acidosis. The method we adopted is suitable in emergency for the diagnosis of acute poisoning, both in attempted suicide and in accumulation during treatment. It is very simple, fast (results are available in 30 min) and has sufficient specificity and sensitivity in case of toxic concentrations.

79. Fatal Outcome in Suicidal Metformin Poisoning Refractory to Treatment

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Objective: In metformin poisoning hemodialyis is recommended as the most important therapeutic tool. However, at a high poison load it may reach its limits. *Case Report:* A 43-year-old male with known history of type II diabetes mellitus ingested 102 g of metformin with suicidal intention. Progressive somnolence and circulatory instability developed together with metabolic acidosis (pH 6.7). After sudden cardiac arrest and respiratory depression the patient was artificially ventilated and stabilized with catecholamines. As the clinical status further deteriorated in the external hospital the patient was transferred to our unit. A total quantity of 2050 mL sodium bicarbonate (8.4%) was infused but did not result in correction of metabolic acidosis. In order to remove the lactate hemodialysis was initiated when he arrived in our ICU despite the unstable circulatory situation. However, the patient's condition did not improve and he expired, in spite of ongoing haemodialysis, due to cardiac arrest 19 hours after primary care. The measured serum peak of metformin was 214 mg/L (HPLC and UV diode array detector). *Conclusion:* To our knowledge this is the highest metformin serum peak in adult patients reported in literature (1,2). Signs and symptoms were presumably amplified by a preexisting renal insufficiency. Metformin is eliminated by proximal tubular secretion and glomerular filtration with an elimination half-life of 4–8 hours (3). Accordingly, renal failure leads to reduced clearance and prolonged excretion as in the present case (4). High water solubility and low plasma protein binding principally enable high efficiency of intermittent hemodialysis with high-volume continuous veno-venous hemofiltration (1). The relatively late onset of hemodialysis in the case reported and the huge amount ingested may be the reason for the fatal outcome. An immediate start of a combined hemodialysis and hemofiltration therapy seems to be paramount in order to prevent a further fatal deterioration of metabolic acidosis. *References:* 1. Panzer U, Kluge S, Kreymann G, Wolf G. Combination of intermittent haemodialysis and high-volume continuous hemofiltration for the treatment of severe metformin-induced lactic acidosis. Nephrol Dial Transplant 2004; 19:2157–8. 2. Schulz M, Schmoldt A. Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 2003; 58:447–74. 3. Linden CH. Antidiabetic agents. In: Brent J, Wallace KL, Burkhart K, Phillips SD, Donovan JW, eds. Critical Care Toxicology. 1st ed. Philadelphia, PA: Elsevier Mosby, 2005:729–742. 4. Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 1996; 30:359–371.

80. Acute Poisoning with Dentocalmin -a Life-threatening Entity in Children

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Objective: To describe signs and symptoms of a new severe poisoning in children - Dentocalmin poisoning. Dentocalmin is a pharmaceutical product used in stomatology as a local anaesthetic, containing in 10 mL: lidocaine 2 g, menthol 2 g and phenol 2 g. We present a series of 7 cases registered in our Department over a period of 5 years. *Case Series:* 1. A 1-year-old boy who ingested an unknown quantity of Dentocalmin presented with generalized tonic-clonic seizures that could not be stopped with anticonvulsants; one hour after arrival he presented with cardio-respiratory arrest and died. 2. A 2-month-old female infant was taken to the Emergency Department presenting with cardio-respiratory arrest; her mother related that 30 minutes earlier she gave the infant an unknown quantity of Dentocalmin instead of vitamin D3 solution; the infant was resuscitated, intubated and ventilated for 48 hours; she developed generalised seizures 1 hour after admission; she was discharged 6 days later completely recovered. 3. A girl of 1 year and 4 months old who ingested 10 mL of this product became agitated, then developed seizures and respiratory arrest at the moment of admission; she was intubated, treated with diazepam and midazolam for convulsions; the progress was favorable: she was extubated 3 hours later and discharged after 3 days. 4. A girl of 2 years and six months with the same history presented with generalized seizures, then became cyanotic with bradypnoea; was intubated for 6 hours and treated with diazepam. 5 and 6. Two boys 2 years and 3 years old who had ingested an unknown quantity of the product came in the first hour to the Emergency Department presenting with somnolence, hypotonia and sinus tachycardia; no other symptoms appeared and they were sent home 3 days later. 7. A 7-month-old female infant was admitted 30 minutes after her mother gave her 2 drops of Dentocalmin instead vitamin D3; she presented with agitation, ataxia, sinus tachycardia and completely recovered. *Conclusion:* Dentocalmin is a very toxic product that causes life threatening symptoms and even death in children. This clinical picture is probably due to its composition with high doses of lidocaine, menthol and phenol in a small volume. *References:* 1. Bates N, Edwards N, Roper J, Volans G. Paediatric toxicology, 1997 2. Goldfrank's toxicologic emergencies, 8th edition, 2006.

81. Pregnancy Outcome of Women using Antiepileptic Drugs

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Introduction: Epilepsy is one of the most common neurological problems in pregnancy and the potential teratogenicity of antiepileptic drugs (AEDs) is a major concern. Complications of epilepsy and AEDs treatment include stillbirths, low birth weight, major and minor malformations, cognitive and behavioral neurodevelopmental effects. Many prospective and retrospective studies have demonstrated that infants of women under antiepileptic treatment have a two to threefold higher risk of congenital malformations compared with the background population. *Results:* In 2005, Bergamo Poison Control Center received 2,843 phone calls about requests for potential effects of drugs and chemicals in pregnancy; 24% of the questions were related to drugs of the central nervous system and 90 patients of these (10.5%) were classified as the group exposed to antiepileptic drugs: 52 (57%) patients used AEDs during any time of the pregnancy as a monotherapy, 16 (18.5%) in polytherapy and 22 (24.5%) in association with other psychotropic drugs. Carbamazepine, valproic acid and lamotrigine were the mainly used drugs (22, 16 and 18 patients respectively), followed by oxcarbamazepine (9), phenobarbital (9), gabapentin (8) and other AEDs (8). We completed follow-up on 50 women, with a median age of 31 (18–42) years old, exposed to AEDs during the first trimester of pregnancy and two groups were evaluated: 1) women exposed to AEDs in monotherapy (39 patients) versus a non-teratogen group and 2) those taking two or more AEDs (11 patients) vs a non teratogen group. Among the outcomes of these pregnancies there were 36 live births, nine pregnancies electively terminated and 5 spontaneous abortions: 3 spontaneous abortions have been observed in the first group (6%) and 2 in the second one (4%). Only one major malformation has been recorded (1 newborn presented with prenatal hydronephrosis) but the difference was not significant. Thirty-five percent of the patients had documentation of folate supplementation at any time during pregnancy. The outcome was compared to that of 82 pregnancies with exposures known to be not teratogenic. Seventy-eight women of this group had normal deliveries and 4 (4.8%) spontaneous abortions were identified. *Conclusion:* Despite the small number of cases in the study, these data indicate that treatment with AEDs during pregnancy do not increase the spontaneous abortions rate, but larger prospective studies are needed to obtain adequate power for statistical analysis. *References:* 1. Yerby MS. Pregnancy, teratogenesis, and epilepsy. Neurol Clin 1994; 12:749–71. 2. Annegers JF, Baumgartner KB, Hauser WA, Kurland LT. Epilepsy, antiepileptic drugs, and the risk of spontaneous abortion. Epilepsia 1988; 29:451–8.

82. Is Pregnancy a Problem in Acute Poisonings?

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Objective: The objective is to present the results of a study of acute poisonings in pregnant women for a 30-year period in Bulgaria. Attention is paid to the outcome of pregnancy, development of fetus and changes in placenta after survival. *Methods:* We have analyzed the medical records of all pregnant women, hospitalized in the Toxicology Clinic of Emergency Medicine Hospital 'Pirogov' due to acute poisonings for the period 1975–2005. The main parameters of the survey are age, conditions and type of the poisoning, severity of intoxication, pregnancy status. The patients were followed-up until delivery, when thorough investigations of the newborn and the placenta have been performed. Various clinical and laboratory methods have been used, including macroscopic, histological, hysto-enzyme and immuno-fluorescent investigations of the placenta. *Results:* We have studied a total of 287 pregnant women with acute poisonings, hospitalized for the period 1975 - 2005. Acute intoxications in pregnant women represent 0.48% of all poisonings. The age of the women varies between 18 and 45 years; most frequently poisonings occur at the age of 25 to 35 years. Severe poisonings are rare (in 15% of the studied patients) and moderate poisonings prevail (60%). The intoxications have occurred mainly between the 3rd and 5th month of the pregnancy. Medicinal poisonings (78%) and suicidal attempts (80%) prevail in the studied group. The treatment of these patients was identical to the accepted standards, including extracorporeal methods for detoxification. All women survived the poisonings and delivered normal babies. The histological changes in the placenta detected after delivery are similar to the changes occurring after severe hypoxia. *Conclusion*: Although rare, pregnancy may be combined with acute poisonings and this combination is a challenge to the clinical toxicologist, who has to pay attention not only to the poisoned patient, but also to the fetus and the possible effects of the poison on the fetus and its development.

83. Fetal Demise Associated with Acute Intentional Salicylate Ingestion

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Objective: The effects of in-utero salicylate exposure on the fetus are not well understood. There are only two reported cases of fetal demise from either acute or chronic salicylate exposures (1,2). We describe a case of fetal demise that occurred after an acute intentional salicylate ingestion. *Case Report:* A 25-year-old woman 20 weeks pregnant presented to the emergency department after an intentional ingestion of an unknown amount of acetyl salicylic acid (ASA). Her initial vital signs included a respiratory rate of 40 breaths/minute with heart rate 125 beats/minute and blood pressure 127/48 mm Hg. Initial arterial blood gas was pH 7.39, pCO_2 13 mm Hg, PO_2 118 mm Hg with calculated bicarbonate 13 mEq/L (13 mmol/L). Alkaline diuresis was initiated. Her initial salicylate level was 81 mg/dL (therapeutic range 15–30 mg/dL). Acetaminophen and ethanol concentrations were non-detectable. Urine drug screen was negative. While awaiting hemodialysis, the patient developed respiratory decompensation requiring intubation. Her acidemia immediately worsened. Subsequent blood gas showed pH 7.13, pCO_2 50 mm Hg, pO_2 70 mm Hg with calculated bicarbonate 14 mEq/L (14 mmol/L). The patient was hyperventilated, and hemodialysis was initiated for four hours. Repeat salicylate after hemodialysis was undetectable. The patient recovered without sequelae; however, an ultrasound obtained during dialysis revealed fetal demise. *Conclusion:* Salicylate exposure can have detrimental effects on both the pregnant patient and her fetus. The fetal environment is relatively acidemic compared to the maternal serum, and the fetus lacks the buffering capacity and respiratory compensation of the mother. Aggressive therapy aimed at enhancing salicylate clearance from the mother may not protect the fetus. In this case, the combination of rapid worsening of maternal acidemia peri-intubation with lack of fetal compensatory mechanisms may have led to fetal demise. *References:* 1. Palatnick W, Tenenbein M. Aspiring poisoning during pregnancy: increased fetal sensitivity. Am J Perinatol 1998; 15:39–41. 2. Rejent T, Baik S. Fatal in utero salicylism. J Forensic Sci 1985; 30:942–4.

84. Analysis of Parotid and Pancreatic Glands in a Murine Model of Intoxicaton with Parathion-methyl and Efficacy of its Treatment

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Objective: To investigate the effect of parathion-methyl (PM) on parotid and pancreatic glands in rats. *Methods:* Seventy-five male Wistar rats were divided into five equal groups. The groups were control (Group I), Group II (received atropine and pralidoxime (2-PAM) for 24 hours, but no PM); Group III, (oral PM but no atropine and 2-PAM); Group IV, (PM and atropine for 24 hours and 2-PAM); Group V, (PM and atropine for 96 hours and 2-PAM). After the administration of the chemicals, blood samples were drawn to test for amylase, lipase, acetylcholinesterase (AChE), and butirylcholinesterase (BChE) while pancreatic and parotid glands of each rat were removed for light microscopic examination. *Results:* Blood levels of amylase were found significantly elevated in groups II ($p = 0.01$), III ($p = 0.0001$), IV ($p = 0.005$), and V ($p = 0.0001$), while lipase were supranormal in groups III ($p = 0.0001$), IV ($p = 0.05$), and V ($p = 0.0001$). The blood levels of AChE decreased in groups III ($p = 0.0001$) and IV ($p = 0.002$) and BChE decreased in II ($p = 0.059$), III ($p = 0.0001$), IV ($p = 0.0001$), V ($p = 0.0001$). Hyperchromasia, irregularity in nuclei and binuclear cells were observed in parotid gland (Fig. 1). Frequencies of other pathological changes were similar in pancreatic and parotid glands (Fig. 2). *Conclusion:* PM may cause elevation in amylase and lipase, decrease in cholinesterases (1–7). Parotitis and pancreatitis were not evident, while new various histologic changes in parotid gland were documented.

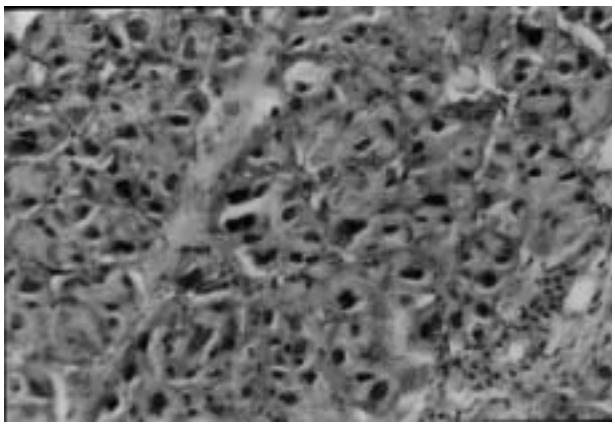

Fig. 1. Nuclear enlargement and double nuclei observed in parotid gland in group V after methyl-parathion ingestion and treatment with atropine and 2-PAM for 96 hours. (Hematoxylene-Eosine × 200).

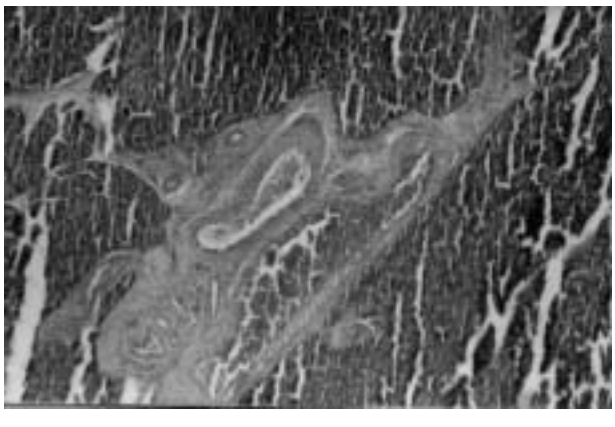

Fig. 2. Interstitial congestion and ductal dilatation identified in pancreatic gland in group IV following methyl-parathion ingestion and treatment with atropine and 2-PAM for 24 hours (Hematoxylene-Eosine × 40).

85. Chronic Chlorpyrifos Exposure Increases Leptin and TNF-alpha Levels in Rats

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Objective: Chronic low-dose exposure of rats to chlorpyrifos at levels of 5 mg/kg gave no acute toxicity but led to weight gain secondary to increases in adipose tissue. The mechanism

of this increase in weight is unknown. Regulation of weight is a complex system involving hormones, cytokines, neuropeptides, and neuronal pathways. The objective of this study is to determine whether serum levels of obesity related tumor necrosis factor alpha (TNF-alpha), insulin, leptin, interleukin-6 (IL-6) and monocyte chemoattractant protein (MCP) are increased in rats chronically exposed to these low levels of chlorpyrifos that have no acute toxicity. *Methods:* Fourteen female, adolescent rats (Long-Evans) were exposed to either chlorpyrifos 5 mg/kg/day, or an equal volume of vehicle (DMSO) by implantation of a subcutaneous osmotic minipump (Alzet). Blood was drawn from all animals at 1 week after pump implantation and at 1 month. Collected serum was analyzed for levels of tumor necrosis factor alpha (TNF-alpha), insulin, leptin, interleukin-6 (IL-6) and monocyte chemoattractant protein (MCP) using a LINCOplex immunoassay kit. All samples were centrifuged at 1,000 g and the serum removed and frozen at −70ºC until ready for use. *Results:* There were also no differences in serum markers at 1 week post-exposure. At the 1-month time point, the animals with chlorpyrifos-containing pumps had significantly increased levels of TNF-alpha (3.78±0.24 vs. 4.53±0.23; p = 0.0041) and leptin (1140.6±105.5 vs. 1883±471.2; p = 0.02). A trend toward higher circulating insulin levels were also noted (208.5± 44 vs. 250.3± 45; p = 0.23). MCP and IL-6 were not significantly different between the groups. *Conclusion:* Chronic exposure to chlorpyrifos is associated with an increase in adipose tissue, elevated levels of leptin, and elevated levels of TNF-alpha.

86. Hepatotoxic Effects in Mouse by Prolonged Exposure to Aluminium

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Objective: Aluminium (Al) is an ubiquitous metal that is potentially toxic. Whereas the adverse biological effects of Al in brain, bone and hemopoietic organs are well described, its effects in other organs are not completely understood (1). Since liver, through the biliary flux, is involved in Al excretion (2), this *in vivo* study focused on the hepatic effects of prolonged Al exposure on mice. In particular we analyzed the iron deposition and transport together with cytoskeletal organization of the biliary tree of hepatocytes, involved in the bile secretion. *Methods:* Balb/C mice (6 animals/each group) were divided into six groups receiving: Al sulphate 2.5% in drinking tap water (correspondent to 33 Al mg/mice/day) (3) for 3, 6, and 10 months; other three groups were housed in similar conditions but drinking tap water only as relative controls. At the end of treatments, all animals were killed and the liver extracted and processed for histopathological (Walton, PAS and Perl's), ultrastructural and immunohistochemical analysis for transferrin receptor, a homodimeric membrane protein that mediates the uptake of iron into the cell and for actin. *Results:* Glycogen deposition was impaired after 3 months of Al exposure that also significantly affected iron deposition (P<0.05). After 6 months of Al exposure, transferrin receptor signal translocated from the sinusoidal side to the cytoplasm of hepatocytes and Kupffer cells. Moreover a time-dependent derangement of actin staining in the biliary side was detected and confirmed also by electron microscopy. *Conclusions:* All these data indicate that both iron homeostasis and cytoskeletal deposition are impaired by prolonged exposure of mice to Al, so probably amplifying hepatotoxic damage and cholestasis. *References:* 1. Stacchiotti A, Rodella LF, Ricci F, et al. Stress proteins expression in rat kidney and liver chronically exposed to aluminium sulphate. Histol Histopathol 2006; 21:131–140. 2. Gonzales M, Roma M, Bernal C, et al. Biliary secretory function in rats chronically intoxicated with aluminum. Toxicol Sci 2004; 79:189–195. 3. Rodella LF, Rezzani R, Lanzi R, et al. Chronic exposure to aluminum decrease NADPH-diaphorase positive neurons in the rat cerebral cortex. Brain Res 2001; 889:229–233.

87. Seromucosal Transport of Acetaminophen and Metabolites after Intravenous Injection into Intestines of Rats: Influence of Activated Charcoal on the Disposition Kinetics

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Objective: To evaluate the effectiveness of orally administered activated charcoal (AC) in enhancing the clearance of 14C-acetaminophen and metabolites (AAP/M) after IV injection (75 mg/kg b.w.). The quantities of AAP/M excreted into bile, urine and intestines were determined. *Methods:* Rats were randomized into four treatment groups of 10 animals each: all underwent single-pass perfusion of the small intestine; two groups received AC (2 g/ kg-1 b.w.; dissolved in balanced polyethylene glycol electrolyte solution (PEG-ELS)) with (AC+BD+) or without cannulation of the common bile duct (AC+BD-). The remaining two groups received solely PEG-ELS with (AC-BD+) or without (AC-BD-) cannulation of the common bile duct. Animals were tracheotomised and ventilated. The right and left internal jugular vein and the left internal carotid artery were cannulated for blood sampling and delivering anaesthesia agents, fluids or acetaminophen. The proximal duodenum and the distal ileum were cannulated through the pylorus and the ileocoecal valve, respectively. In the (BD+)-group, bile was collected continuously from the cannulated common bile duct. The urinary bladder was exposed and urine was collected continuously after being punctured with an intravenous catheter. Animals were observed for 210 min after IV injection and euthanized finally. AAP in plasma was determined using a FPIA-based method. Radioactivity of 14C-AAP (and metabolites) in perfusate, bile, urine, liver and kidney was determined by liquid scintillation counting after combustion. *Results:* The cumulative amount of AAP/M which was exsorbed into the small intestine 210 min after IV injection was about 20% of dose in (BD-)-animals and about 7% of dose in (BD+)-animals. Correspondingly, about 13% of the dose was detected in the externalized bile. AC did not influence the amount exsorbed into the small intestine. Half-life in plasma ranged between 35 and 51 min between the four treatment groups without significant difference (p = 0.152). Correspondingly, the AUC did not vary significantly and ranged between 2.6 and 3.3 g•min•L-1 (p=0.392). Deposition of AAP/M in liver and kidney was marginal and below 1% of dose within all groups. Excretion of AAP/M into urine varied strikingly between 31 and 56% of the dose within all groups and correlated with diuresis. *Conclusion:* AC did not enhance the clearance of AAP/M significantly. The lack of effect of AC on the elimination of AAP/M may be due to the small amount of the drug being exsorbed into the intestine or the reduced adsorbent capacity of AC to AAP/M, which also could be influenced by solvents or by inadequate luminal stirring.

88. Place for Endoscopy in Gastrointestinal Decontamination

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Objectives: After ingestions of large amounts of highly toxic substances, early gastrointestinal decontamination by gastric emptying may be desirable. As considerable proportions of toxic material may remain within the stomach after gastric lavage, visual confirmation of the completeness of the procedure is desirable. Moreover, bulky masses, concretions of toxic substances or simply big tablets cannot be removed from the stomach by gastric lavage because they cannot enter the lumen of the lavage tube. While esophagogastroduodenoscopy is the method of choice to achieve this, there is a lack of systematic investigation on the use and benefit of this approach. We therefore aimed to search the medical literature for data on endoscopic decontamination of the upper gastrointestinal tract. *Methods:* The medical literature was searched using "endoscopic," "endoscopic removal," "gastroscopy," and "endoscopy" together with decontamination, poisoning, overdose, and bezoar as search terms. In addition, textbooks of clinical toxicology were searched for descriptions or recommendations of endoscopic gastrointestinal decontamination. *Results:* No randomized and/or controlled trials were found studying this topic. Only anecdotal case reports or small case series could be retrieved. Most publications deal with the ingestion of batteries (1,2) and of drug packets (body packers). There are some reports about endoscopic treatment of tablet concretions (pharmacobezoars) or tablets sticking to the stomach wall (3). Much larger is the literature about endoscopic treatment of foreign bodies in the upper gastrointestinal tract. There is no report on endoscopic removal after highly toxic plant ingestion such as taxus, colchicum, aconite, and digitalis, or of removal of toxic liquids (such as paraquat) under visual control. Medication bezoars, after overdoses or due to motility disorders of the gut (4), have been successfully removed by endoscopy in the case of theophylline (5,6), propaphenone (7), and bromide sedatives (8). Pollmann and Zillesen (9) reported having successfully removed remains of tablets sticking to the gastric mucosa in 93% of cases with medication overdoses by endoscopy after they have been lavaged. Therefore, endoscopic removal of tablets from the stomach instead of gastric lavage, which is often only partly successful, has been advocated, particularly by German gastroenterologists in the 1970s and 1980s (10,11). However, there is some evidence that attempts to endoscopically remove toxic substances from the stomach may be either unsuccessful (12) or even dangerous (13,14). There have been, particularly, warnings about the endoscopic removal of cocaine containing drug packages in body packers because of the risk of rupture and consequent massive cocaine toxicity (15–17), although there are reports on uncomplicated extraction (18,19). *Conclusion:* While the body of the literature does not answer the question whether endoscopic decontamination should be performed at all, it at least shows impressively that it is possible by this technique to reliably evacuate the stomach and to remove masses of toxic material. Indication is more clear if medications form a foreign body in the stomach or esophagus (bezoars) or if they are solid (button batteries, drug packets). Endoscopic removal may be the method of choice if gastric lavage would be indicated but not technically feasible because of the bulky or sticky nature of the toxic substance. *References:* 1. Litovitz TL. JAMA 1983; 249:2495–500. 2. Litovitz TL, Schmitz BF. Pediatrics 1992; 89:747–57. 3. Marsteller HJ, et al. Leber Magen Darm 1978; 8:136–44. 4. Taylor JR, et al. Ann Pharmacother 1998; 32:940–6. 5. Coupe M. Hum Toxicol 1986; 5:341–2. 6. Cereda JM, et al. Br Med J 1986; 293:1143. 7. Schranz W. Dtsch Med Wochenschr 1991; 116:1573–4. 8. Iberti TJ, et al. Arch Intern Med 1984; 144:402–3. 9. Pollmann H, Zillesen E. Dtsch Med Wochenschr 1992; 117:643. 10. Saetta JP, et al. J Roy Soc Med 1991; 84:35–8. 11. Classen M, Wurbs D. Z Gesamte Inn Med 1979; 34:211–5. 12. Michaux I, et al. J Toxicol Clin Toxicol 2000; 38:471–6. 13. Lapostolle F, et al. J Toxicol Clin Toxicol 2000; 38:477–82. 14. Nelson L. J Toxicol Clin Toxicol 2000; 38:483–4. 15. Malbrain MLNG, et al. Acta Clin Belg 1994; 49:12–8. 16. Traub SJ, et al. New Engl J Med 2003; 349:2519–26. 17. Robinson T, et al. Surgery 1993; 113:709–11. 18. Choudhary AM, et al. J Clin Gastroenterol 1998; 27:155–6. 19. Sherman A, Zingler BM. Gastrointest Endoscopy 1990; 36:152–4.

89. Poisoning-Induced Hypotension-Why not to Follow the Rules

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Objective: To determine if the catecholamine pressors typically administered to hypotensive patients in the Intensive Care Unit (ICU) are the most effective treatment for drug-induced hypotension in poisoned patients. *Methods:* Comparison of etiology and physiology of poisoning-induced hypotension to hypotension caused by other medical conditions. Evidence-based literature analysis is also included. *Results:* Treatment recommendations for hypotensive ICU patients are based on studies in elderly, chronically ill, or acutely ill patients with an infectious process. Average age of study patients is 64 years. Administration of fluids followed by catecholamine pressors is the usual treatment. However, hypotension in the poisoned patient is caused by receptor blockade, myocardial depression, cardiac ion channel blockade, drug-induced vasodilatation, acidosis or mechanisms unique to the individual drug (e.g., clonidine). Treatment must address the cause of the hypotension and not assume that all hypotensive patients can be treated in a similar manner. The young healthy poisoned patient responds to hypotension with adrenal outpouring of endogenous catecholamines. Adrenergic receptors are sensitive in the young patient. Administering exogenous catecholamines is unlikely to be of benefit as all catecholamine receptors are already stimulated by endogenous catecholamines. Administration of glucagon or insulin/glucose should be considered a first line therapy for the hypotensive poisoned patient. Glucagon is a polypeptide that interacts with catecholamine-independent receptors to stimulate adenyl cyclase and increase cyclic adenosine monophosphate (cAMP). The inotropic effect of glucagon occurs before production of cAMP which may be due to movement of calcium into cardiac cells. Glucagon reversal of hypotension in poisoned patients has been demonstrated in case reports and case series, but prospective evidence is lacking. Insulin and glucose administration stimulates myocardial metabolism of carbohydrate instead of fatty acids during stress. It improves cardiac compression independent of myocardial carbohydrate usage. As with glucagon, insulin/glucose administration has improved hypotension in case reports and series of poisoned patients, but again, prospective evidence is lacking. There have been no trials comparing catecholamine pressors to glucagon or insulin/glucose. Sodium channel blocking drugs (NCBD) bind to cardiac sodium ion channels and prolong conduction through the ventricles, depress the slope of phase 0 of the action potential, and decrease the force of contraction. Alkalosis, sodium loading or a combination may increase dissociation of the drug from sodium channels. Glucagon may reverse hypotension as it increases the slope of phase 0 of the action potential. Cocaine-induced hypotension has

been reversed by administration of drugs that move more quickly on and off the sodium channel. Naloxone administration may reverse the hypotension caused by overdose of drugs (clonidine) which stimulate the α2 adrenoreceptor and the imidazoline receptor and thereby decrease the release of norepinephrine. Sympathetic outflow is decreased which slows heart rate and lowers blood pressure. In a subset of patients with preexisting hyperadrenergic sympathetic tone, naloxone reverses clonidine-induced hypotension. This subset of patients may have a higher baseline concentration of endogenous opioids. Alternatively, clonidine administration to these patients may release greater concentrations of endogenous opioids compared to patients with lower resting sympathetic tone. Naloxone will reverse the clonidine-induced hypotension in the subgroup of patients with significant concentration of endogenous opiates. Calcium channel blocking (CCB) drugs reduce the rate of pacemaker cell depolarization and decrease excitation-contraction coupling. Drug-induced vasodilatation varies among the various CCB drugs. Administration of calcium may increase blood pressure in moderately poisoned patients. Glucagon and insulin/glucose may reverse the hypotension. Beta blockers block the beta-1 receptor and modulate ion channels. Hyperpolarization of cell membrane occurs with decreases inotropy and chronotropy. Treatment is drug specific, but once again, glucagon or insulin/glucose should be considered as first line therapy. It is extremely important to reverse acidosis in the patient with a cardiotoxic overdose. Acidosis decreases myocardial oxygen consumption, impairs myocardial contractility and inhibits the slow inward calcium current. *Conclusions:* Drug-induced hypotension requires specific treatment modalities to address the cause of the hypotension. It is clear that the cause of drug-induced hypotension is multi-factorial, dependent on the characteristics of the individual drug as well as age and health of the patient, and cannot be treated with the same catecholamine pressors typically used to treat hypotensive ICU patients. *References:* Den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. NEJM 2001; 345:1359–67. Stone C, Thomas S, Koury S, et al. glucagon and phenylephrine combination vs glucagon alone in experimental verapamil overdose. Acad Emerg Med 1996; 3:120–25. Farsang C, Kapocsi J, Vajda L, et al. Reversal by naloxone of the antihypertensive action of clonidine; Involvement of the sympathetic nervous system. Hypertension 1984; 3:461–67.

90. Antidote use in Pre-Hospital and In-Hospital Treatments: Are the Rules Identical?

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The mission of pre-hospital emergency care units (MECU) is to take care of critically ill patients, including severely poisoned patients, as early as possible to stabilize them before and during the transport to the most appropriate hospital for further management. The aim is to prevent early complications, thereby decreasing the number of fatalities. Actually, few data are available about the epidemiology of clinical toxicology-related MECU activity: as much as 5 to 10% has been reported by some centers, but many interventions involved non life-threatening situations. An important point is to define which treatment should be started in the pre-hospital phase and which others should be restricted to in-hospital care; until now however, guidelines have only been produced for a limited number of situations. In most poisoning conditions, the primary stabilization of the patient consists of appropriate non-specific and supportive care with special attention to neurological, respiratory and cardio-circulatory conditions. Although the qualification level of the pre-hospital teams varies in different EMS systems, they are usually well trained to deliver such care. Beside these non-specific measures, early intervention of the MECU also gives the opportunity to start more specific treatments including decontamination (eyes, skin, GI tract) and administration of antidotes. Patients transported by ambulance to hospital have a shorter time interval from ED arrival to GI decontamination than patients arriving by other means. Whether they would additionally benefit from pre-hospital decontamination is unclear and administration of activated charcoal (AC) by EMS personnel remains a controversial issue: indeed, some studies have suggested that the risk of aspiration in low-risk patients overdosed with sedatives could overcome the potential benefit in the small number of patients who are at higher risk. It has also been advocated that the small number of high-risk ingestions does not justify the expense in training required to implement AC use in the pre-hospital setting. Such a conclusion is of course not valuable in countries in which the MECU team consists of experienced physicians and nurses from the staff of the emergency department. Actually, it is likely that depending on the training level of EMS personnel, a selected subset of patients who are at significant risk of developing severe poisoning could benefit from early AC administration in the field provided usual guidelines for its proper use are respected. Although, antidotes are only available for a small number of poisons, they may be an essential part of the treatment in some life-threatening situations. Several surveys conducted in different countries have shown the inadequate in-hospital availability. Their availability in pre-hospital emergency services has been rarely evaluated and very few data are available about current practices. Examples of agents that are likely to save lives in the pre-hospital setting include oxygen: 100% oxygen is especially required in carbon monoxide, cyanide or hydrogen sulphide intoxication; atropine is an essential part of moderate to severe intoxication with anticholinesterase insecticides and nerve agents. High doses may be needed until pulmonary muscarinic signs and symptoms are alleviated, so that conventional amounts transported by the MECU may be rapidly depleted, especially when facing multiple causalities. Oxime administration must only be started after atropinization and reoxygenation: it is usually not required at the scene and may be delayed until hospital admission, but the pre-hospital use must be considered in the field in multiple casualties incidents when hospital admission is delayed by field triage and stabilization before transport. Diazepam has been shown to decrease neurocognitive dysfunction after anticholinesterase poisoning but this agent is commonly available in MECU. Prehospital administration of naloxone should be restricted to patients with opiate or opioid overdose that are found with bradypnea. In those with severe overdose complicated by severe hypoxemia (inhalation or respiratory arrest) or hypothermia, intubation, respiratory support and copious oxygenation is preferable. Rules for safe use of naloxone include dilution, titration, and close continuous observation of the patient because of possible adverse effects and short lasting action. Recently, intranasal instillation of naloxone has been reported a valuable pre-hospital alternative to intramuscular injection in patients with difficult venous access. Sodium bicarbonate is indicated for widening of QRS complex associated with hypotension due to membrane stabilizing effect. The primary end-point is the narrowing of the QRS complex, but bicarbonate infusion may also improve blood pressure. The main adverse effects are fluid overload and hypokalemia by transmembrane shift. Patients exposed to smoke from fires may suffer direct injury from hot and irritant gases, and soot, but also poisoning by carbon monoxide and cyanide, so that rapid copious oxygenation is mandatory in all victims. Significant cyanide poisoning is more likely in those with cardiac arrest, unconsciousness, haemodynamic compromise or severe dyspnea at the scene and anti-cyanide antidotes may be needed. Methaemoglobin-inducing agents are hardly used in the pre-hospital setting because of hypotension, lack of methaemoglobin control. The decrease of the blood oxygen-carrying capacity may be especially harmful in patients with anaemia or significant carboxyhaemoglobinaemia. Thiosulfate alone has a too slow detoxifying effect to be useful in the pre-hospital setting and EDTA-dicobalt has adverse effects especially in the absence of significant cyanide poisoning. In the pre-hospital context, hydroxocobalamin certainly appears as the safer antidote. In countries in which an adequate formulation is distributed, its cost unfortunately prevents a wide availability in every MECU. Beside the potentially life-saving value, decision to embark other antidotes in the MECU should take some factors into account: the mechanism of action: only antidotes with toxicodynamic effect are likely to be required in the prehospital setting, especially if the time interval between MECU intervention and hospital admission is short; as the confirmation of the diagnosis will probably be delayed after hospital admission, the use of antidotes in the pre-hospital setting is more likely to be directed against toxidromes than against specific poisons; the ease of use and safety, only requiring monitoring commonly available in the MECU; the cost/benefit assessment; the local incidence of indications and / or the local risk assessment (industrial threat, bioterrorism); the qualification level of the pre-hospital emergency personnel (physicians, paramedics, EMTs, etc). *Conclusion:* Only the use of a few antidotes is likely to be of life-threatening importance in the pre-hospital setting. These agents should be part of the equipment of every MECU and transported at the scene of their interventions and teams should be trained to use these agents properly. For some agents, "strategic stores" should be available when facing multiple casualties. Decision to embark other agents in the MECU should be based on a local risk/benefit assessment based on various criteria, including the professional qualification level of the EMS personnel, the mean delay between intervention at scene and hospital admission. Proper indications for the use of these agents in the pre-hospital setting may not be the same as in the in-hospital environment.

91. The Use and Hazards of EDTA as an Alternative Medicine

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Objective: To discuss the use and hazards of ethylene diamine tetra-acetic acid (EDTA) in current alternative and complementary medicine practice. *Methods:* A review of three databases, Medline 1966–2006, Google Scholar, and Lexis-Nexis 1997–2007, was undertaken to retrieve pertinent articles regarding the practice of using EDTA in alternative medicine practice and the risks of such treatment. *Results:* In recent years, there has been a resurgence in the use of alternative medicines. In the U.S. alone, visits to alternative medicine providers account for 629 million clinic visits costing over $20 billion. Alternative approaches that have been advocated include routine heavy metal screening with provocative challenges, and chelation therapy for a variety of non-traditional indications. Alternative and complementary medicine professional associations include the American College of for the Advancement of Medicine, International Society for Orthomolecular Medicine, International Board of Clinical Metal Toxicology, and the American Board of Chelation Therapy advocate these approaches. In particular, EDTA has been touted for the treatment of cardiovascular disorders (1). Although sometimes not well appreciated, there are two different types of EDTA approved by the U.S. FDA. In 1953, Edetate calcium disodium also known as Calcium EDTA (marketed under the trade name Calcium Disodium Versenate®) was approved for the treatment of lead poisoning. Three years later in 1956 a related EDTA compound, Edetate disodium, was also approved for clinical use. This compound, also known as Disodium EDTA, has been marketed under the trade names Disotate® and Endrate®. The essential difference between these two compounds is that Calcium EDTA's structure has an incorporated Ca^{2+} moiety while Disodium EDTA does not. The use of the latter compound Disodium EDTA has been associated with life threatening and fatal hypocalcemia (2). It has been estimated that between $400 million and $3 billion have been spent annually in the U.S. for the use of EDTA in the treatment of cardiovascular diseases (3). Proponents have argued that this is safe therapy citing the safety record of Calcium EDTA in the treatment of lead poisoning, despite the fact that it is Disodium EDTA that is used in the treatment of cardiovascular diseases. Advocates have cited several small non-controlled studies that suggested that EDTA provided benefit. Proposed mechanisms to explain an advantageous effect include liberating calcium plaque, free radical scavenging function, inhibition of lipid oxidation, arterial dilation to by possible calcium channel blocking actions, stimulation of prostacyclin production and improvement in arterial wall elasticity, and increased production of nitric oxide. However, in 2002, a Canadian RCT study failed to find a benefit for EDTA (4). When its finding were not accepted by chelation proponents, the U.S National Institutes of Health decided to fund a much larger $30 million study in attempt to settle the question of EDTA efficacy in the treatment of cardiovascular disease (5). This study is currently ongoing. *Conclusions:* Medical toxicologists should recognize that the alternative and complementary medicine community accounts for an increasing and very significant component of the health care delivery system and that the continued use of EDTA, particularly Disodium EDTA for non-approved indications requires vigilance and education. *References:* 1. Ernst E. Chelation therapy for coronary heart disease: An overview of all clinical investigations. Am Heart J 2000; 140:139–41. 2. Brown M, et al. Deaths resulting from hypocalcemia after administration of edetate disodium: 2003–2005. Pediatrics 2006; 118:534–536. 3. Seely DM. EDTA chelation therapy for cardiovascular disease: a systematic review. BMC Cardiovasc Disord 2005; 5:32. 4. Anderson T, et al. Effect of chelation therapy on endothelial function in patients with coronary artery disease: PATCH substudy. Am Coll Cardiol 2003; 41:420–425. 5. Kinsel J, et al. Complementary and alternative therapeutics: Rigorous research is needed to support claims. Annu Rev Pharmaco Toxicol 2003; 43:463–84.

92. Quality assurance of Poisons Centre Work - Perspective from Denmark

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Objective: On August 15, 2006, the Danish Poisons Information Centre (DPIC) inaugurated a telephone service for all citizens and medical practitioners in Denmark, the Faeroe Islands, and Greenland. DPIC replaces the closed information service which has been reserved for direct

doctor-to-doctor contact since 1972, answering approximately 4,000 calls a year. *Background:* Denmark, the Faeroe Islands, and Greenland have 5.4 million inhabitants all served by a highly developed, tax-financed, public health system. According to international standards it is possible to serve this population sufficiently with one fully equipped poisons information centre. In the autumn of 2005 the Danish Parliament decided to comply with the WHO / EAPCCT- recommendations defining the demands of a professional poisons information centre and granted eight MDDK/ 1.2 MEUR a year for the purpose. Ten months later the fully functional DPIC manned the telephone lines with the expectation of 35,000+ tox calls a year after a period of two to three years of implementation, equivalent to 700 calls per 100,000 citizens a year. From January 1, 2007, Denmark was reorganized into five main regions, subdivided into 98 municipalities. All public health obligations rest with these regions complemented with selected national institutions like DPIC. *Objective:* DPIC requires upgrading to the highest international level in order to secure wise spending of public finances through prevention of unnecessary use of ambulances, visits to emergency units and GPs regarding harmless poisonings. Another purpose is to promote swift, qualified counselling for the layman to act correctly in order to prevent undue death or disease without time consuming intermediaries. Medical counselling for professionals will continue according to international standards. All counselling will be developed continuously through documentation, critical analysis and clinical research. DPIC has an obligation to educate relevant partners. An open PIC optimises the possibility to survey and document poisoning patterns in preparation for initiating preventative measurements. *Method:* DPIC is a joint venture between Dept. of Anaesthesiology Z (DAZ), Clinical Pharmacological Unit (CPU) and Clinic of Occupational & Environmental Medicine (COEM) at Bispebjerg University Hospital in Copenhagen. This construction is expected to combine high levels of theoretical toxicological skills with the manual toxicology resulting in updating of clinical procedures from primary treatment to intensive care unit therapeutic levels. An innovative approach from DPIC is to engage experienced nurses to answer the tox calls. The nurses possess substantial knowledge of intensive care therapy and have experience from emergency wards or acute internal medicine. They are actively supported by a staff of experienced medical specialists. DPIC is an independent organisational unit within DAZ and holds direct responsibility for services and the securing of professional clinical and theoretical standards. DPIC is a 24-hour-service manned with one secretary, ten nurses, one staff nurse / team leader, one staff doctor with clinical responsibility and one part-time staff doctor. Outside normal office hours medical backup is provided by one of eight specialists in anaesthesiology belonging to ICU/DAZ. COEM provides one consultant and one staff doctor. CPU provides a part-time secretary, one staff doctor and one consultant. Each department contributes with administrative representatives who form a coordination group. If consensus fails to appear, decisions maybe appealed to a committee consisting of the three administrative leaders. Staff members from the three departments frequently participate in formalized personal development sessions, staff meetings, quality assurance committees and research committees. Every nurse has completed a two-month intensive course in toxicology, including professional telephone training, use of advanced computer technology and action cards, documentation and registration techniques and supervised practical exercises. Immediate medical backup is always available to the nurses. All staff doctors and consultants are specialists with substantial toxicological experience. New doctors are trained and introduced to DPIC trough formalised educational programmes. *Quality Assurance:* Joint Commission accredited DPIC in December 2006. The unit is connected to the hospital quality assurance activities. The telephone system is state of the art and monitors all calls, client categories, duration of call, interrupted calls and time variation with reference to statistics. The system can tape the calls to improve documentation and feedback, DPIC awaits the permission to do so. The physical surroundings are above average as are the PCs and other communication equipment. All systems give access to a vast number of databases and have emergency backups. Action cards and instructions follow a systematized template, more than 1,000 has been produced so far. They automatically become obsolete after two years, new approval requires peer-review. All action stations are supplied with relevant literature. Tox calls are all registered electronically. The staff specialists evaluate all calls daily. Comments are presented at the morning conference and are widely discussed. The conclusions are presented in a report which is distributed to the entire staff. Relevant information is collected from the users of DPIC for evaluation, immediate follow-up, educational purposes, research and reporting. DPIC databases are compared to other national or international databases of toxicological relevance. Special or repeated cases are presented at a monthly meeting. DPIC produces posters, manuscripts, lectures, and educational material. All employees are requested to participate in courses and congresses. Professional networks are constantly improved. DIPC publishes a detailed yearbook. *Visions:* To optimize the professional standards and to extend the knowledge of DPIC. To attract and maintain a highly qualified staff. To develop analytical methods to secure optimal handling of all clients and to increase the quality of treatment of the toxicological patient in all departments of the Danish health system.

93. Quality Assurance in Poisons Centre Work: Perspective from Greece

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Poisons Centres were first developed in Europe, the UK, and in F.R.W. Germany (Munich) in the mid 1960s (1963). After the foundation of EAPCCT (1964), consecutively during the next decade, Poison Centres were established in almost all the countries of Europe. The idea behind this was the quick response of physicians to poisoning. Subsequently and as a result of this, the substantial decrease in morbidity and mortality associated with toxic exposure became evident. Poisoning by chemicals is a significant risk in all countries, where substantial quantities and increasing numbers of chemicals are being used in the development process. Most of the European countries have already well-established facilities for the prevention and control of poisoning. Although the needs and the goals of our Health Systems do change over time, prevention of poisoning remains the ultimate goal, along with the public education in a well-constructed program of public safety. In a changing environment, medical personnel have to keep up through medical education, which is the tool. Nowadays, the operation of a Poison Information Centre in a satisfying way depends on two cornerstones: a well-educated and specifically trained staff on one hand, and reliable, up-dated and easily manageable information sources on the other. Once a poisons information service has started to operate, it must more or less instantly launch a process to develop and continuously check the standards and the quality of the service. Poison Centres continue to face old challenges but cannot ignore the new ones that appear in the globalized world. So, not only the European's, but also the World's needs, demand from the PICs to work together in order to develop multidisciplinary strategies to achieve not only the standards of the every day service, (in accordance with the self assessment checklist for minimum and optimum standards which the EAPCCT has developed), but also to prepare the PICs for the coming years and quality aspects of the future. European PICs must schedule new activities in an organized manner capable of being engaged by the European Union, in the fields of prevention of acute poisoning, real time surveillance system of detecting chemical releases and other environmental hazards, as well as, recognizing new objects and ways of intoxication (toxicovigilance). Fundamental aspects for quality assurance in the PICs work are: 1. 24-hr availability to provide information via telephone from trained medical staff preferably for complex and serious poisoning cases. 2. Location within or close to a hospital. 3. Reliable, adequate and easy to use database of all the drugs and poisons. 4. Cases data base with classification into therapeutic and follow up protocols. 5. Analysis and publication of epidemiologic studies, at least as annual reports, and use of specialized surveys to elaborate the policy and operation of their strategies in prevention and education. The Greek National PIC is located in Athens and was established in 1975 as the only Greek PIC. It is a part of the Aglaia Kyriakou Children's Hospital Complex - one of the two biggest Greek Children's Hospitals. The number of calls from 4,000/per year back in 1975 has risen over the years to about 40,000/per year. Our PIC exceeds basic quality standards such as those described above: 1. a 24-hr available line open to the public, as well as to health professionals and to Emergency Services. 2. a physician in charge every 24hrs, and a pharmacist till 22.00 pm. 3. Poisindex-R used as information source in routine daily basis, as well as bibliography documents for plants and agro-chemicals. 4. Laboratory analysis of drugs levels in emergency cases and also measurements for the daily hospital routine. 5. The Greek National PIC is also a member of the ENTIS. Our perspectives are the improvement of additional activities which are already in operation: 1. Computerized data: a) creation and installation our own data base for chemicals; b) link over the net with the Hellenic Ministry of Rural Development for the creation of an updated database of pesticides and other agrochemicals in commercial use in Greece; and c) drugs linked over the net with the National Organization for Medicines. 2. The built up of an archive system for the safety data products documentation for all chemical products and drugs existing in the Greek market. 3. Education activities like: a) poisoning prevention in childhood (targeted population groups such as parents, teachers, etc.); b) poisoning prevention in collaboration with Public Health Authorities, organizations or industries (targeted population: farm workers, industrial workers, etc.); c) special educational courses in the Medical and Nursing School of the universities across the country; and d) training of paediatricians and internal medicine physicians - in the form of CME courses - in the field of emergency medicine and especially in poisoning. 4. Publication of our annual epidemiologic reports and the documentation of the treatment protocols and the follow up results. 5. Critical analysis of our studies' results in order to create new policies and identify new target groups of population for our education activities on poisoning prevention. Three of our studies will be presented in this congress. 1. Availability of CNS acting drugs or agrochemicals in persons with intentional intoxication (prescriptions from psychiatrists or commercial delivery from agriculturalists). 2. The results of education activities in farmers (performed in collaboration with Hellenic Ministry of Rural Development and industries selling highly toxic products). 3. Availability of antidotes in Greek Hospitals. The results will be the basis for farther suggestions to the health authorities. Athens' PIC is part of Public National Health System. It is covered financially from the budget of the Hospital that it belongs to, but there are a lot of demands for inputs to initiate new activities and achieve continuous quality control. *References:* Erik A. Comparison between eight poisons information centres in Europe. Clin Toxicol 2006; 44:345–350.

94. An EAPCCT Pilot Project for Europe-Wide Common Data Collection in Poisons Centres

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Objectives: Globalization in trade of chemicals and products with transboundary availability of all kinds of products, increasing migration, and the threat from chemical terrorism imposes a need on Poisons Centres to have access to an international database. The American Association of Poison Control Centers (AAPCC) has developed a Toxic Exposure Surveillance System TESS (1,2), which is funded by the U.S. government and involves all Poison Centers in the U.S.A. Participation is mandatory for Poison Center accreditation. The TESS includes upload of newly entered cases every couple of minutes to a central server, thus creating the basis for continuous toxicosurveillance and signal detection. There is no comparable system in Europe with the most important barriers being differences in language, classification, and database structure. While the ASHT project (Alerts and Surveillance for Health Threats) aims to investigate the feasibility of an EU-wide surveillance system for syndromes associated with deliberate chemical releases, the EAPCCT Board has decided to set up a pilot project for a common European poisoning data collection tool as a technical proof of principle. *Methods:* The database has the purposes to serve as a tool for improving the management of cases of poisoning, to create a standardized basis for risk assessment and dose-response analysis, to detect new features of poisoning (signal detection), and to generate data on the epidemiology of poisoning. The data will be collected in coded form on a central server, uploaded from the local Poisons Centres' databases. Software interfaces will have to be programmed locally to export data and translate them from local language and classifications into common code automatically. Definitions will be agreed upon and provided in English language. The dataset chosen for common data collection is limited to items needed for the purpose of the project, and also limited to standardized ("controlled") terms which can translated unambiguously. *Results:* The pilot project will show the feasibility of common data collection in Europe and problems arising from it. It is planned that the system will provide first results until May 2007. *Conclusion:* Common data collection provides rapid dissemination of information for increased networking among Poisons Centres. It will hasten harmonization in data handling and lead towards a more unified standard in Poisons Centres. It increases the visibility of the work and services which Poisons Centres provide to all stakeholders, and highlights the position of the Poisons Centres in health improvement towards governmental and non-governmental, on an European level. *References:* 1. Wolkin AF, et al. Ann Emerg Med 2006; 47:170–6. 2. Watson WA, et al. Toxicol Appl Pharmacol 2005; 207:S604–10.

95. Provision of High Quality Cost-Effective Poisons Information

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Introduction: The New Zealand National Poisons Centre (NPC) was established in 1964 and provides poisons information to New Zealand (population 4 million) and, recently, a number of Poisons Centres worldwide. In an effort to provide high quality cost effective poisons information the NPC developed its own Internet accessible database, TOXINZ (www.toxinz.com) and backed this with a range of mechanisms to ensure its quality. *Background:* TOXINZ currently contains poisoning treatment recommendations for the management of some 134,000 chemicals, pharmaceuticals, plants and hazardous creatures. Simple first-aid advice is free for the public, but a subscription is required to access full medical treatment recommendations. An exception is made for recognised Poisons Information Centres who are provided free entry on application. There are currently 33 Centres in 27 countries that have gained access to TOXINZ in this way. Considerable effort has gone into the quality assurance of the content of this resource including extensive research of the toxicology literature to develop monographs; robust internal mechanisms to review submissions; the establishment of an international editorial board; two yearly (2001, 2003, 2005) quality assurance surveys of sentinel Emergency Department database users; and regular analysis of poison centre enquiry statistics. When surveyed in 2005, 88.5% of New Zealand Emergency Department users considered TOXINZ good or excellent, and clearly preferred its use to other information sources. *Discussion:* A significant feature following the introduction of Internet access to poisons information was the decline in use by hospital staff of the traditional telephone consultation service provided by the NPC. Since the introduction of TOXINZ the number of telephone calls received by the NPC from hospital based staff in New Zealand dropped by 76.6%. Initially there was concern that reduced direct access to the poisons information service may potentially lead to a decline in Centre funding. However, when enquiries to TOXINZ were included, total enquiries from hospitals increased 420%. Clearly, these users preferred to access their poisons information via TOXINZ, rather than telephone, and were utilising this information more than ever before. Indeed, yearly enquiries from New Zealand based subscribers and free access first aid users of TOXINZ for the year to October 2006 outnumbered telephone calls received by the NPC (37,490 to 30,041). Totalled, this gives a "penetrance" of 16.9 enquiries per year per 1,000 population served (up from 4.75 in 2001, the year prior to the introduction of TOXINZ). Given that the funding provided to the NPC had not similarly increased during this period it is evident that the NPC service is now significantly more cost effective at disseminating poisons information than when using the 'telephone only' model. A number of steps have been taken to ensure the quality of the product. Each poisoning management monograph is researched by a NPC medical toxicologist or trained Poisons Information Officer. A review process is subsequently undertaken within the Centre, initially by a Poisons Information Officer, then a Medical Toxicologist. The monograph is then sent for external review by a member of the International Editorial Board. Once corrections are completed, the monograph is made live on the TOXINZ website. Feedback from overseas Poisons Centres has provided valuable recognition of areas where the database can be extended or content improved. Indeed, in an effort to further progress the range and quality of information, software development is being considered to allow International Poisons Centres to contribute more directly to TOXINZ. Such a mechanism will allow country specific details, such as trade names, to be added to the database. This will allow users from other parts of the world to recognise such products and their composition, reducing problems associated with the international trade of chemical goods, or, for instance, the arrival of tourists with pharmaceuticals with unrecognised trade names. Such an interaction can further be extended to allow participating Centres to contribute full poisons management documents and participate in the peer review of monographs prepared by other Centres, thereby, ensuring high quality contributions. In this way, a truly international database of poisoning recommendations can be developed, and, as TOXINZ is free to participating Centres, achieved in a highly cost effective way for all. It is recognised that different geographic regions may use differing treatment protocols for the management of poisoning. This may be due to local practice, resourcing constraints, or lack of or different antidote(s). To allow for this, versions of TOXINZ can be formatted to provide geographically appropriate information should the need arise. *Conclusion:* The New Zealand National Poisons Centre has adopted innovative strategies in the use of information and communication technologies to improve its provision of poisons information. Its service is now not only of high quality, but more cost effective (given its increased usage) than ever before. This approach can also allow access to quality assured poisons information to other Centres around the world and potentially provides a mechanism for international contribution. TOXINZ therefore has the potential to enhance the provision of high quality, cost effective poisons information internationally.

96. Evolution of Quality Indicators of Toxicological Care in an Emergency Department

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Objectives: The quality of care offered to intoxicated patients in the Emergency Department (ED) can be measured by indicators. We compared the results obtained by measuring the quality of health care in acute poisonings before and after the administration of corrective measures. *Patients and Method:* Twenty-six quality indicators of the care of intoxicated patients were designed. Five were structural (availability of protocols, antidotes, gastric lavage tubes and qualitative and quantitative analytical tests), 17 were procedural (time between reaching hospital and receiving medical attention, time between reaching hospital and initiation of decontamination measures, record of vital signs, suitability of indications for the administration of flumazenil, naloxone and gut decontamination, and others), 2 results (mortality in medical drug and non-medical drug poisonings), 2 administrative (legal record and compliance with minimum data base), and 1 perceived quality (complaints). In the first stage (October 2004), these indicators were measured in 139 consecutive patients. After analyzing the results, a protocol of good toxicological practise was drawn up and distributed to ED physicians and 8 training sessions for medical residents and nurses were organized. In the second phase (October 2005), the same indicators were investigated in 142 patients. Data were analysed using the SPSS program version 10.0. The level of statistical significance was established as $p<0.05$. *Results:* A total of 281 intoxicated patients were evaluated; 139 in the first stage and 142 in the second stage. No significant differences were found between the two groups with respect to sex, age, type of poison, intentional poisonings or Glasgow Coma Score at admission. No significant differences were found between the two groups of patients with respect to the 5 structural indicators. There was a significant improvement in the recording of vital signs (heart rate [$p = 0.041$], respiratory frequency [$p = 0.026$] and temperature [$p = 0.027$]) and a worsening in the waiting time before intoxicated patients were seen [$p = 0.024$] and the time to gut decontamination [$p = 0.022$]. No significant changes in the administrative or perceived quality indicators were observed. *Conclusions:* The quality of toxicological care in an ED is measurable and the use of indicators allows its evolution to be compared. Indicators of structure, results, administration, and perceived quality did not change significantly. Indicators of process were modified: those related to nursing care (record of vital signs) improved and those related to triage worsened (delays in care and initiation of gut decontamination). Improvements in the quality of care of intoxicated patients in an ED requires continued effort and increased awareness on the part of all health care professionals.

97. User Satisfaction and Health Economic Effects of a Poisons Information Centre - Norwegian Experiences

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Objective: To assess the user satisfaction and the impact of the Norwegian Poisons Information Centre (NPIC) on national health economics. In addition, to discuss the methodological challenges by performing user group studies. *Methods:* In 2004, two separate studies were carried out. The first evaluation was a questionnaire study performed by a Masters degree student in 200 consecutive adults over two months who called NPIC regarding drug exposure in children below five years. Callers were invited to participate in the study by NPIC duty personnel during their first phone conversation. Informed consent was an inclusion criterion. All interviews were done by telephone 2–5 days after the call. The other study was designed and carried out by the University of Oslo to survey user satisfaction of callers in acute exposed cases among the public and health personnel in hospitals as well as in emergency centres. In addition, this study assesses the impact of NPIC on national health economics. Callers were invited by NPIC personnel to participate and had to give informed consent. Private citizens were interviewed by telephone using a structured questionnaire form with 22 questions within 10 days of the NPIC call. Only cases where NPIC considered a visit to a health care facility unnecessary were selected. Questionnaire forms were submitted to physicians and nurses who consented to participate in the study. All participants (private citizens as well as health personnel) were asked about user satisfaction and what they would have done if NPIC was not available. Reductions in costs by keeping the exposed citizen at home were calculated. The health care cost savings for in-patients and policlinic patients were based on the answers given by health care providers, change in use of time and hospital stay of patients. Calculated cost savings used standardized fees. *Results:* In the call back study in 200 citizens asked for advice in exposed children, 99 % were satisfied with the form and content of answers given. 12% found the telephone response time too long. 100% said that they will call NPIC again. In the other study, 309 out of 310 private citizens interviewed were satisfied with the information received. 83% of the 435 physicians and 89% of 233 nurses who completed the questionnaire forms were satisfied with the information received from NPIC. Regarding health economic effects calculated from the second study, 75% of the private citizens said they will call and 9% go straight to the nearest health service (medical officer, emergency ward, hospital) if NPIC had not been available. In 2004, NPIC received 13,591 calls from the public where no health care intervention was deemed necessary. Based on various assumptions, the avoidance of unnecessary use of health service may save costs between 0.7–3.3 mill. NOK. In the health service, the summarized cost savings, based on the replies obtained from medical officers, emergency wards and hospitals, were 2.3 mill. NOK due to increased time consumption (about 50 min), increase (1 day) in hospital stay of patients and 4.6 mill NOK due to further patient referral. The total calculated cost savings were thus estimated in the range of 10–13 mill. In 2004, the budget for NPIC was around 13 mill. NOK. *Conclusion:* User satisfaction was very good among the general public and good among health personnel. In particular, parents were very satisfied with the service of NPIC when small children have been acutely exposed to various agents. However, selection bias caused by NPIC duty personnel excluding participants and limited reply response by users must be considered. The health cost savings were equal to or somewhat less than the budget of NPIC. However, it is difficult to apply health economic principles to NPIC activities, which also comprise other services as well as the 24-hr telephone service. In addition, the cost savings have taken into consideration neither time used by private citizens, transport and anxiety nor possible change in treatment quality.

98. Health Economic aspects of Poisons Centre Work

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Objectives: Today, Poison Centres do not only have to follow the evidence base in medicine, but also to show the cost effectiveness of their services in order to maintain proper funding. Under this financial pressure the number of Poison Centres has decreased considerably during the last 5 to 10 years, not only in the United States, but in European countries as well (1). The aim of this exercise is to give an overview of health economic aspects of Poisons Centre work. *Methods:* The medical literature was searched using "Poison* Centre/Center" together with "economy" and "cost effectiveness" as search terms. In addition, related citations were searched related to relevant articles. Results from the Swedish and Swiss Poison Centres were included in the analysis (2,3). *Results:* Miller and Lestina (4) have performed a benefit-cost analysis based on published literature, including two reports which suggest that 33% to 42% more cases of poisoning would be medically treated without Poison Centres; both studies examined the change in use of other services after Poisons Centres ceased operation. For the U.S., Miller and Lestina calculated that the use of a Poisons Centre reduced the number of patients who were medically treated but not hospitalized for poisoning by 350,000, and reduced hospitalizations by 40,000 in the year 1992. The average public call to a Poison Centre prevented USD 175 in other medical spending. Harrison et al. (5) performed a cost-analysis to determine if Poisons Centres were economically justifiable. An expert panel evaluated the morbidity and mortality of four common toxic exposures (overdoses of cough or cold medications in children, paracetamol, tricyclic antidepressants, and pediatric exposure to cleaners). When a Poisons Centre was used in the management of a poisoning, the cost per successful outcome was approximately 50% less than without the service of a Poisons Centre. Bindl et al.

(6) performed a survey of callers who were asked which medical aid they would have sought without the availability of a Poisons Centre in Germany. They based their calculation of savings on the total number of calls and a standardized fee for medial treatment. Savings in cost for health insurance was 20% to 50% of the annual budget of the Poisons Centre. Personne & Persson (2) in Sweden performed an inquiry in public callers by telephone interview. Without poisons information services the general public would have gone directly to a hospital (37%) or to a general practitioner (7%). The total savings were estimated to be 15 million Swedish Crowns. A similar approach was chosen by Fehr and Kupferschmidt in Switzerland (3), and they found that they could prevent 5,000 cases annually from contacting health care services unnecessarily on the basis of 7 million population and 21,000 public calls to the Poisons Centre per year. There are other studies with similar approaches (8,9). Götschi and Kupferschmidt (7) investigated the benefits of the Poisons Centre services for physicians, and found that 65% said that the call to the Poisons Centre was time-saving, and 96% said that retrieval of information from other sources would be more time-consuming or impossible. Personne & Persson (2) performed an inquiry in hospital doctors (by questionnaire) 85% of whom answered that they would have spent more time on searching toxicological information, and 15% answered that the hospital stay of their patients would have been prolonged, leading to estimated savings of 7 million Swedish Crowns. *Conclusion:* There is a lot of evidence that the services of Poisons Centres lead to considerable cost savings in public health. Using a Poison Centre is always more cost-effective than the alternative without, regardless of average inpatient and emergency department costs (5). While savings by Poisons Centre services to the general public from preventing unnecessary medical action are well shown in the literature, the economic impact of recommendations to physicians is less well studied. The economic aspect is an important argument for Poisons Centres to not only answer calls from medical professionals but from the general public as well (10). *References:* 1. Krenzelok EP. J Toxicol Clin Toxicol 1998; 36:545–7. 2. Personne M, Persson H. J Toxicol Clin Toxicol 2002; 40:294. 3. Fehr M, Kupferschmidt H. J Toxicol Clin Toxicol 2002; 40:294–5. 4. Miller TR, Lestina DC. Ann Emerg Med 1997; 29:239–45. 5. Harrison DL, et al. Arch Intern Med 1996; 156:2601–8. 6. Bindl L, et al. Vet Hum Toxicol 1997; 39:48–50. 7. Götschi S, Kupferschmidt H. J Toxicol Clin Toxicol 2004; 42:503–4. 8. Darwin J, Seger DL. *Ann Emerg Med* 2003; 41: 59–60. 9. Geller RJ, Looser RW. *Vet Hum Toxicol* 1985; 27: 521. 10. Mathieu-Nolf M, Furon D. Vet Hum Toxicol 1990; 32:32–4.

99. Translating the Evidence Base into Clinical Practice and Behaviour

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In the last 50 years, the process of changing medical practice has been a predominantly driven by evidence derived from clinical trials. Where such information is less convincing, or essentially absent, consensus groups may be established to guide policy. Increasingly funding agencies, either government or insurance, wish that the care provided should be optimal. All medical specialties therefore have to address the issue of identifying best practice, and then implementing it. The challenge of moving from the individual physician as expert to the "expert" group policy applied by an individual is therefore universal. Many specialties through their academic societies promote what they believe to be best practice. Some governments have also gone further by delineating acceptable clinical care strategies, which may often be based on financial assessments (1). Clinical toxicology is no exception and has, through the joint and individual activities of academic societies produced guidelines. Unfortunately, in part due to attitudinal differences, and in part local practice, these guidelines have not always appeared to agree (2,3). Poisons Information Services are almost unique in that physicians and nurses from organisations other than those in which they are based will ask for treatment advice. It is now clear that such advice is likely to differ if a different "expert" is asked. Within a country's health service it is not unreasonable to expect care to be of a similar standard. As a starting point processes for agreeing and delivering that standard within hospitals need to be clear. The forces that make change, particularly forceful personality and a well-expressed view, may also be the ones to obstruct it. In toxicology some clear examples can be presented. Opinions on the roles of ipecac, gastric lavage, activated charcoal, whole bowel irrigation, indications for physostigmine and flumazenil, and intervention plasma concentrations for paracetamol poisoning are some of the more obvious that have afflicted clinical toxicology. Similar arguments about best practice have also affected cardiology and the management of acute myocardial infarction and oncology and management of specific cancers. The approach here has been to identify areas of uncertainty and mount targeted clinical trials. This has been facilitated by the cohesiveness of the professional groups, the selection of patients into specialist treatment areas, and very significant financial investment in clinical trials by the pharmaceutical industry. Within individual countries best practice in clinical toxicology can however be developed based on a collaborative approach with a common format for presenting treatment advice, and mechanisms for formal review of that advice. Clinical toxicologists may also influence patient care by alerting regulatory authorities to toxic hazards and hence changing practice in a more direct way (4). The process of change within the United Kingdom may serve as a model for other countries. A single national service is endorsed by relevant government agencies (NPIS). Core agreed policies for managing cases of poisoning nationally are agreed by an expert clinical group of UK clinical toxicologists at regular meetings. Treatment guidance is transmitted via a single database, TOXBASE, supported by a network of Poisons Information Centres which in turn is supported by a UK single clinical toxicology rota of approximately 12 consultants actively involved in managing poisoned patients (5). This group also meets regularly and exchanges information on difficult clinical cases. As government supports the NPIS its advice is also promoted by official publications, including the British National Formulary. The advice is therefore perceived as being accurate, authoritative and peer reviewed by other clinical groups. Active interaction is also sought with these groups in order to strengthen confidence. Common strategies promoted by the NPIS include: abandonment of ipecac; strict limitation on gastric lavage; targeted use of activated charcoal; paracetamol treatment lines for acetylcysteine intervention. Evidence suggests that these changes in policy have influenced local practice more than international practice (6,7). Key problems facing toxicology in the future are those of patient recruitment to clinical trials and defining objective questions for such trials. Financial restraints will be significant unless major pharmaceutical companies invest in the projects or national governments or EC funding of health care research shifts its focus. Finally only if there are clinical facilities able to conduct targeted poisons research within a clinical toxicology or emergency care framework will such projects be deliverable. Implementation requires agreed consensus and local acceptance. Evidence of disagreement between what are perceived to be opinion leaders is a key barrier to such progress (8). *References:* 1. Nice self-harm guideline. Available at, http://www.nice.org.uk/guidance/CG16. 2. Position paper: Ipecac syrup. J Toxicol Clin Toxicol 2004; 42:133–43. 3. Manogurera AS, et al. Clin Toxicol 2005; 43:1–10. 4. Afshari R, et al. B J Clin Pharm 2005; 60:444–447. 5. Good AM, et al. Clin Toxicol 2006; 44:417. 6. Good AM, Bateman DN. Clin Toxicol 2005; 43:533. 7. Juurlink DN, McGuigan MA. J Toxicol Clin Toxicol 2000; 38:465–70.

100. How to Ensure that Poison Centers adopt New Clinical Evidence

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Objective: It is estimated that information will double every 73 days by the year 2020 (1). To prevent the data explosion from incapacitating poison centers, they must review emerging clinical evidence, filter it to determine what is relevant, and then apply the new clinical evidence to the management of the poisoned patient. What is currently a daunting task has the potential to become overwhelming. The objective of this presentation is to address the application of new clinical evidence to patient management by poison centers and to suggest strategies on how this can be facilitated in the future. *Discussion:* Poison center professionals utilize their knowledge (a combination of information, clinical evidence and experience) to make decisions regarding the impact of poisons on the environment and humans, how to manage the poisoned patient, how to determine appropriate educational tactics, etc. Until the last three decades, there was limited information available to poison centers. The number of toxicology-related reference texts has grown from a scant few to hundreds; information databases have emerged from card systems, to microfiche and now to electronic systems that have nearly infinite storage and retrieval capability; and the clinical toxicology literature is immense, making it impossible to maintain awareness of the contemporary literature. With this abundance of information, the ability of the poison center staff to address challenging issues and to improve patient care has been enhanced. While the quantity of reference material has increased dramatically, the quality of the information has been addressed only over the last two decades with the emergence of evidence-based medicine. This concept embodies a robust system of examining and grading the evidence. Theoretically, this should provide poison center staff with levels of evidence that facilitate the application of clinical research to actual practice. However, the taxonomy associated with grading the levels of evidence has not been standardized and is often confusing. An estimated 100 grading scales are used by various medical journals and the evidence scales even vary within the same issue of some journals (2). Given the imposing nature of the information explosion, every poison center could justify having a fulltime information officer to address new clinical evidence and determine if it has a role in patient management. However, most poison centers do not have the resources to commit to this type of position, nor does the staff have the time to interpret the daily influx of literature and assimilate it into clinical practice. Even if there was time for evidence-based literature evaluation, there are very few poison center professionals who are experts in critical literature appraisal. Therefore, new evidence is incorporated very slowly into poison center practice. While the toxicology societies strive to improve patient care through the publication of evidence-based position papers and practice guidelines, there is not uniform agreement between the societies on some of the issues. For example, in 1997 the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) published a position statement that discouraged the use of ipecac syrup (3), as did the American Academy of Pediatrics 2003 (4). Yet, in 2005 the American Association of Poison Control Centers (AAPCC) published a guideline that concluded that there was an acceptable benefit-to-risk ratio with regard to the use of ipecac syrup (5). Similar discordant and confusing evidence abound. AAPCC data were used in a 2003 publication to demonstrate that the ingestion of elemental iron 61 mg/kg did not adversely affect patient outcomes (6). The AAPCC 2005 guideline on iron ingestion recommended hospital referral for patients who ingest more than 40 mg/kg of elemental iron (7). The voluminous amount of literature and the apparent dissonance between the positions taken between and within professional societies add further confusion for poison center professionals with regard to applying evidence to clinical practice. *Conclusions:* Within the near future it is not possible to ensure that poison centers will be capable of adopting new clinical evidence in an organized fashion. However, it is clear that standardization of the taxonomy that is used to describe the levels of evidence in the toxicology literature, especially in Clinical Toxicology, the flagship journal of the AACT, AAPCC and EAPCCT would assist poison centers in their quest to adopt clinical evidence uniformly. Professional societies should work toward achieving consistency when similar position papers/statements and guidelines are produced. Furthermore, the professional societies should consider the establishment of a proactive scientific review committee that works under an umbrella of cooperation to address new clinical evidence so that a uniform interpretation can be shared with all poison centers. Finally, poison centers should consider adding an information officer who is responsible for the daily review, interpretation and assimilation of clinical evidence into poison center practice. *References:* 1. Krenzelok EP. Poison centers at the millennium and beyond. J Toxicol Clin Toxicol 2000; 38:693–696. 2. Ebell MH, Siwek J, Weiss BD, et al. Simplifying the language of evidence to improve patient care. J Fam Pract 2004; 53:111–120. 3. Krenzelok EP, McGuigan M, Lheureux P. AACT/EAPCCT position statement: Ipecac syrup. J Toxicol Clin Toxicol 1997; 35:699–709. 4. American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention. Poison treatment in the home. Pediatrics 2003; 112:1182–1185. 5. Manoguerra AS, Cobaugh DJ. Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons. Clin Toxicol 2005; 43:1–10. 6. Benson BE, Cheshire S, McKinney PE, et al. Do poison center guidelines adversely affect patient outcomes as triage referral values increase? J Toxicol Clin Toxicol 2003; 41:585–590. 7. Manoguerra AS, Erdman AR, Booze LL, et al. Iron ingestion: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol 2005; 43:553–570.

101. Developing Multicentre International Research

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Background: Multicentre international research has been utilised in many areas of medicine, especially in industry-funded trials. However, this type of research approach is rare in toxicology

especially if you exclude observational and data audit studies. This may be the result of relatively poor funding in clinical toxicology but it is more likely to be due to the lack of a central driving force to address the practical issues. *Methods:* A literature search examining design and development of multicentre research (either national or international) was undertaken. Existing SACTRC procedures and experiences were reviewed. *Results:* There was no literature on the process of developing international multicentre research. Although there are numerous guidelines concerned with proper research conduct. Most evidence based literature focuses on approaches for ethical review for multicentre research within countries. A number of areas were identified in the SACTRC experiences which have been important in the development of multicentre research within Asia. *Discussion:* There are many reasons for Clinical Toxicology to explore international multicentre research. Such partnerships allow the research to draw upon particular strengths of individual members (e.g., analytical, statistical, and clinical). Multicentre projects allow a greater chance of accumulating the numbers of patients required to make clinically and statistically useful observations especially for poisonings that are relatively rare. There is a greater chance of getting heterogeneity of study population and of compounds being studied. Also, such results may be more generalisable and easier to translate into practice as the ownership is wider and there is greater chance of local advocacy. There are real and perceived barriers to establishing such research. Lack of funding is important in trials which require costly logistics (e.g., transport, analysis consumables). Logistics can also be complicated by local customs regulation. For research based on information collection and transfer logistics is not such a barrier. As multiple centres requires multiple research partners with a high level of consensus and co-ordination, these partners need to be engaged, interested and active. Identifying a relevant research question is pivotal in this process and ideally early consultation in the study design of the team members allows identification of leaders, passengers and observers. The partnership is important as successful implementation of trials often depend upon knowledge and accommodation of local political and socioeconomic realities. The type of research can be very important in the success of the implementation, in general observational clinical hospital based research sits at one end of a continuum of cost, complexity and controversy that spans to more complex RCTs with community follow-up. If we accept that in many important areas of toxicology there is no well-defined treatment this can lead to a significant variation in the local standard practice, this variation may be based on scientific & cultural beliefs or economic reality, Asian studies involving gastric decontamination provide a good example. Such variation may be more easily encompassed in observational studies but is potentially a barrier in interventional studies. Ethical permission is difficult to coordinate. Despite the development of central ethical review boards for multicentre studies at national levels, local centres will have a legitimate need to review protocols which has been shown to slow processing. While this may be appropriate in view of local conditions most protocols cannot withstand too much local variation. Moving research into multiple countries reveals wide variability in ethical experience, medico legal and confidentiality requirements. In such settings using well-defined international guidelines as an ethical basis to ensure appropriate collection, use, and sharing of data and samples is an important benchmark to underpin the master protocol. The effects of site-specific variations from protocol on the study results have to be considered a priority, in all cases the master protocol needs to be appended to any local application. Special attention needs to be directed to consent and patient information in multiple languages, blinded reverse translation is mandatory to ensure compliance with the original protocol. Research involving patients with deliberate self harm are often out of the experience of the individual ethics committee and so the issues related to self harm need to be explored carefully. In practice this may mean that initial trials are often observational or very simple and non-controversial. *Conclusion:* The establishment of multicentre trials networks in toxicology has great potential but it is complex. It is useful to consider it as an iterative building process towards a long-term research network rather than a single project.

102. Two Lethal Poisonings with Fat Burner Containing 2,4-Dinitrophenol in Germany

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Objective: 2,4-Dinitrophenol (DNP) has been used as drug (1) and pesticide and is used as a chemical intermediate. DNP causes hyperpyrexia and death by uncoupling mitochondrial phosphorylation. Poisonings occurred in industrial productions, especially when it was used as a drug for weight-loss (withdrawn from market by FDA in 1938) (2) and as a lifestyle product for the same purpose in the US in recent years (3). In summer 2006, the GIZ-Nord Poisons Centre in Göttingen, Germany, was consulted in two lethal DNP poisonings. *Case Series:* (A) A 19-year-old previously healthy but obese woman ingested half a teaspoon of a "fat-burner" purchased from an internet advert. Several hours later she suffered from vomiting, headache, hypertension (180 mm Hg), and tachycardia. When she noticed an increasing body temperature (up to 41 degrees Celsius) she was admitted to hospital. Laboratory findings showed an increase of creatine kinase. Within four hours she developed pulmonary edema and died of multiorgan failure. The post-mortem examination showed brain edema, lung edema, fatty degeneration of the liver, and shock-induced renal lesions. DNP and its metabolite 4-amino-2-nitrophenol were detected in urine sampled at time of admission, DNP concentration was 54.6 mg/l. Post mortem DNP concentrations have been determined to be 19.3 mg/l in peripheral blood and 8.6 mg/l in heart-blood. (B) Four weeks later a 19-year-old man suffering from depression took about 4 grams DNP in suicidal intention after reading newspaper reports of the first case. He was found unconscious with hypertension (170/100 mm Hg), tachycardia, increased body temperature (above 41 degrees Celsius) and massive metabolic acidosis. He died from respiratory failure within two hours. Rigor mortis occurred already during unsuccessful reanimation procedure. *Conclusion:* In the 1980s DNP has reappeared in lifestyle products without official approval in the US. Today, it can be purchased as a powdered substance or capsules via the Internet everywhere. DNP causes severe poisoning in moderate overdose. Therapy is mainly supportive, but dantrolene may improve outcome (4). This case series demonstrates that DNP poisonings do also occur in Europe. Evaluation of an unknown cause of a hyperthermia should include ingestion of DNP, toxicovigilance seems to be necessary. *References:* 1. Cutting WC, et al. JAMA 1933; 101:193–195, 2. Parascandola J. Mol Cell Biochem 1974; 5:69–77. 3. Hsiao AL, et al. Clin Toxicol 2005; 43:281–285. 4. Barker K, et al. Clin Toxicol 2006; 44:351.

103. Acetic Acid Ingestion – Corrosive Injury and Systemic Toxicity

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Objective: Food preservative containing 80% acetic acid water solution is commonly used in the Balkans and ex-USSR countries. Ingestion of this agent produces corrosive injury of digestive tract mucosa and systemic toxicity including acidosis, haemolysis and acute renal failure (ARF). We investigated the correlation of acetic acid toxic effects, with the severity of digestive tract injury and sequelae development. *Methods:* Analysis included 72 patients admitted due to suicidal ingestion of acetic acid, divided into groups according the grade (I-III) of digestive mucosa injury diagnosed by emergency endoscopy (or necropsy). Acid-base status was estimated by arterial blood gas analysis. Tests for haemolysis included plasma determination of unconjugated bilirubin and lactic dehydrogenase (LDH) activity. Renal function was estimated by measuring blood BUN and creatinine, and urine diuresis. Management of the acute phase was supportive and symptomatic, including sodium bicarbonate for acidosis correction, H2 receptor antagonists or proton pump inhibitors (PPIs), diuretics and haemodialysis in case of oliguric/anuric ARF. Patients were followed for sequelae development up to one year. *Results:* Emergency endoscopy (or necropsy) revealed grade I injuries in 8 patients, grade II injuries 33 patients and grade III injuries in 31 patients. Systemic effects were not present in cases with grade I injuries. In cases with grade II injuries, laboratory signs of haemolysis were observed in 40% of patients, causing renal impairment in 27% of patients, including a single case of anuric ARF. Grade III injuries were accompanied by renal function disturbances in 84% of patients, with high incidence of oliguric/anuric ARF (71%). There were statistically significant differences between the groups regarding the incidence of renal disturbances ($p<0.01$), as well as their severity estimated by the need for haemodialysis ($p<0.001$). Mortality was 18%, and all patients with lethal outcome had grade III corrosive injury. Within the group with grade III injuries, patients treated by haemodialysis and patients with lethal outcome were significantly older ($p<0.05$). The incidence of sequelae development in survivors with grade II-III corrosive injuries was 14%, with more frequent distal esophagus stenosis (10%) than stenosis of pylorus (4%). Endoscopic balloon dilatation was treatment of choice, and was successful in all cases. *Conclusion:* The study confirmed strong association of corrosive injury severity and systemic toxic effects. Because of ARF high incidence, the mainstream of initial treatment should be maintenance of adequate renal perfusion and reduction of intravascular haemolysis by correction of acidosis. Though acids typically produce antropyloric stenosis, this study demonstrated more frequent development of moderate stenosis of distal oesophagus which could be corrected by endoscopic balloon dilatation.

104. Permethrin Poisoning in Cats: A Case Series

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Objective: Since cats are very susceptible to pyrethroids, exposure to insecticides like permethrin often lead to a severe poisoning. We present here a survey covering all episodes reported to the Swedish Poisons Information Centre (SPIC) during the last seven years. *Case Series:* During 2000–2006, the SPIC received 96 telephone inquiries regarding cats exposed to permethrin. Seventy of these calls (73%) came from veterinarians who were able to give reliable and useful information. This report is based on the 77 cases where pertinent data were available and in which all cats had been exposed to a small volume (<1 ml) of a highly concentrated (744–750 mg/ml) permethrin product. In 73 of the 77 episodes (95%), the cats had been erroneously treated by their caretakers (these products are designed for dogs as tick-insecticides). Dermal exposure was the primary route in 95% of the cases, a few oral exposures were also present. The symptoms developed most often within a few hours after exposure, but in five of the 77 cases (6%) a symptom-free interval of 12 hours or longer (12–72 h) was noted. Significant symptoms consisted of twitching or tremor in 34 cases (44%) and repeated seizures in 40 (52%). More infrequent symptoms included ataxia, agitation, vomiting, mydriasis, salivation, hyperventilation, confusion, CNS-depression, tachycardia, hyperthermia, hyperglycemia, hypocalcemia and heart failure. The treatment was symptomatic. In several cases the administration of antiepileptic drugs was needed to control seizures. Despite repeated administration of anticonvulsant drugs, sometimes in conjunction with general anaesthesia, seizures continued in six cases. Therefore these cats were euthanased. The total mortality rate was 7/77 (9%). *Discussion:* The clinical features in this case series are principally in accordance with the present literature (1,2), but this survey displays a higher frequency of seizures and fatal outcome in comparison to the study by Martin and Campbell (2). The reason for the high sensitivity to permethrin in cats is that the substance is partly metabolised by the hepatic enzyme glucuronosyltransferase. The low enzyme levels in cats cause accumulation of toxic metabolites. Low body weight and relatively large skin area are other reasonable explanations. Dermal decontamination with excessive amounts of surfactant (e.g., hand dish detergent) is crucial since most of the permethrin stays in dermal depot vesicles. *Conclusion:* Despite warning labels there are still several severe poisonings in cats due to inadvertent administration of permethrin products. These exposures often result in repeated seizures and sometimes a fatal outcome. *References:* 1. Meyer EK. J Am Vet Med Assoc 1999; 215:198–203. 2. Martin A, Campbell A. Vet Rec 2000; 147:639.

105. Acute Carbon Monoxide Poisoning During Pregnancy Maternal and Fetal Outcome

Mathieu-Nolf M[1], Mathieu D[2], Durak C[1], Linke JC[1,2]. *[1]Centre Antipoison, Centre Hospitalier Régional Universitaire*; *[2]Service d'Urgence Respiratoire, Réanimation Médicale et Oxygenothérapie hyperbare*, *Lille, France*.

Carbon monoxide is known to be extremely harmful to the fetus, leading to death, fetal malformations, and intellectual retardation. Due to ethical reasons, double blinded randomized study to evaluate the potential beneficial role of HBO_2 would be difficult to perform in this specific sub group of CO-poisoned pregnant women. A cohort study seems to be a suitable way to study this question. *Method:* From January 1983 to December 2004, all women, admitted in our emergency department for CO poisoning and who claimed to be pregnant were enrolled in a prospective survey program. All were treated with HBO_2 within 24 hours of CO exposure. Maternal and fetal data were recorded during hospitalisation and follow up after hospital discharge was done by phone interviews with patients, GPs and obstetricians. *Results:* During

the 22-year study period, 568 women claiming to be pregnant were admitted in our emergency department for CO poisoning. 40% had minor symptoms, 39% neurological signs but had not experienced any loss of consciousness, 19% had lost consciousness during CO exposure but were conscious on hospital admission, and 2% remained comatose. Detailed follow-up was obtained in 509 cases (90%). Maternal outcome was death in 2 patients (0.3%), long term manifestation in 14 (2.5%), not statistically different from the outcome of non pregnant CO poisoned women. 8 women asked for elective abortion. Thus, evaluation of fetal outcome is possible in 501 cases. Fetal loss occurred in 14 cases (3.25%), an overall risk not statistically different from the general population, but there was a 3.17 fold increase in the risk of stillbirth ($p<0.001$ when compared to the general population). 476 pregnancies (95 %) ended with the delivery of a normal baby. Malformations were observed in 11 babies (2.5%), a rate not statistically different from that of the general population. *Conclusion:* In this series of CO poisoned pregnant women, treated by HBO_2 within 24 hours from CO exposure, the risk of stillbirth remains increased when compared to that of the general population but the malformation rate is not different. We do not recommend that therapeutic abortion remains systematically proposed to CO-poisoned pregnant women.

106. Increasing Number of Child Accidents Involving Fire-Lighting Fluids - A Project to Break the Trend

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Objective: Ingestion of fire-lighting fluids and lamp oils cause many accidents among children each year in Sweden. One sip might lead to serious pulmonary complications due to aspiration. The Swedish Poisons Information Centre (SPIC) noticed an increase of inquiries regarding fire-lighting fluids by 40% during the years 2000–2003. Furthermore, it was observed that children surprisingly often were capable of opening the so-called child-resistant caps. In an attempt to break this alarming trend a prevention project was started in 2004. *Methods:* A working group was formed at the Poisons Centre. The problem was analyzed and a prevention strategy involving two parallel activities was established. 1. Persuasion of the authorities to put regulatory pressure on the producers. 2. Information to the general public about the danger of fire-lighting fluids by means of newspapers, television and radio. The messages to parents were: don't let the barbecue end at children's hospital; Never leave an opened bottle of fire-lighting fluid and don't trust child-resistant caps; Use safer methods to light the charcoal grill. *Results:* The Chemicals Inspectorate realized the importance of the problem and arranged a meeting with producers of fire-lighting fluids and child-resistant packages together with the Consumer Agency and SPIC. It was revealed that the former well-functioning screw caps of polyamide had been replaced by cheaper caps of polypropene some years ago. Polypropene expands in contact with hydrocarbons and the child-resistant function disappears. Though the producers claimed that the caps fulfilled the international testing procedure (1) some of the manufacturers voluntarily changed back to polyamide when made aware of the problem. In addition the Chemical Inspectorate started a campaign named "check the cap" in some districts of the country. To inform the general public the Chemical Inspectorate and the Consumer Agency financed the production of a one-minute-film, which was shown many times on national television. As a consequence the inquiries to SPIC, regarding fire-lighting fuel incidents in children 0–4 years, decreased markedly. The number of yearly inquiries four years preceding the campaign was 326-356-399-464 respectively, and after the project had started the numbers went down to 437-267-280 during the following three years. *Conclusion:* Poisons Information Centres have unique possibilities to observe new trends in the patterns of poisoning. When necessary they should alert authorities, producers and the general public and thereby prevent accidents and reduce the number of poisonings. It is remarkable that manufacturers can interpret the international testing procedure wrongly; this regulation ought to be re-written. *References:* 1. International standard ISO 8317:2004.

107. Evolution of Clinical Features and Management of 228 Viper-Bitten Patients in Italy

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Objective: To describe the clinical course of Vipera-bitten patients in Italy in order to identify a correlation between clinical gradation at admission and evolution/severity of clinical course, and between these two parameters and antidotal treatment (Fab). Furthermore, to compare Fab prescription released by the Pavia Poison Centre (PPC) in two different periods of time. *Methods:* All cases of Vipera bites referred to PPC over 2002, 2005, and 2006 (79, 76 and 73 cases, respectively) were retrospectively studied. Patients were evaluated for clinical grading at admission and during clinical course according to the Grading-Severity-Score (GSS) (1), and for overall management. Fab prescription was evaluated comparing the first and last year studied (2002 vs 2006). *Results:* 228 Vipera-bitten patients were included: at PPC first evaluation, 132 (57.9%) patients presented with fang marks only (GSS0), 77 (33.8%) with local edema (GSS1), 18 (7.9%) with regional edema and/or mild systemic manifestations (GSS2), 1 (0.4%) with severe local and systemic manifestations (GSS3). Among GSS0-patients, dry-bite was assessed in 92/107 cases (85%), whereas 15/107 patients (14%) had local signs (GSS1) and 3 presented also mild systemic effects (GSS2), requiring antivenom. All of the 60 GSS1-patients developed worsening of local edema, 11 (18.3%) presented also systemic symptoms; 12 patient of this group needed antivenom. 15/15 GSS2-patients evolved with severe local symptoms, and 12/15 with severe systemic symptoms; Fab was required in 12 cases (80%). Worsening of clinical picture was observed in 14% of GSS0 and in 82% of GSS1-patients during the first 12 hours; the severity of envenomation increased in 80% of GSS2-patients during the following 24 hours. The total number of envenomed patients (excluding the 45 drop-outs and the dry-bites) was 91, Fab was needed in 28 (30.7%); no fatal cases were reported. The comparison between 2002 and 2006 demonstrates an increase in Fab prescription by toxicologists: from 20 to 40% of GSS0-presenting-patients and from 75 to 100% of GSS2-presenting-patients, whereas no differences appear between GSS1-presenting-patients (20 vs. 21%). *Conclusions:* Viper bite is a potentially serious event that requires immediate hospital care and toxicological evaluation. Despite the high percentage of dry-bites, some GSS0-patients worsen and require antidote: observation of at least 12 hours is advisable for a correct management in all cases. The absence of fatal cases can be related to prompt Fab prescription by toxicologist during assiduous follow-up necessary to properly evaluate the clinical course. *References:* 1. Audebert F, Sorkine M, Robbe-Vincent A, Cassian B. Human and Experimental Toxicology 1994; 13:683–688.

108. Multiple Chemical Sensitivity: Analysis of 52 Cases

Nogué S[1], Fernández-Solá J[2], Rovira E[1], Montori E[1], Fernández-Huerta JM[2], Munné P[1], Montero M[1], Salmerón JM[1]. [1]*Clinical Toxicology Unit*; [2]*Chronic Fatigue Unit, Hospital Clínic, Barcelona, Spain*.

Background and Objective: Multiple chemical sensitivity (MCS) is characterized by a progressive loss of tolerance to various environmental chemicals. The objective of this study was to describe patients with MCS seen in our hospital. *Patients and Method:* Patients consecutively seen by the Clinical Toxicology and Chronic Fatigue Units during a 10-year period who presented with symptoms of MCS were included. The diagnosis was clinical and was based on six consensual criteria. All patients completed the Quick Environmental Exposure and Sensitivity Inventory (QEESI). *Results:* Fifty-two patients were included. The average age was 47.2 +7.6 years and 46 (88%) were female. The QEESI questionnaire showed mean scores of 72.9+18.6 on the chemical inhalant intolerance scale, 45.5+20.6 on the other intolerances scale, 69.8+ 20.6 on the symptom severity scale, 4.4+1.8 on the masking index scale and 66.6+21.7 on the life impact scale. The origin of the syndrome was related to occupational exposure to various chemical agents in 31 cases (59.6%), including occupational accidents in 14 patients (fumigation of the workplace with insecticides). In 20 patients, the syndrome could not be associated with any toxic exposure and was considered a manifestation of chronic fatigue syndrome. Twenty-one patients (40.4%) were on work disability at the medical visit and seven (13.5%) had permanent work disability. All patients were followed up for a minimum of 12 months, during which time they remained stable with no deaths. *Conclusions:* Multiple chemical syndrome normally affects middle-aged women. It is frequently triggered by exposure to chemical agents, especially insecticides. An association with chronic fatigue syndrome is common. The prognosis is good but patients' quality of life is seriously affected.

109. Ingestion of Calcareous Surfaces Polishing Paste Causing Intoxication

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Objective: The toxicity of the products used for marble polishing is well-known, containing substances like magnesium fluorsilicate, hexafluorsilicate. It is necessary to know the exact composition of the product for it may behave as an acid or as a base. The main toxic effect is causing calcium and magnesium chelation and secondary clinical effects. A severe acute intoxication is reported. *Case Report:* A male aged 57 years with medical history of type 2 diabetes mellitus, attended the emergency department after an accidental ingestion of a mouthful of calcareous surface polishing paste containing magnesium fluorsilicate. The patient had dysphagia, pyrosis, sweating and anxiety. The label of the product was obtained, showing pH 2.4. Clinical examination revealed heart rate of 90 bpm and tachypnoea of 35 bpm. Blood pressure was 100/45 mmHg, and temperature 35ºC, with signs of low tissue perfusion. Disseminated rhoncus in bilateral lung regions in auscultation were found. The analytical findings were the following: glucose 356 mg/dl, sodium 140 mmol/l, potassium 6.4 mmol/l, calcium 5.6 mg/dl, magnesium 1.4 mg/dl, urea 38 mg/dl, creatinine 1.45 mg/dl, pH 7.32, pCO_2 27 mmHg, pO_2 100 mmHg, HCO_3 16 mEq/l, BEb -12 mEq/l, and lactate 4 mmol/l. Gastric lavage with calcium gluconate irrigation and nasogastric tube insertion were performed. The patient was admitted to ICU where magnesium sulphate and calcium chloride were administrated, requiring later orotracheal intubation and mechanical ventilation because of cardiocirculatory worsening. During the following hours the patient developed seizures and ventricular fibrillation treated with electrical cardioversion, and later several episodes of torsade de pointes. Gastroscopy revealed a grade II caustic gastritis. The clinical course was satisfactory and the patient was discharged after 10 days. *Conclusions:* Immediate treatment is necessary in these intoxications because of their potential seriousness. Knowing the exact product and its composition is of vital importance to achieve the best treatment. A small quantity of only 25 ml may be lethal, particularly in children. Neutralization or activated charcoal administration are contraindicated, while dilution with albuminous water and gastric lavage with calcium gluconate are useful if used during the first hour. Deep burns may be caused after ocular or cutaneous splashes. An immediate EKG and clinical monitoring with intensive calcium and magnesium replacement must be performed.

110. Dynamic Analysis of Hydrofluoric Acid Penetration and Decontamination on the Eye by means of Optical Coherence Tomography

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Hydrofluoric acid (HF) burns up to now are evaluated by experiments derived from heuristic expositions of different types and uncertain therapeutical regimes. There is a lack of analytical methods to define the penetration and the effect of decontamination within biological structures for this type of injury. The use of high resolution optical coherence tomography (OCT) has the potential to close this gap. In this study this method is used to evaluate the penetration characteristics and the decontamination of HF in the *ex vivo* rabbit cornea within the *ex vivo* eye irritation test (EVEIT). Corneas of rabbit eyes *ex vivo* were exposed to 2.5% HF solution. Cross-sectional images of the corneas were recorded using high-resolution OCT with imaging rates of up to 30 frames/min. Here, changes of the microstructure induced by the corrosive are correlated with a substantial increase in OCT signal amplitude. It is shown, that corneal penetration with 2.5% HF is complete within 270 seconds after exposure resulting in opacification throughout the whole cornea. Using rinsing solutions of tap water, calcium gluconate solution (1%), and Hexafluorine (a specific antidote for HF) the deep corneal stroma remained clear until rinsing was stopped after 15 minutes. This status was preserved over one hour after rinsing for Hexafluorine only. Using tap water and calcium gluconate solution (1%) further opacification of the deeper layers of the corneas was observed after rinsing. All burnt corneas except the ones rinsed

with water shrank significantly in thickness. This was not the case for rinsed healthy eyes except for Hexafluorine. We interpret the shrinkage as a result of osmolar changes and of loss of water binding capacity with shrinkage after HF burn. This work demonstrates that OCT can enhance the EVEIT system by providing valuable information on kinetics of HF penetration into the cornea and changes in corneal thickness due to interaction with the corrosive. Furthermore, the efficiency of decontamination after HF burn can be demonstrated by means of OCT resulting in good decontamination of HF by Hexafluorine.

111. The Use of the Molecular Adsorbent Recirculating System in Case of Acute Hepatic Failure, Caused by Disinfectant Poisoning

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Objective: Mass poisonings by "moonshine" alcohol, with disinfectant polyhexamethylene guanidine hydrochloride, have been widely spread in many Russian regions in 2006. A typical clinical picture included toxic liver damage with the development of severe cholestatic hepatic failure. The molecular adsorbent recirculating system (MARS) in some cases resulted in a short-term effect, that is why the aim of this study is to find the efficiency criterion for MARS in the treatment of hepatic failure, caused by the acute polyhexamethylene guanidine hydrochloride poisoning. *Methods:* Forty-two patients underwent treatment in the toxicology unit. Seven patients received 1–4 sessions of MARS-therapy with the average duration 8.3+/-0.46 hours. All in all 14 sessions were conducted. Three of seven patients died. The indication for MARS-therapy was a hepatic encephalopathy (psychosis or coma) with a bilirubin level more than 500 mcmol/l. Bilirubin clearances in albuminous boundary were measured at the beginning of the manipulation and in 3, 6, and 8 hours. The acetyl cholinesterase (AChE) concentration and total bilirubin were also measured before the manipulation and the next day after it. *Results:* The average bilirubin clearance in the albumin circulation system was 46.5+/–4.98 ml/min, the highest clearance rate was at the beginning of the session −78+/–6.1 ml/min. The total bilirubin before the MARS-therapy was on average 569.7+/-22.1 mcmol/l, after the treatment – 432.8+/–17.4 mcmol/l (p>0.001). Three patients during 2–3 days after the treatment had bilirubin rise up to the basal value. These patients died within a month. In four patients bilirubin growth did not reach the basal value, after one session, and the patients recovered. One of the hepatic dysfunction indicators is the decrease in cholinesterase activity. The basal value of AChE died patients who later died was from 987 to 1815 U/l (normal 2150 – 4900 U/l). After the first sessions the AChE rate increased and on average was 151.9+/-29.97% from the basal value. The last sessions, vice versa, were marked by cholinesterase activity decrease, which on average was only 76.15+/-4.63% from the basal value before the MARS-therapy. It was also accompanied by a sudden decrease of the MARS-therapy clinical performance – despite the high bilirubin clearances, its decrease in blood was slight and the patients remained unconscious. In recovered patients the cholinesterase activity was initially normal, and it did not change or increase after the manipulation. Meanwhile the psychosis remitted. *Conclusion:* The cholinesterase activity decrease after the MARS-therapy or the common low levels of cholinesterase activity before and after the manipulation, correspond to the absence of the MARS-therapy effect.

112. A Fatal Case after Accidental Dermal Exposure of Ethylene Chlorohydrin

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Objectives: Ethylene chlorohydrin (CAS 107-07-3), a colorless liquid at room temperature, is a toxic solvent with industrial poisonings reported. It also is used broadly in agriculture to hasten grape germination in the central area of Taiwan, where most grapevines are planted. Farmers usually add red dye to the solution as a warning color. Several acute intoxications were reported before and most of the fatal cases were caused through oral ingestion with high concentration and larger amounts of ethylene chlorohydrin. We present the case of one elderly female patient who died within 24 hours of dermal exposure to diluted ethylene chlorohydrin solution in a work accident. *Case Report:* An 84-year-old woman, with a history of chronic hepatitis C, was accidentally sprayed on her left foot with diluted ethylene chlorohydrin solution which is used to hasten grapevine sprouting. She did not wash her feet at once. Progressive dizziness, nausea with vomiting, and chest tightness were present about 3 hours after exposure. Initial laboratory data was relatively normal except mildly elevated GPT level (65 IU/L). Changes of breathing pattern and conscious status, and drop in blood pressure were observed 2 hours later in the Emergency Room. One episode of seizure happened. She was transferred to ICU after emergency endotracheal intubation with ventilator support. Severe metabolic acidosis followed but persisted even with aggressive alkalinization correction. High blood ammonia (446 umol/L) was found, too. Her general condition deteriorated under supportive medical treatment including N-acetylcysteine and lactulose enema, and resuscitation. She passed away about 15 hours after poisoning. *Conclusion:* Ethylene chlorohydrin is well absorbed orally, by inhalation and dermally, and is toxic even in diluted solution. The cause of death in acute poisonings is thought to be due to failure of the respiratory center and metabolic acidosis. Performing complete decontamination immediately after poisoning is very important. Impaired liver function could be a risk factor in ethylene chlorohydrin intoxication. We strongly recommend not using ethylene chlorohydrin as a sprouting agent because of safety concerns.

113. Intoxications with Essential Oils Reported to the Slovak National Toxicological Information Centre during the Period 1998–2006

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Objectives: Essential oils are potentially toxic substances. To obtain more information about this problem, we undertook a retrospective study. *Methods:* All telephone inquiries involving essential oil exposures were extracted from our databases for the period January 1998–October 2006. The following data were analyzed: age, sex, intent of exposure, type of essential oil, and clinical severity. All intoxications were classified according to the Poison Severity Score. *Results:* We reported 104 cases of essential oil intoxications during the 9-year period. Essential oil exposures in males (56%) were more frequent than those involving females. The majority of intoxicated patients were children (83%), 81% of them were less than 5 years old. All intoxications except one were accidental. In this suicidal case the patient drank essential oil with floor cleaner. Most of the cases were caused by parents' mistakes; essential oils were given to children instead of cough syrup. Oil of eucalyptus, oil of pine and oil of *mentha piperita* were most frequently misused. Most of the patients had none or only minor symptoms (48%, resp. 42%). The majority (88%) of the symptoms were nausea, vomiting and cough. We reported also flushing and somnolence. 9% of patients had moderate symptoms of intoxication: cough, fever (38 – 40.2°C) and RTG signs of aspiration pneumonitis. We reported 1 case of severe intoxication. 1.5-year-old boy required mechanical ventilation after drinking about 50 ml of essential oil. *Conclusions:* Essential oils can cause severe or lethal intoxications, patients should be carefully observed. Parents should be warned about toxicity of essential oils and producers should mark their products with the sign "for external use only."

114. What are the Differences between Ethanol and Medical Drug Poisonings Admitted to the Emergency Department?

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Background: The most frequent poisonings seen in Emergency Departments (ED) are due to ethanol (ET) and medical drugs (MD). *Objectives:* To compare the epidemiological profile, clinical manifestations, medical procedures carried out, treatment administered and the evolution of patients attended for ET and MD poisonings. *Methodology:* Patients admitted to the ED during October 2004 and October 2005 due to poisoning by ET or MD were selected. Epidemiological (sex, age), clinical (Glasgow Coma Score, vital signs), procedures (complementary tests, analyses), treatment (antidotes and other drugs) and evolution (survival) variables were analyzed. Results were entered in a database and analysed using the SPSS program version 10.0. The level of statistical significance was established as $p<0.05$. *Results:* A total of 190 patients were included: 105 (55.3%) due solely to ET poisoning and 85 (44.7%) due to MD poisoning. There were no differences in age between the two groups, but ET group had a higher predominance of males ($p = 0.002$) and initial admission to psychiatric care ($p < 0.001$). MD poisonings were admitted more frequently in the evening ($p=0.002$) and ET at night ($p < 0.001$). ET patients were more often symptomatic ($p<0.001$), especially with respect to neurological manifestations ($p = 0.002$), but the Glasgow Coma Score was lower in MD poisonings ($p = 0.014$). Although there were no differences in the total number of procedures carried out in the two groups, more analytical tests were made in ET poisoning ($p = 0.020$) and more ECG and venous lines in MD intoxications ($p<0.001$). There were no differences in the total number of treatments administered. However, the MD group had more gut decontaminations ($p<0.001$) and were administered more antidotes ($p = 0.003$), whereas ET patients needed more mechanical and pharmacological restraint and more non-antidote drugs ($p = 0.002$). The outcome was satisfactory in both groups, with no patient dying. *Conclusions:* Poisonings due to ethanol and medical drugs have a different epidemiological profile. MD patients are more frequently asymptomatic, but their Glasgow Coma Score is lower if neurological symptoms are present. Intoxications by MD need more venous lines, gut decontamination and antidotes, whereas ET patients require greater mechanical restraint and non-antidote medicines. The prognosis is good in both groups.

115. Methemoglobinemia and Hemolysis Caused by Aniline in a Patient Treated with Methylene Blue

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Objective: Aniline is a colorless aromatic liquid that is widely used in the manufacturing of synthetic dyes and in the rubber industry. It is rapidly absorbed by all routes and induces methemoglobinemia by indirect, autocathalytic routes. A Heinz-body hemolytic crisis may follow the development of methemoglobinemia in 2 to 7 days, especially if methylene blue as antidotal therapy has been administered. Hemolysis is aggravated when there is an obscure G6PD deficiency. *Case Report:* A 40-year-old male ingested 150 ml of diethylaniline. He was admitted to a regional hospital 26 hours later with typical signs of methemoglobinemia. His serum methemoglobin level was moderately high, 26.9%, which was treated with 10 ml of methylene blue. In the subsequent 3 days he had no complaint, except slightly elevated total serum bilirubin. His blood and urine analysis was normal. Because of his permanent suicidal intention he was transferred to a psychological department. Here, five days after exposure his condition suddenly worsened, he complained of high fever, cold, shiver and crural ache, icterus, anemia developed, therefore he was admitted to our department of toxicology. The laboratory analysis confirmed a rapidly decaying severe intravascular hemolytic anemia with reticulocytosis, leucocytosis, elevated transaminases, D-dimer, fibrinogen, otherwise normal coagulogram and intact kidney functions. Abdominal ultrasonography showed mild hepatomegalia, structured spleen and kidneys of normal size. Color Doppler verified on the left leg a crural level thrombosis. We measured a normal level of G6PD. The patient recovered after packed blood transfusions and supportive therapy. *Conclusion:* A toxicologist nowadays rarely meets a potentially life threatening aniline poisoning. Not all, but most severe cases require treatment with methylene blue that may produce the same complications as aniline itself. Antidotal therapy needs care even if there is no evidence of G6PD deficiency, as in our case.

116. The Evaluation of Hydrogen Cyanamide-Related Inquiries to the New Zealand National Poisons Centre Between 1990 and 2006

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Introduction: Hydrogen cyanamide (Hicane) is a plant growth regulator used in New Zealand to induce bud break in kiwifruit. In early spring of each year (August and September), the agricultural community can use as much as 216 tonnes. The aim of this study is to evaluate the calls received by the New Zealand National Poisons Centre (NPC) regarding Hicane and ascertain the effect of exposure on agricultural workers and those living in close proximity to its area of use. *Method:* A retrospective analysis of all Hicane-related poisoning inquiries to the NPC was undertaken for the years 1990 to 2006. *Results:* The NPC received a total of 145 Hicane-related calls; 47 requested information and the remaining 98 involved poison exposure (30 were animal related and 68 were human). Almost all calls were logged during August and September

of each year. From 1990 to 1998, the NPC only received 1 to 2 calls per year, but this substantially increased to 17 in 1999, and peaked in 2003 with 26 inquiries. Subsequently there has been a steady decline in inquiries. In humans, most calls on exposure concerned inhalation (54%) and skin contact (28%). The majority of reported symptoms were only mild to moderate; these included nausea and vomiting (29%), headache (22%), contact dermatitis (19%), and erythema (17%). Surprisingly, only 8% of calls received involved alcohol. *Conclusion:* This study suggests that despite its extensive use, workplace exposure to Hicane has not posed a major threat to health. This may in part be due to education on its use that includes the importance of abstaining from alcohol. There is also no indication that spray drift represents any health threat to the public.

117. Morbidity of Agricultural Chemical Use in Guyana

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Objective: To report on the morbidity of agricultural chemical use in the developing nation Guyana and determine the contributing factors. *Methods:* Direct interviews were conducted with 195 farmers of non-traditional crops in four of the six growing regions in Guyana. Poor or illegible histories were excluded. A questionnaire detailing demographic data, crops, pesticide type and frequency of application, and adverse events and treatment was done with each farmer, working family member, or hired laborer. All surveys were done on the farm property, with attempts to verify which chemicals and self-protection efforts were used by visually inspecting chemical containers and protective equipment available. *Results:* 190 farmers were studied, of which 167 (88%) were male. The mean and median age was 40 years old (S.D.+13.4) and 40 years old, respectively, with a range of 14 to 78 yrs. 143 of the farmers owned the farm they worked on, with 31 non-owner but related, and 16 hired laborers. Exposure to agricultural chemicals was routine with 153 farmers (80%) spraying at least weekly. Morbidity from agricultural chemical exposure was common, with 87 farmers (46%) reporting having experienced at least one episode of illness after agricultural chemical exposure. More commonly reported symptoms included headache (22%), dermal irritation (18%), nausea and vomiting (16%), weakness (7%) and increased secretions (7%). Significant symptoms such as loss of consciousness and peripheral neuropathies were rare, less than 1% of the total reported. Relatively few of the farmers sought medical assistance for their symptoms, with only 20 farmers (11%) visiting a local doctor and only two farmers (1%) reported going to a hospital for treatment. Local farmer use of protective equipment was very limited. 92 farmers (49%) reported using no protective equipment at all and 79 farmers (42%) used simple barrier efforts such as long sleeve shirt, boots and a kerchief to cover their mouth. Only 18 farmers (9%) described using a respirator, and goggles. Organophosphate and carbamate insecticides were encountered routinely, but were in the minority. The pyrethroids and the herbicides paraquat and glyphosate were the most common agricultural chemicals found. *Conclusion:* Actual morbidity from the use of agricultural chemicals may be much higher than WHO estimates (1). Contributing factors may be the diverse assortment of generally unregulated chemicals available, poor education regarding safe and effective use, and the lack of affordable protective equipment. *Reference:* 1. Litchfield MH. Estimates of acute pesticide poisoning in agricultural workers in less developed countries. Toxicol Rev 2005; 24:271–278.

118. Simultaneous Poisoning with 1-Propanol and 2-Propanol

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Objective: 1-propanol and 2-propanol are isomers of an alcohol with three carbons. They are colourless liquids with a sweet odour. 1-propanol is metabolized by alcohol dehydrogenase to propionic acid and presents with metabolic acidosis and elevated anion gap, while 2-propanol is metabolized via alcohol dehydrogenase to acetone and presents with ketosis and ketonuria, but without metabolic acidosis. Searching Medline we have found no report of simultaneous 1-propanol and 2-propanol poisoning. We present here a patient who survived respiratory arrest after 1-propanol and 2-propanol ingestion. *Case Report:* A 37-year-old man simultaneously ingested a lethal dose of 1-propanol and 2-propanol as a hand disinfectant in hospital. The patient lost consciousness and stopped breathing within half an hour after ingestion. He was intubated and artificially ventilated. Initial laboratory results revealed mixed acidosis with elevated anion gap due to lactic and propionic acid formation from 1-propanol, and hydrocarbonic acid through hypoventilation. He awoke after 6 hours and artificial ventilation was stopped. Ketonuria due to acetone formation from 2-propanol appeared only 12 hours after admission, when he was already conscious. Therefore laboratory results in simultaneous poisoning with two isomers of alcohol are not just a sum of laboratory results obtained in isolated poisoning with each isomer since they influence each other's metabolism: 1-propanol retards the metabolism of 2-propanol to acetone. *Conclusion:* 1-propanol and 2-propanol poisoning presents early with mixed acidosis and elevated anion gap, and only later with ketonuria.

119. Moderate to Severe Eye Injury Due to Sulfamic Acid Exposure

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Objective: Limited reports of human eye exposure to sulfamic acid are present in the literature. According to Micromedex Poisindex, sulfamic acid is corrosive at concentrations > 10% (1). Products containing sulfamic acid are to be be labelled as irritant if the product contains more than 20% sulfamic acid, and never labelled as corrosive regardless of concentration (2). We describe a case with eye exposure to a cleaning and decalcifyng product containing 5% sulfamic acid and 1% non-ionic detergent which resulted in moderate to severe eye injury. *Case Report:* A 69-year-old man spilled by accident some of the cleaning product in his eye. After a short time of inadequate decontamination he continued his work. Due to progressing pain, the emergency department was contacted 1.5 hour after exposure. The eye was then rinsed for 1/2 hour, and examined by an ophthalmologist. Small spots of fluorescein positive and light conjunctival injection were seen, but the exposure was regarded as rather harmless. This evaluation was also partly based on the labelling and declaration of the product. The content of sulfamic acid was not stated in the declaration, and the label defined the product as irritant. The injury of the eye progressed during the following 4 days, peaking with fluorescein uptake in 50% of the cornea, edema, descemet reaction and lack of vision of the exposed eye. The eye was treated with chloramphenicol and steroids for eight days, and recovered without sequelae. *Conclusion:* This product was labelled according to current labelling regulations. This case illustrates that the information in the product labelling is not a reliable source for risk assessment of eye exposure. Sulfamic acid is one example of a chemical substance that shows corrosive potency, but due to current labelling regulations it will not be labelled as corrosive. This is important to bear in mind when dealing with eye exposures of products containing sulfamic acid such as decalcifyng cleaning agents. *References:* 1. Micromedex Health Care Series Poisindex vol. 130. 2. The council of the European economic community: Council Directive 67/548/EEC and Directive 1999/45/EC.

120. Fatal Case of Sodium Chlorate Self Poisoning

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Objective: Chlorate salts (Ch-s) poisoning is associated with high mortality rate (1) and requires prompt supportive and antidotal treatment: the role of invasive depuration procedures is not established. The main mechanism of toxicity of Ch-s is related to the strong oxidative action on all cells and tissues, mainly on erythrocyte cell membrane and haemoglobin: this causes massive haemolysis and methaemoglobinaemia (metHb) (2) followed by disseminated intravascular coagulation and acute renal failure. We describe a case in which all the available treatments were ineffective. *Case Report:* A 28-year-old man was admitted to the emergency department (ED) 1.5 hours after voluntary ingestion of unknown amount of the Radical® herbicide (sodium chlorate 38%). At admission, the patient showed only diarrhoea, without other symptoms or cyanosis: the first laboratory investigations and blood gas-analysis were normal. An extensive gastric lavage was immediately performed, followed by activated charcoal and magnesium sulphate administration. Sub-cyanosis (labial, ungual) and then massive cyanosis with metHb 54.4%, trismus and respiratory arrest (requiring mechanical ventilation) progressively appeared in 90 minutes. Three hours later the clinical course was characterized by hypotension (requiring fluids and sympathomimethics), rhabdomyolysis, massive haemolysis, renal failure, metabolic acidosis, coagulation disorders and cardiac tissue hypoxia: metHb reached 81%. Intravenous high dose sodium bicarbonate was administered to treat both metabolic acidosis and rhabdomyolysis. Antidotal treatment with methylene-blue (2.5 mg/kg) and Na-thiosulfate (5 g), associated with 3 exchange-transfusion sessions combined with continuous haemodialysis, fresh frozen plasma and blood transfusion were applied. Despite this, the patient died 20 hours after admission. *Conclusions:* Ch-s poisoning is a potentially fatal event in which diarrhoea can be the only symptom on presentation. Cyanosis and metHb are the specific signs of poisoning, but chlorate chromatographic analysis is unavailable in EDs (3). Massive haemolysis, coagulation dysfunction, renal failure and cardiovascular collapse complicated the clinical course. Methylene-blue can reduce metHb to haemoglobin in the first phase, but this efficacy can be limited by Ch-s effect of inactivation of glucose-6-phosphate-dehydrogenase (4), or by the presence of haemolysis; Na-thiosulfate may inactivate the chlorate-ion, but its use is controversial. *References:* 1. Helliwell M, Nunn J. Mortality in sodium chlorate poisoning. Br Med J 1979; 1:1119. 2. Steffen C, Wetzel E. Chlorate poisoning: mechanism of toxicity. Toxicology 1993; 84:217–231. 3. Eysseric H, Vincent F, Peoc'h M, et al. A fatal case of chlorate poisoning: confirmation by ion-chromatography of body fluids. J Forensic Sci 2000; 45:474–477. 4. Singelmann E, Wetzel E, Adler G, et al. Erythrocyte membrane alterations as the basis of chlorate toxicity. Toxicology 1984; 30:135–147.

121. Severe and Lethal Acetic Acid Poisonings: A Multicentre Case Series

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Objective: Acetic acid is often used in Russia to preserve vegetables and is easily available to the general public. During recent years about 10% of all poisoning cases reported to nine poisons centres were due to acetic acid exposures and the mortality rate has previously been estimated as 6% (1). These acute poisonings represent a serious toxicological problem. Prediction of severity and outcome after acetic acid poisonings has been made (2,3) but the corrosive damage is dependent on amount, concentration and also route and time of exposure. An estimated lethal dose of acetic acid (70%) per os is 50–70 ml. No previous case series regarding acetic acid ingestions have been published. *Case Series:* This retrospective multicentre case series includes all patients reported to nine Russian poisons centres (covering 6 million inhabitants) due to ingestion of acetic acid. Data were collected during 1998–2000 and included age, sex, dose, route of exposure, concomitant substances, symptoms and vital signs, laboratory values, time (number of days) in the intensive care unit (ICU), hospital stay (number of days) and outcome. Entrance into the study required a diagnosis of acute acetic acid poisoning. A total of 29601 patients were admitted to hospital because of acute poisonings. Corrosive liquids were the poisoning agent in two 133 cases (7.2%) and one in 84 cases (3.7%) were due to acetic acid ingestions. Mean hospital stay in patients poisoned by acetic acid was 10.12 ± 5.54 days and mean time spent at the ICU was 5.60 ± 2.35 days. The total mortality rate was 832/29 601 (2,8%) and corrosives were the causing agents in 230 (28%) of these lethal cases with 157 (19%) due to acetic acid ingestion. Main causes of death after acetic acid poisonings were acute renal failure, disseminated intravascular coagulation and acute prehospital bleeding. *Conclusions:* Acute acetic acid poisonings require extensive treatment and multiple days of observation at the ICU. Ingestions of acetic acid often lead to severe intoxications and the mortality is high. *References:* 1. Ostapenko YN, et al. Epidemiology and medical aid at acute poisoning in Russia. Przegl Lek 2001; 58:293–296. 2. Sarmanaev SKh, et al. The use of tables for prognosis

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122. Hepatitis, Renal Failure, Thrombocytopenia, and Hemolysis after Large-Volume Injection of Castor Oil

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Objective: The use of unconventional medical options for cosmesis in the transgender community is common. We report a case of toxicity from large-volume subcutaneous injection of castor oil in a male to female transsexual for hip augmentation with subsequent multisystem organ failure. *Case Report:* A 28-year-old transgender individual permitted an unlicensed practitioner to inject 600–720 mL of oily substance mixed with "silicone" bilaterally to hips and buttocks. Immediate local pain and erythema were followed by abdominal and chest pain, emesis, headache, hematuria, jaundice and tinnitus. Twelve hours post-injection she presented to the ED afebrile, pulse 56/min, BP 140/81 mmHg, respirations 12/min, room air oxygen saturation 97%. She had mild diffuse abdominal tenderness, significant tenderness without crepitance where injected, and produced only 10 mL of bloody urine. Multiple untestable, hemolyzed specimens complicated laboratory analysis; BUN 17.8 mmol/L and creatinine 442 micromol/L were eventually determined. After initial treatment with antibiotics and hydration, she rapidly deteriorated and developed fever (39.1 C), hemolysis (5 g/dL hemoglobin decline), thrombocytopenia (platelets 44 x10^9/L), hepatitis (AST 679 U/L; ALT 154 U/L; total and conjugated bilirubin 92 and 65 micromol/L) and anuric renal failure. Salicylate, acetaminophen, ethanol, and HIV test were negative. The patient disclosed that the injected product was locally obtained castor oil, which was identified and retrieved from the point of purchase. Following intensive care for multi-system organ failure, she was discharged eleven days later with persistent renal dysfunction. Urine ricinine level was 41 ng/ml. *Conclusion:* Substantial castor oil injection caused hemolysis, thrombocytopenia, hepatitis, and anuric renal failure. Castor oil content absorption was inferred from urine ricinine. Ricinoleic acid, which is cytotoxic to intestinal epithelial cells and sub-epithelial neurons, is the primary castor oil fatty acid component (1). Ricinine, a castor bean alkaloid with CNS stimulant and neuroleptic effects in high doses, is a biomarker for ricin exposure and detectable in castor oil (2). Ricin is reportedly eliminated during castor oil manufacture. It may be possible that given the volume of injection, normally insignificant amounts of ricin may have contributed to toxicity. Clinicians should anticipate complications following novel methods of cosmetic enhancement. *References:* 1. Burdock G, Carabin I, Griffiths J. Toxicology and pharmacology of sodium ricinoleate. Food Chem Toxicol 2006; 44:1689–98. 2. Johnson R, Lemire S, Woolfitt A, et al. Quantification of ricinine in rat and human urine: a biomarker for ricin exposure. J Anal Toxicol 2005; 29:149–155.

123. Can Biomonitoring of Mercury Distinguish between Patients with Complaints Attributed to Dental Amalgam and Healthy Amalgam Carriers? A Diagnost Case-control Study

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Objective: The suitability of concentration measurements of mercury (Hg) to identify patients complaining of health problems attributed to dental amalgam fillings was investigated. *Participants and Methods:* The study comprised 54 amalgam carriers, half cases with amalgam-related complaints and half healthy controls (I), and 27 healthy amalgam-free controls (II). Total, inorganic and organic Hg was determined in erythrocytes and plasma, and total Hg only in urine (before and after mobilisation with 2,3-dimercapto-1-propanesulfonic acid = DMPS) and in saliva (before and after stimulation with chewing gum). *Results:* Concentrations of inorganic mercury in blood and total mercury in urine and saliva differed significantly between individuals with amalgam fillings and amalgam-free volunteers, but not between symptomatic patients and healthy volunteers with amalgam fillings. Concentrations of total mercury in urine before and after DMPS, and in saliva before and after chewing gum had a strong correlation (r = 0.723 and 0.882, respectively). Urine Hg levels tended to be better correlated with blood than with saliva data; they also permitted estimation of the Hg uptake from amalgam at about 1.2 µg/d. Levels of organic Hg were equal in all groups. *Conclusion:* Measurements of inorganic Hg in blood and total Hg in urine represent reliable indicators of amalgam-related Hg exposure; they were, however, not able to separate amalgam patients from healthy amalgam carriers. *Reference:* Schuurs A, Exterkate R, ten Cate JM: Biological mercury measurements before and after administration of a chelator (DMPS) and subjective symptoms allegedly due to amalgam. Eur J Oral Sci 2000; 108:511–522.

124. "Off Gassing" following Fatal Aluminium Phosphide Ingestion

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Objective: Aluminium phosphide is used as a fumigant and reacts with moisture to liberate phosphine gas which is potentially toxic by inhalation (1). Ingestion is associated with a high mortality and phosphine gas liberated in the stomach may result in "off gassing" presenting a potential post-mortem hazard (1,2). We report two enquiries from hospital emergency departments involving fatal ingestion of aluminium phosphide, one involving "off gassing". *Case Report:* Case 1. A 35-year-old male suffered cardiac arrest 3 hours after ingesting a 3 gram pellet of "Phostoxin A," a proprietary product containing aluminium phosphide 56% and ammonium carbamate 44%. The patient was pronounced dead during the conversation with the poisons centre. Information was requested about decontamination and risks to hospital staff. Local public health services were involved and advised thorough ventilation of the emergency department and "double-bagging" of the body to minimise the risk from continued exposure. A subsequent enquiry was received from mortuary staff concerning the possible risks of autopsy. An occupational and environmental toxicologist advised that the amount of phosphine expected to be liberated was unlikely to pose a risk and standard personal protective equipment was sufficient. Case 2. An adult male suffered cardiac arrest (pulseless electronic activity) following ingestion of an unknown amount of aluminium phosphide. CPR was in progress and a clinical toxicologist contacted the caller directly, by which time the patient was asystolic and unlikely to survive. Continuing exposure to phosphine gas following cadaveric "off gassing" was discussed and the use of a chemical resistant body bag and thorough ventilation of the emergency department and mortuary were advised. A further enquiry was received regarding decontamination of the emergency department. Ventilation of the windowless treatment room had been problematic and fumes were still present 12 hours after the body had been removed. The advice provided was to use the room's air-conditioning system on a high setting if this vented externally or alternatively obtain high pressure ventilation fans from the fire service. *Conclusion:* Availability of aluminium phosphide is restricted in the United Kingdom and ingestion is uncommon (2). Of 48,471 enquiries received by NPIS (Newcastle) between April 2003 and November 2006, 8 (0.02%) involved aluminium phosphide. Two of these enquiries involved ingestion, both with a fatal outcome. Post-mortem "off gassing" poses a potential hazard to hospital staff and requires use of a chemical resistant body bag. Adequate ventilation of the mortuary and treatment areas is required as phosphine fumes may persist for several hours following removal of the body. *References:* 1. Christophers AJ, Singh S, Goddard DG. Dangerous bodies: a case of fatal aluminium phosphide poisoning. MJA 2002; 176:403. 2. Bogle RG, Theron P, Brooks P *et al.* Aluminium phosphide poisoning. EMJ 2006; 23:e3.

125. When to Stop Fomepizole Administration? Is 20 mg/dl too Low?

Akhtar J, Peterson BA, Krenzelok EP. *Pittsburgh Poison Center, University of Pittsburgh, Pittsburgh, Pennsylvania, USA*.

Objective: An important question in the treatment of ethylene glycol (EG) toxicity is when to stop fomepizole administration. The American Academy of Clinical Toxicology practice guidelines on the treatment of EG poisoning suggest to continue fomepizole until EG is undetectable, or less than 20 mg/dl, and the patient is asymptomatic with a normal pH. We report a case of EG poisoning where fomepizole therapy was stopped earlier than recommended without any consequences. *Case Report:* A 37-year-old male presented to the hospital after allegedly drinking half of gallon of antifreeze along with alcohol. The time of ingestion was 30 minutes prior to presentation. His physical examination was remarkable only for tachycardia with heart rate of 113 beats per minute, and tachypnea with a respiratory rate of 18 beats per minute. The patient's pH at presentation was 7.407 with normal electrolytes, bicarbonate of 26 and an anion gap of 11. The creatinine was 0.8. His blood alcohol was 296 mg/dl. EG level was 393 mg/dl. The patient was started on fomepizole without dialysis. The patient's next EG level 31 hours later was 66 mg/dl. The patient was given his last dose of fomepizole 6 hours after this. An EG level done 24 hours later was 29 mg/dl. The extrapolated EG level at the time the next fomepizole was due would have been 36 mg/dl. Electrolytes and renal functions remained normal 24 hours later, and the patient never developed renal failure on follow up. *Conclusion:* Fomepizole, a new medication for ethylene glycol toxicity, has changed the management of this poisoning. In our patient stopping fomepizole at an EG level of 29 mg/dl was not associated with any renal damage or development of acidosis. We feel that a level of 20 mg/dl may be too low and fomepizole therapy may be stopped earlier. Prospective studies are necessary to redefine this level and will result in significant economic saving.

126. Don't Let the Crystal Fool You

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Objective: The diagnosis of ethylene glycol (EG) toxicity includes the presence of calcium oxalate crystals in urine. Two types are seen on urinalysis, the monohydrate (needle-shaped) form and the dihydrate (envelope–shaped) form. The laboratory falsely identifies monohydrate calcium oxalate crystals as hippuric acid crystal, although X-ray diffraction techniques can definitely distinguish hippuric acid crystals from monohydrate calcium oxalate crystals. Failure to recognize this error could result in inability to recognize ethylene glycol ingestion. *Case Report:* A 53- year-old male was admitted with nausea, vomiting, and diarrhea. Patient initially denied any toxic ingestion. He has an anion gap metabolic acidosis and an initial creatinine of 1.9 mg/dl, which increased to 5.6 mg/dl on day #3. The patient was thought to have pre-renal azotemia from dehydration. His urinalysis showed needle-like crystals identified as hippuric crystals by the laboratory. Serum creatinine increased to 7.5 mg/dl on day #5. The poison center was consulted to find out the etiology of hippuric acid crystals. On the request of the poison center admission blood was checked for ethylene glycol, and the level was found to be 38 mg/dl. Patient was dialyzed for renal failure. The patient on confrontation admitted to drinking "moonshine". He was discharged home for outpatient hemodialysis. *Conclusion:* Monohydrate calcium oxalate crystals may be misinterpreted as hippuric acid crystals. A urine reported as showing hippuric acid crystals may be a significant finding that can facilitate early recognition of an unknown EG ingestion. Failure to recognize this may delay appropriate treatment of ethylene glycol toxicity.

127. Nephrotoxic Effects of Isopropanol?

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Objective: Isopropanol is the main component in many frost removers and is often abused by chronic alcoholics in Norway due to the high price of ethanol in our country and easy access

of isopropanol in the form of anti-icers. The toxic effect of isopropanol is 2–3 times higher than ethanol. Ingestion of isopropanol may result in symptoms that involve the gastrointestinal tract, central nervous system and at high doses cardiovascular manifestations may appear. Ketonemia and ketonuria may be present, generally without metabolic acidosis. Isopropanol is metabolized much more slowly in humans than is ethanol and plasma levels remain higher for a longer period of time than for a similar ethanol intoxication. Approximately 20 percent of an isopropanol dose is excreted unchanged in the urine. Isopropanol is metabolized to acetone, with urinary acetone becoming measurable after about 3 to 4 hours and peaking at 7 to 50 hours. *Case Report:* A chronic alcoholic was admitted to the hospital 3½ hours after drinking 400 ml of an anti-icer containing isopropanol. At presentation he is awake, smells of acetone, breaths effortlessly and has regular pulse beat, pH 7.57, pCO_2 2.92, pO_2 10.0 and blood sugar 6.0. He had an osmolality of 363 mosmol/kg, an anion gap of 16.6, CK 373 U/L and s-creatinine 248 micromol/L. Blood concentration of ethanol was 0.4g/L and isopropanol was 0.4 0/00. Due to the rise in s-creatinine our poison centre was contacted with the question whether isopropanol could have nephrotoxic effects? *Conclusion:* Spuriously raised serum creatinine concentration can be due to the presence of acetone. Creatinine measurement by alkaline picrate reagents is subject to positive interference from acetone (1). This phenomenon is known from diabetic patients with ketoacidosis (2) where the ketoacids interfere with the plasma creatinine assay. Rise of serum creatinine has to be verified by other enzymatic methods or chromatography when isopropanol is consumed. *References:* 1. Blass KG, Ng DS. Reactivity of acetoacetate with alkaline picrate: an interference of the Jaffe reaction. Clin Biochem 1988; 21:39–47. 2. Kemperman FA, Weber JA, Gorgels J, van Zanten AP, Krediet RT, Arisz L. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. J Intern Med 2000; 248:511–7.

128. Correlation between S-K And PH on Admission in Methanol Poisoned Patients: A Study from two Large Outbreaks

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Background: Hyperkalemia is a common finding in acidotic patients, due to the H^+-K^+ shift in the cells with decreasing pH. *In vitro* and experimental studies in animals indicate an increase of 0.3–0.6 mmol/L per 0.1 decrease in pH. Since other factors than pH may affect this K^+ -shift, clinical studies in defined patient populations, where the mechanisms of the acidosis is known, may reduce possible influence from other variables. We therefore studied the pH/ K^+ -relationship in patients from two recent outbreaks of methanol poisoning. *Methods:* Retrospective study of the corresponding S-K^+ and pH on admission in 74 methanol poisoned patients. The samples were drawn before any treatment was initiated. S-creatinine was normal in all patients. *Results:* Median (range) S-K^+ was 4.7 (2.6–8.1) mmol/L and pH was 7.27 (6.34–7.57). As expected, S-potassium increased with decreasing pH. The correlation between the two parameters was good (R2 = 0.70; Fig. 1): In these patients, S-K^+ increased 0.28 mmol/L per 0.1 decrease in pH. *Conclusion:* The present close correlation between S-K^+ and pH in the lower end of the anticipated range (0.3–0.6 mM per 0.1 pH-unit) indicate that methanol poisoned patients may be a suitable *in vivo* model for such studies. Further studies in other defined groups of acidotic patients may confirm this correlation.

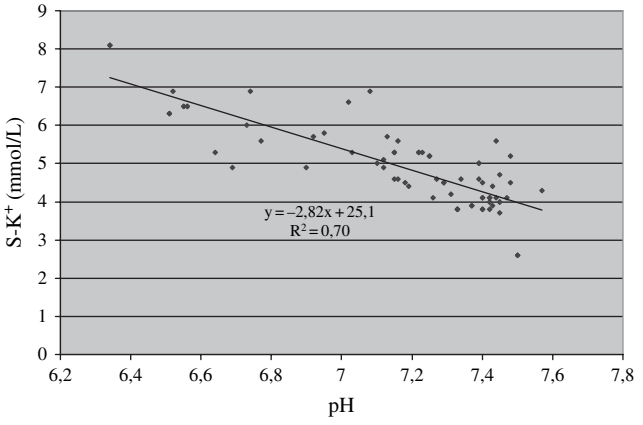

Fig. 1. pH vs. S-K^+ on admission in 74 methanol poisonings.

129. Trends in Ethylene Glycol Poisoning and Treatment Reported to US Poison Centers, 2000–2004

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Objective: The evaluation and treatment of ethylene glycol poisoning requires extensive health care resources. The objective of this study is to describe the epidemiology, clinical effects, treatments and outcomes from ethylene glycol exposures reported to all U.S. poison centers over a five-year period. *Methods:* This is an observational case series. The data is collected prospectively by poison centers using a standard format to ensure data consistency and entered into the American Association of Poison Control Center's Toxic Exposure Surveillance System (TESS) database. Only human exposure cases are entered into the database. Cases were retrospectively identified by substance codes for "ethylene glycol" (chemical and automotive products) for the years 2000–2004. Frequencies and cross-tabulations were used to describe the data. *Results:* Poison center data covered 96% to 99% of the U.S. population during the study period. A total of 29,863 ethylene glycol exposures were voluntarily reported over the 5-year period. Ethylene glycol was the sole substance in 27,742 cases (93%). The yearly exposure rate (total TESS exposures/ethylene glycol exposures) remained constant over the study period (0.24%-0.27%). A bimodal exposure peak for age occurred at 0–5 years (3,805, 13%) and 20–49 years (15,423, 52%). The rate of evaluation in a health care facility was equal for both adults and children (32%). Intentional ingestion was more likely to result in moderate effects, major effects or death (71%) compared to unintentional ingestion (13%) (Odds ratio 16.7, 95% CI 15.2–18.4) Routes of exposure other than ingestion included inhalation (n = 1,616), dermal (n = 1,276) and ocular (n = 956). These routes resulted in local effects only. There were no cases of metabolic acidosis or renal injury associated with these routes of exposure. The frequency of ethanol therapy decreased and fomepizole therapy increased each year in both adults and children. Fomepizole (n = 361) surpassed ethanol (n = 252) use in 2002. The rates of hemodialysis remained relatively constant for both age groups over the 5 years. *Conclusion:* Ethylene glycol exposure frequently results in evaluation at a health care facility. Moderate and major outcomes occur more frequently with intentional ingestions but also occur in a minority of unintentional ingestions. Inhalation, dermal and ocular exposures were not associated with systemic toxicity. Fomepizole appears to be replacing ethanol as therapy but the use of hemodialysis remained constant.

130. Acute Poisoning with Arsenic – A Case Report

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Objective: To present a case of acute intentional poisoning with a lethal dose of arsenic in a patient with a combination of gastrointestinal and neurological symptoms. Changes in urine arsenic concentrations and clinical features are described, as well as the therapeutic approach within the limitations of type and quantity of available antidotes. *Case Report:* A 36-year-old woman intentionally ingested 20 g of As_2O_3. One hour later she developed headache, dizziness, nausea, and diarrhoea. 24 hours after ingestion the patient was in severe shock with pronounced gastrointestinal disturbances which persisted for a further 12 hours with instability of haemodynamic parameters. Ophthalmological examination revealed concentrically limited peripheral vision with preserved central vision. The urine arsenic concentration on admission was 4.74 µmol/l (reference range of up to 0.13 µmol/l), falling to 1.13 µmol/l on day 3 and 1.54 µmol/l on day 7. Treatment started immediately after hospitalization and within 2 – 3 hours post ingestion and consisted of: repeated gastric lavage with charcoal and enema; haemodialysis (twice within 24 hours; the first being done immediately after hospitalization) despite prolonged exotoxic shock; cardio-circulatory resuscitation with intravenous fluids, dopamine, etilefrine, epinephrine and terlipressin in a dose of 3 õ 0.2 mg intravenously. Antidote treatment consisted of Unithiol (500 mg intramuscularly) and sodium thiosulphate (2 × 10 ml intravenously) for the first 24 hours, followed by dimercaprol (800 mg daily intramuscularly) for the next 4 days (total 3.2 g) and D-penicillamine (4 g daily orally) for the next 7 days. On the 15th day after ingestion the patient was discharged healthy with no complications. *Conclusion:* The complex therapeutic approach with constant monitoring and treatment modifications reflecting the changes in the patient's condition are the main reasons for the favourable outcome of this severe poisoning with ingestion of arsenic in a dose many times above the lethal threshold. Severe prolonged exotoxic shock is not an absolute contraindication to performing extracorporeal elimination techniques in cases of such severity. The change in antidote treatment was dictated by the limitations in type and quantities of the available antidotes in the country. Although not recommended as routine practice it may be useful in some critical situations.

131. Blood and Urine Lead Concentration Association in 506 Cases Referred to Toxicology Laboratory from 2000 to 2005, Mashhad, Iran

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Background: It has been shown that chronic occupational lead poisoning may induce kidney problems (1, 2). It is not clear, however, if the kidney eliminates lead from the blood proportionately to the blood lead level. We thus aimed to investigate the existence of a potential cut off point in which the kidneys might be compromised. *Methods:* All (506 cases) who were occupationally exposed to lead between 6 months and 14 years. They were tested in Toxicology Laboratory in Imam Reza University Hospital from 2000 to 2005. Two extreme cases were excluded. Blood and urine lead concentrations were determined by an atomic absorption (Perkin Elmer, Model 3030) using heated graphite atomization technique in the Toxicology Laboratory of the Centre. *Results:* Almost all (96.8%) of the patients were male. Mean blood lead concentration was 266 (187 SD) micg/L with a minimum of 40 and a maximum of 1300 micg/L. Mean Urine lead concentration was 98 (195) micg/L with a minimum of 10 micg/L (detection limit). Blood and urine lead concentrations were significantly correlated with each other ($r = 0.499$, $P < 0.001$) as shown in Figure 1. However, it seems from the graph this association is relatively compromised at higher concentrations of blood lead. *Conclusion:* Occupational exposure to lead is still an important health problem in this country. In this study we showed that blood and urine lead concentration are correlated well with each other. Although this article is not confirmatory, it raises the issue of altered lead renal elimination at higher blood lead concentration. *References:* 1. Loghman-Adham M. Renal effects of environmental and occupational lead exposure. Environ Health Perspect 1997; 105:928–39. 2. Chow KM, Liu ZC, Szeto CC. Lead nephropathy: early leads from descriptive studies. Intern Med J 2006; 36:678–82.

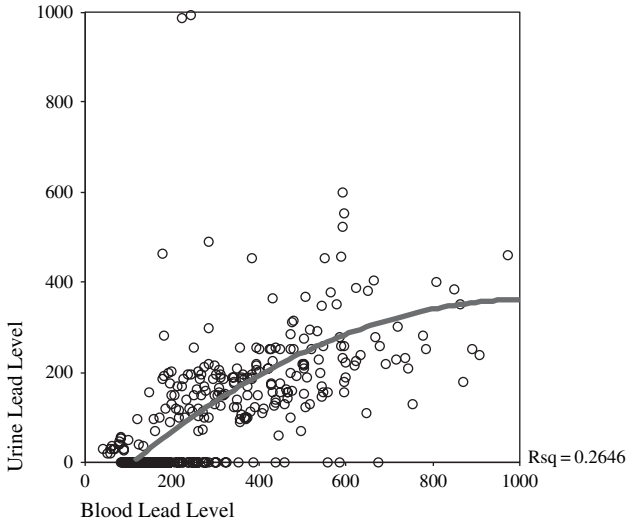

Fig. 1. Blood lead level.

132. Exposure to Mercury and Arsenic from Herbarium Specimens in the National Museum Wales (NMW), Cardiff

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Background: As early as the 17th century collectors of zoological and botanical specimens realised the importance of preservation of samples from attack and destruction by various pests and employed measures to prevent infestation. The herbarium at NMW has a collection of 520,000 specimens of plants dating from the late 1600s to the present day. It is known that the majority of older specimens were treated with arsenic and mercury salts. Curators and conservators in the herbarium routinely handle specimens for re-classification / identification or re-mounting etc. and the possibility of absorption of toxic agents dermally, through inhalation or ingestion is of concern. In 1998, recommendations for handling specimens in NMW were brought in to minimise potential absorption of toxins. The recommendations were: informing visitors to the collections of potential contamination problem; ensuring work is carried out in well ventilated areas; use of disposable protective gloves when accessing the collection and washing hands after handling specimens. *Objectives:* The aim of this study is to assess urinary concentrations of mercury and arsenic in employees who have direct contact with herbarium specimens before and after change in practice was introduced. *Method:* Urine samples were taken from six curators and conservators in the herbarium in 1998 and repeated in 2000. Samples were tested for mercury and arsenic by cold vapour atomic absorption spectrophotometry. Individuals were advised to avoid fish for a period of seven days prior to giving a sample. *Results:* Results are given in ratio to creatinine to account for different concentrations in urine. One individual had slightly elevated concentrations; arsenic levels were12 µg/g (normal range 0–10 µg/g) in 1998 and fell to 5 µg/g in 2000, mercury concentrations were 6 µg/g (normal range 0–5 µg/g) in 1998 and 3 µg/g in 2000. The remaining three individuals all had concentrations within the normal range ranging from 1 to 8 µg/g arsenic/creatinine and 0.6 to 6 µg/g mercury/creatinine. *Conclusion:* One of the individuals tested may have benefited by a change in work practice as concentrations dropped to within normal range from being slightly elevated. The other results show that these individuals were not exposed to high enough levels of mercury and arsenic to absorb significant quantities. As work practice involves varying degrees of exposure to specimens it is prudent to continue with the safe working practices implemented in 1998. Studies are ongoing to test actual levels of mercury and arsenic in the specimens themselves.

133. Environmental Manganese Exposures: A Risk to Children's Health?

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Objective: Manganese, a metal responsible for parkinsonian-like symptoms in adults with chronic occupational exposures, can contaminate water and soil either naturally or from industrial sources. WHO has recommended an action level for Mn (500 mcg/L) in drinking water; EPA set a similar level at 300 mcg/L. The toxic effects of low-level environmental exposures on children's health are not well described. One recent study of 10-year-old Bangladeshi children (N = 143) drinking contaminated tube well water (mean Mn levels 793 mcg/L) found they had reduced full-scale, performance and verbal IQ scores (1). Our pilot study of 32 children aged 11–13 years living in an industrially contaminated area of Oklahoma, found those with higher hair Mn and arsenic levels had lower IQ scores and poor verbal learning and memory (2). Here we describe two Mn-poisoned children seen in our clinic. *Methods:* Case series. *Results:* A10-year-old male whose family was drinking contaminated well water (Mn 1,210 mcg/L) for 5 years had an unusual profile of visual, verbal, and general memory deficits despite normal WISC scores (3). Brain MRI was normal. His hair Mn was 3,091 ppb (normal < 200 ppb); highest whole blood Mn 3.82 mcg/dL (normal < 1.4 mcg/dL); 24-hour urine Mn 8.5 mcg/L (normal < 1.06 mcg/L). A second unpublished case involved a 7-year-old girl with elevated blood/urinary copper, cobalt, and manganese levels, polycythemia, abnormal iron kinetics, pica, movement disorders, and dysarthria. Well water at a summer cottage revealed elevated Mn (2,100 mcg/L). Her liver biopsy revealed tissue Mn 34 mcg/gm (11x normal). MRI showed abnormal signal intensities in basal ganglia, white matter, and brain stem. WISC scores were discrepant: vIQ 105/pIQ 84; verbal learning scores -1 to -2.5 SD below age; non-verbal problem solving skills in 7th % tile; her Connors Attention Deficit Hyperactivity Index consistent with DSM IV diagnosis of ADHD. *Conclusions:* Children may suffer neurological toxicity from low-dose chronic exposures to environmental manganese. Genetic susceptibility or other individual factors might explain the differences in clinical severity between the two cases, given their comparable Mn exposures. *References:* 1. Wasserman GA, Liu X, Parvez F, et al. Water manganese exposure and children's intellectual function in Araihazar Bangladesh. Environ Heal Persp 2006; 114:124–9. 2. Wright RO, Amarasiriwardena C, Woolf AD, Jin R, Bellinger DC. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology 2006; 27:210–6. 3. Woolf A, Wright R, Amarasiriwardena C, Bellinger D. A child with manganese exposure from drinking water. Environ Heal Persp 2002; 110:613–6.

134. Phenytoin-Induced Hypothermia in a Patient with Mental Retardation

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Objective: Phenytoin toxicity typically presents with ataxia and nystagmus, but a wide range of symptoms may manifest. Hypothermia is a rarely described condition occurring in the setting of phenytoin toxicity. Two previous case reports of patients with mental retardation (MR) with phenytoin toxicity are published with no causative explanation mentioned in either case (1,2). We report a case of phenytoin-induced hypothermia in a patient with MR who had documented adrenal insufficiency, presumably due to phenytoin toxicity. *Case Report:* A 50-year-old male resident of a group home presented to the emergency department (ED) for decreased responsiveness. His past medical history was significant for mental retardation (MR) and seizure disorder treated with phenytoin and phenobarbital. His serum phenytoin level had been elevated at a routine visit to his primary care provider earlier that week. In the ED he was hypothermic with a rectal temperature of 33.1°C (91.6°F). The physical examination was unremarkable except for a depressed level of consciousness. The results of a complete metabolic panel, complete blood count, urinalysis and chest x-ray were within normal limits. His initial serum phenytoin level was 37 µg/mL (147 µmol/L). Serum amylase and lipase were elevated at 460 and 324 U/L, respectively. The serum cortisol level was 12.4 µg/dL (342 nmol/L). A cosyntropin stimulation test showed adrenal insufficiency. Blood and urine cultures were negative. A computed tomography (CT) scan of the brain showed no acute pathology, and a bedside EEG determined that the patient was not having convulsive activity. A CT scan of the abdomen showed only mesenteric stranding of undetermined significance. The patient was endotracheally intubated for airway protection, and given intravenous glucose, antibiotics, hydrocortisone, and fluids. Phenytoin was discontinued. He was warmed with external heat over a period of 12 hours. The patient's hemodynamic and metabolic parameters improved with therapy but his mental status remained impaired from baseline. He was discharged after ten days in hospital. *Conclusion:* Significant hypothermia may occur in the setting of prolonged phenytoin use and toxicity. Patients with MR appear to be at risk of developing this condition. To our knowledge this is the first case in which documented phenytoin-induced adrenal insufficiency may have played a role. Clinicians should be alerted to the possibility of phenytoin-induced hypothermia and obtain core temperatures on all patients with a depressed mental status and phenytoin toxicity. *References:* 1. Alhaj E, Alhaj N. Hypothermia and phenytoin toxicity: A case report. Clinical Neuropharmacology 2001; 24:239–241. 2. Newberger DS, Blyth SA. Hypothermia and phenytoin toxicity. Clinical Neuropharmacology 2003; 26:172–173.

135. Signs and Symptoms (SS) of Antidrepessant Tricyclics (ADT) Overdose and ADT Plasma Levels of 173 Patients Attended by Unicamp Poison Center, Campinas City, S. Paulo State, Brazil, January 1997 – September 2006

Vieira RJ, Moretti TBC, Madureira PR, De Capitani EM, Bucaretchi F, Toledo AS. *Unicamp Poison Center University of Campinas, Brazil*.

Objectives: To present a retrospective study looking at the distribution of ADT plasma levels, ADT ingested doses, SS, and outcome in 173 cases of ADT poisoned patients attended by UPC from January 1997 to September 2006. *Case Series:* Only 173 out of 898 cases attended by UPC had a determined ADT plasma level, with 66.5% attended at the University Hospital and 33.5% at different hospitals. The most frequent ADT in 2003 were amitriptyline 65.7%, imipramine 12.6%, clomipramine 7% and nortriptiline 4.2%. In terms of association with other drugs, 29.5% ingested ADTs alone, 56.1% also took other drugs and in 14.4% it was not determined. The most frequent associations were benzodiazepines 64.5%, carbamazepine 20.8%, ethanol 9.3% and phenobarbital 5.2%. The mean of ADT plasma levels in relation to ingested dose were: 212.88 ng/mL for less than 20 tablets, 276.53 ng/mL between 20 and 40 tablets and 542.83 ng/mL for more than 40 tablets. For the 51 patients poisoned only by ADTs, the most frequent SS of the 34 ADT poisoned patients with ADT plasma level less than 300 ng/mL were somnolence 21, agitation 7, confusion 6, tachycardia 4, diaphoresis 3, hypertension 2, coma 1 and 16 others. The most frequent SS of 13 ADT poisoned patients with ADT plasma level between 300 and 1000 ng/mL were somnolence 6, coma 6, tachycardia 4, agitation 2, hypotension 2, stupor 1, hypertension 1, and 10 others, one died. The most frequent SS of 4 ADT plasma levels of 1000 ng/mL or more were coma 2, stupor 1, confusion 1, slurred speech 1, agitation 1, salivation 1, delirium 1, and 2 others, one died. The most frequent SS of the 62 ADT poisoned patients who also took other drugs, with ADT plasma levels less than 300 ng/mL, were somnolence 44, coma 16, agitation 14, tachycardia 11, confusion 6, stupor 6, mydriasis 5, and 35 others, one died. The most frequent SS of 27 patients with ADT plasma levels between 300 and 1000 ng/mL were somnolence 14, coma 12, agitation 7, stupor 6, tachycardia 3, hypotension 2, and slurred speech 1, two died. The most frequently SS of 8 ADT poisoned patients with ADT plasma level of 1000 ng/mL or more were coma 8, tachycardia 3, confusion 2 and agitation 1, one died. *Conclusion:* The most frequent signs of patients with ADT plasma level of 1000 mg/mL or more was coma while somnolence occurred when less then 1000 mg/mL.

136. Comparative Evaluation of Different Methadone Dosages on Qt Interval

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Objective: Methadone is used for the treatment of opioid dependency. Methadone causes QTc prolongation and occasionally torsade de pointes (1). Because of the wide availability of methadone in methadone maintenance treatment (MMT) centers (2), dose-related effects of methadone on QT interval were evaluated. *Methods:* The study was a clinical trial. Ninety patients who were under methadone maintenance treatment in the MMT center of Noor hospital and Ghaedi Clinic were evaluated. According to methadone doses the patients were divided into three groups (0–59 mg, 60–109 mg, 110–150 mg). Twelve-lead electrocardiograms (ECGs) were performed in patients at both baseline and after the maximum daily doses of methadone therapy. The ECGs were manually interpreted. The QTc intervals were calculated for each patient. In different groups, comparison of mean differences of QTc interval between baseline and follow up were analyzed by ANOVA. *Results:* There were significant differences between means of QTC interval before and after treatment with methadone in all groups. Methadone modestly increased QTc interval. *Conclusion:* Although QTc interval prolongation may occur after methadone treatment, the risk for torsade de pointes arrhythmia is low. *References:* 1. Krantz MJ, Lew Kowiez l, Hays H, et al. Torsade de pointes associated with very high dose methadone. Ann Intern Med 2002; 137:01–504. 2. Bridgest A, Julid H, Mare N. The impact of methadone induction on cardiac conduction in opiate users. Ann Inern Med 2003; 139:155.

137. Domperidone Toxicity and Literature Review

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Objective: To present a case of sudden death possibly linked to oral domperidone use and critically review the literature. *Case Report:* An 18-year-old-female with no history of cardiac disease or intentional overdose suffered a presumed cardiac arrest several days after initiating amitriptyline, prescribed in addition to domperidone and ondansetron for gastroparesis. All three medications are cyp 3A3/4 substrates and each has been implicated in prolonging the QTc via various mechanisms. A post-mortem exam was declined and thus a definitive cause of death could not be established; however, physicians felt a cardiac arrhythmia was the most probable etiology. The case prompted a review of the safety literature written about IV vs. oral domperidone, particularly in the pediatric population. *Conclusion:* A peripheral D2-receptor antagonist, domperidone has reported efficacy in the treatment of gastric motility disorders, chemotherapy-induced nausea/vomiting, anti-Parkinson medication-related nausea/vomiting, and lactation enhancement. Several studies cite a favorable safety profile, noting that domperidone does not cross the blood-brain-barrier in most patients, thus resulting in fewer CNS-related toxicities when compared to metoclopramide (1,2). However, the Food and Drug Administration has consistently declined to approve domperidone for use in the US, citing cardiac toxicity concerns (3). Primarily reported with IV domperidone, severe cardiac arrhythmias including torsade de pointes are thought to occur most often in the presence of hypokalemia and are secondary to blockage of the rapid component of the IKr current (4). The channels are encoded by the human ether-à-go-go-related gene (HERG), and blockade inhibits release of potassium from myocytes (5). Subsequently, oral domperidone has also been reported to prolong the QTc interval (6). Other medications implicated in a similar blockade of the hERG channels include pentamidine, certain antimicrobials, neuroleptics and antiarrhythmic agents. Medications such as domperidone should be used cautiously in patients with additional risk factors such as multiple-drug regimens, genetic predisposition, organ dysfunction or electrolyte imbalance. *References:* 1. Barone JA. Domperidone: peripherally acting dopamine2-receptor antagonist. Ann Pharmacother 1999; 33:429–40. 2. Ahmad N, et al. Making a case for domperidone in treatment of gastrointestinal motility disorders. Curr Opin Pharmacol 2006 Sep 22; [Epub ahead of print]. 3. US Food and Drug Administration Talk Paper June 7, 2004. 4. Drolet B, et al. Domperidone should not be considered a no-risk alternative to cisapride in treatment of gastrointestinal motility disorders. Circulation 2000; 102:1883–85. 5. Classen S, Zunkler B. Comparison of effects of metoclopromide and domperidone on HERG channels. Pharmacology 2005; 74:31–36. 6. Rocha CMG, Barbosa MM. QT interval prolongation associated with oral use of domperidone in an infant. Pediatr Cardiol 2005; 26:720–723.

138. A Case Report of Chronic Doxepin Toxicity

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Objective: There is very little literature regarding chronic tricyclic antidepressant toxicity. We report a case of chronic doxepin toxicity with an absence of electrocardiographic manifestations. *Case Report:* A 58-year-old recovering alcoholic man with past medical history of hypertension, prostate cancer, bleeding cerebral aneurysm, gunshot to the chest, and depression presented to the local Veteran's Administration hospital complaining of drowsiness of several hours duration. During this admission, he had an extensive neurologic examination which included a head CT and EEG. The patient's hospital stay was uneventful and no specific neurological cause could be elicited for his symptoms. Two days after discharge, the patient presented to the hospital again complaining of continued weakness and inability to walk. On initial examination, the patient had stable vital signs, but was found to be lethargic with slurred speech. He was also found to be alert and oriented to name and place, had difficulty following commands and a shuffling, unsteady gait. A noncontrast head CT was negative and a neurology consult was obtained. Once again, the head CT was interpreted as normal. Electroencephalography showed diffuse beta activity, suggestive of drug effect. The patient was admitted to the neurology service and was found to have a doxepin level of 523 ng/ml and a nordoxepin level of 323 ng/ml on serum drug screening. An electrocardiogram demonstrated a normal sinus rhythm at a rate of 80 bpm with QRS duration of 92 msec without rightward deviation of the terminal 40 msec. The patient was advised to decrease the amount of doxepin from 50 mg at bedtime to 25 mg at bedtime and discharged. Three days after discharge, the patient presented again with continued complaint of weakness, lethargy, ataxia and confusion. Repeat levels of doxepin and nordoxepin were obtained with an elevation of his doxepin level to 745 ng/ml and nordoxepin level to 447 ng/ml. Repeat electrocardiography demonstrated normal sinus rhythm at a rate of 95 bpm with a QRS duration of 94 msec without rightward deviation. The patient was admitted to the medicine service on continuous telemetry and his doxepin was held. Over the next 4 days, his neurologic symptoms resolved with the exception of his intention tremor. Upon discharge, the patient's doxepin level was 209 ng/ml and nordoxepin level was 455 ng/ml. *Conclusion:* The patient's neurologic complaints were likely caused by chronic doxepin toxicity without concurrent changes in the electrocardiogram.

139. Incidence and Outcome of Intoxication with Tricyclic or Newer Antidepressants in Suicidal Attempts

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Objective: Although there is evidence that tricyclic antidepressants (TCA) are more harmful than the newer ones, we performed this study in order to reveal the existing current use of TCA and their effects in intentional intoxication compared with the newer antidepressants. *Materials and Methods:* Ninety-three cases of intentional intoxication with ingestion of newer antidepressants and 60 cases of intentional intoxication with ingestion of TCA were studied over a period of 6 months, during which we recorded the quantity of the drugs taken, as well as the severity of the cases, based on the clinical status and the duration of hospitalization. *Results:* Among the 93 cases of intentional intoxication with ingestion of newer antidepressants no clinical effect was noted in 54%, mild clinical effects (dizziness, drowsiness, tachycardia) were observed in 41% while severe intoxication (coma), occurred in 5% (ingestion of a highly toxic dose). A 24-hour medical observation was provided in the hospital in 56% of the cases. Although they had received a moderate to severe dose, 38% remained at the hospital for 48 hours, and only 6% were hospitalized for more than 72 hours. Among the 60 cases of intentional intoxication with ingestion of TCA, absence of clinical effect was noted in just 16% of the cases, mild clinical effects occurred in 59% and coma was observed in 25%. Only 15% remained in the hospital for just 24 hours, 37% for 48 hours and 48% were hospitalized for more than 72 hours. *Conclusions:* In cases of intentional intoxication with newer antidepressants the clinical effects were significantly less severe, and the duration of hospitalization was significantly shorter, compared to those of tricyclic antidepressants. In order to prevent severe cases of intoxication, communication between toxicologists and psychiatrists would be rather useful, so that prescription of tricyclic antidepressants is limited to the cases they are strictly indicated for.

140. An Unusual Intoxication of an Infant with Olanzapine

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Objective: The aim of this study was the differential diagnosis of an intoxicated infant within the framework of the emergency toxicological analysis. *Case Report:* A four-month infant was hospitalized with miosis, drowsiness and extrapyramidal symptoms. No other pathological findings were present. It was also reported that his mother was receiving therapeutically olanzapine and thus there were suspicions of intoxication of the infant, although, the infant was not breast fed during the last few days. The investigation of the case revealed that the mother had breast fed the infant two hours before the incident (1,2). The concentration of olanzapine in the breast milk was extraordinarily high (102.5 μg/ml). The plasma and gastric fluid olanzapine concentrations of the infant were also high (0.42 and 12.7 μg/ml, respectively). In contrast, the concentration of olanzapine in mother's plasma was (0.02 μg/ml). Nevertheless, she was receiving 10 mg of olanzapine every 48 hours. *Conclusion:* The investigation and presentation of this unusual case contributes not only to the differential diagnosis of an infant's intoxication, but reminds the doctors of the dangers involved when the mother is under antipsychotic therapy and breastfeeds her infant irregularly as in this case. *References:* 1. Croke S, Buist A, Hachkett I, et al. Olanzapine excretion in human breast milk: estimation of infant exposure. Int J Neuropsychoph 2002; 5:243–247. 2. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. Psychiatry 2004; 38:1265–1271.

141. Cardiac Conduction Defects following Mirtazapine Overdose

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Objective: We report an enquiry to a poisons centre regarding mirtazapine overdose in which transient cardiac conduction abnormalities occurred in a healthy patient. *Case Report:* A previously healthy 31-year-old male presented to hospital following intentional overdose of 780 mg of mirtazapine. An enquiry was made to the poisons centre 2.5 hours post ingestion. The timing of the ingestion was believed to be accurate and no co-ingestants were reported. On presentation to the emergency department blood pressure, arterial blood gases, urea, and electrolytes (including potassium) were within normal values. Mild drowsiness was reported (Glasgow Coma Scale 15/15) with no other obvious symptoms. An ECG taken 2 hours post ingestion showed sinus tachycardia (rate 112/min) with left bundle branch block and a wide QRS complex (194 ms). Information was requested about pharmacological treatment of QRS prolongation and advice was sought from a clinical toxicologist who recommended conservative management with repeat measurement of urea and electrolytes and blood gases and correction of any abnormalities. The QRS widening resolved over 1 hour without any specific treatment. A subsequent ECG showed persisting sinus tachycardia (104/min) with a QRS width of 102 ms and QTc interval of 394 ms. An ECG from a previous routine hospital admission was normal. *Conclusion:* There is limited published data of the effects of overdose with mirtazapine, an atypical antidepressant. Central nervous system depression, including disorientation and prolonged sedation and cardiovascular effects, including tachycardia and mild hypertension or

hypotension have been reported following intentional overdose. Orthostatic hypotension is a side effect of therapeutic use. This is the first report of cardiac conduction defects with mirtazapine. Cardiac conduction abnormalities have not been reported in the manufacturer's data (1). QT prolongation and bradycardia has been reported in a profoundly hypothermic patient with mirtazapine overdose although hypothermia may have been the precipitating causal factor (2). No additional reports of cardiac conduction abnormalities were identified in a Medline literature search. *References:* 1. Organon Laboratories Ltd. Summary of product characteristics Zispin, 2006. 2. Retz W, Maier S, Maris F. Non-fatal mirtazapine overdose. Int Clin Psychopharmacol 1998; 13:277–279.

142. Withdrawal after Discontinuing Vigabatrin Therapy

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Objective: Vigabatrin, an analogue of gamma-aminobutyric acid (GABA), is used as an adjunctive therapy for refractory epilepsy. By irreversibly inhibiting the enzyme responsible for GABA catabolism (GABA transaminase or GABA-T), vigabatrin increases brain GABA levels. Adverse events with therapeutic dosing include irritability, insomnia, and behavior changes (1). We report symptoms consistent with sedative-hypnotic withdrawal that developed after discontinuing vigabatrin therapy. *Case Report:* A 9-month-old boy born with refractory epilepsy was started on zonisamide therapy at two weeks of age. After four months, vigabatrin was added. Due to a lack of response and potentially deleterious visual side effects he was slowly tapered from his daily dose of 600 mg to zero over two weeks. His zonisamide dosing remained unchanged. Ten days after starting the taper he was noted to be irritable. Two days after finishing the taper he became more irritable, inconsolable, and developed a temperature of 40ºC. He was admitted to the hospital. A sepsis evaluation including blood, urine, and spinal fluid cultures was negative. Continuous EEG monitoring showed no seizure activity. He was transferred to intensive care after developing tachycardia (HR 200 beats/min) and tachypnea (RR 80 breaths/min). Diazepam was administered for irritability and agitation. His mother then described him as "normal" and his vital signs returned to baseline. He received 4.5 mg of diazepam every eight hours with additional "as needed" doses being given in between for the following two days. Cross-tolerance was suggested by his receiving approximately 20 to 30 mg of diazepam per day without sedation. After two days of diazepam therapy, he was restarted on vigabatrin at 75 mg/day. One week later, his diazepam had been tapered down to a dose of 3 mg a day while his vigabatrin dosing was 100 mg twice daily. No further withdrawal symptoms were described on this regimen. *Conclusion:* Discontinuing vigabatrin may produce a clinical syndrome similar to sedative-hypnotic withdrawal, with a similar response to benzodiazepine therapy. It is likely that the similarity of vigabatrin withdrawal to that of sedative-hypnotic withdrawal may be related to their similar effect on brain GABA levels. *References:* 1. Grant SM, Heel RC. Vigabatrin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 1991; 41: 889–926.

143. Delayed Torsade de Pointes (TdP) Associated with Ziprasidone Overdose

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Objective: In 2005, the United States FDA recommended a black box warning for ziprasidone due to increased risk of sudden death in treated patients when compared to placebo. It is believed that QT interval prolongation and subsequent TdP may explain sudden death from anti-psychotics. However actual cases of TdP associated with ziprasidone have been notably absent from the literature. We report fatal delayed TdP following a ziprasidone overdose. *Case Report:* A 30-year-old woman was found unresponsive with empty bottles of ziprasidone (60 mg tablets), amantadine (100 mg tablets), and ibuprofen (600 mg tablets) present nearby. On arrival to the ED, her vital signs were: BP, 118/76 mmHg; HR, 60 beats/min; RR, 16 breaths/min; and oral temperature, 37ºC. She was lethargic but the remainder of her examination was normal. An electrocardiogram was notable for sinus bradycardia at 55 beats/min with a normal axis, QRS of 92 milliseconds (ms), and a QTc of 458 ms. Occasional premature ventricular beats were noted. Consequential serum chemistries included: potassium, 3.0 mEq/L and magnesium, 1.9 mEq/L. Serum paracetamol, ethanol, salicylates, and a pregnancy test were all negative. Approximately 8 hours after arrival to the ED, the patient lost consciousness with simultaneous appearance of TdP on the bedside monitor. She rapidly received a total of 5 defibrillations with subsequent return to a perfusing normal sinus rhythm. An ECG post-resuscitation revealed that the repeat QTc had increased to 483 ms. She was admitted to the cardiac intensive care unit where she eventually expired 10 days later from complications of her cardiac arrest. *Discussion:* Given the history and clinical circumstances, we believe the episode of TdP was secondary to drug-induced QT prolongation. The history and findings at the scene were consistent with overdose of her medications, which included ziprasidone and amantadine. This patient had an 8-hour delay between arrival to the ED and the TdP, which represents an important delay in cardiac toxicity. Although amantadine can cause TdP, delayed TdP has not been reported with either drug. This patient's delay may have been due to the effects of ziprasidone alone, or a combined effect of ziprasidone with amantadine. *Conclusion:* We report a case with a strong association between ziprasidone overdose and delayed onset TdP.

144. Methylphenidate Overdose in Adolescents and Adults – Experience in Sweden

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Objective: Methylphenidate was introduced on the Swedish market at the end of 2002 for treatment of ADHD (attention deficit hyperactivity disorders). The prescription rate of methylphenidate has more than doubled since its introduction, and an increasing number of inquiries related to overdose has been observed. In order to assess the acute toxicity of methylphenidate in human overdose, a retrospective survey of the telephone inquiries and hospital case records received by the Swedish Poisons Information Centre (SPIC) was carried out. *Case Series:* Since the introduction of methylphenidate in 2002 the SPIC has received 242 calls concerning overdose in adolescents and adults. In many of these cases more than one drug was ingested, and in some there were insufficient data. Thus, during the actual period 25 cases of pure methylphenidate poisoning could be analysed in detail by studying hospital case records. Around two thirds of the patients were young (10–19 years old). There were 64% females and 36% males. The ingested dose varied from 140 mg to 1620 mg (medium 480 mg, median 468 mg). In 18/25 cases methylphenidate was prescribed for the patient. The reasons for overdosing the drug were suicidal attempt (18/25), abuse (1/25), therapeutic error (1/25) and unknown (5/25). The severity of poisoning was graded according to the Poisoning Severity Score (PSS). Three patients were asymptomatic, 19 patients developed mild symptoms (PSS 1) whereas 3 patients developed moderate symptoms (PSS 2). In this material there were no severe cases nor any fatalities. The most frequent symptoms were tachycardia (17/22), tremor (8/22), restlessness (6/22), mild hypertension (5/22), fever (3/22), gastrointestinal discomfort (3/22), mydriasis (3/22), hallucinations (2/22), mild CNS-depression (2/22). Occasionally tachypnea, muscle fasciculations, miosis, headache, dry mouth, stereotype movements and mild hypotension occurred. The severity of symptoms did not differ between the patients who were already treated with methylphenidate and those who were not. Eight patients admitted early were given activated charcoal. In four patients diazepam was administrated for sedation. Otherwise no active treatment was required. *Conclusion:* The use of methylphenidate is steadily increasing in Sweden. In this material most cases of methylphenidate poisoning were benign. The symptoms seem to be far less severe than those observed in amphetamine overdose.

145. Quantification of Methadone-Induced Respiratory Depression using Toxicokinetic/Toxicodynamic Relationships: A Case Report

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Objective: Methadone, the most widely delivered maintenance therapy in heroin addicts, may be responsible for life-threatening poisonings with respiratory depression. The available marketed methadone is a racemic mixture of two stereoisomeric forms, the R- and S-enantiomers. R-methadone is the main pharmacologically active isomer, believed to account for most if not all of the therapeutic effects of methadone maintenance treatment. However, although lacking strong opioid effects, S-methadone may play a significant role in the adverse responses to R,S-methadone The toxicokinetics and the toxicokinetic/toxicodynamic (TK/TD) relationships of methadone enantiomers have been poorly investigated in acute poisonings. The aim of this study was to understand the relationships between methadone-related respiratory effects and the concentrations of its two enantiomers. *Case Report:* We report a 44-year-old methadone-maintained patient who ingested a 240 mg dose of methadone. He was found comatose, with pinpoint pupils, and respiratory depression. He was successfully treated with intravenous naloxone infusion during 31 hours, at a rate adapted to maintain normal consciousness and respiratory frequency. We performed a TK/TD analysis regarding the naloxone infusion rate to normalize his respiratory frequency (as TD parameter) versus plasma R,S- and R-methadone concentrations (as TK parameter), determined using an enantioselective high performance liquid chromatography assay. Initial plasma R,S-methadone concentration was 1,204 ng/ml. Decrease in plasma R- and S-methadone concentrations was linear and demonstrated a first-order pharmacokinetics (Cmax: 566 and 637 ng/ml; half-lives: 16.1 and 13.2 h, respectively). TK-TD correlation between naloxone infusion rate and R,S- and R-methadone concentrations well fitted a sigmoidal Emax model (EC50: 334 and 173 ng/mL and Hill coefficient: 10.0 and 7.8, respectively). In our chronically-treated patient, EC50 values were in the range of the previously reported values regarding methadone analgesic effects, suggesting that plasma methadone concentrations to prevent withdrawal are similar to those associated with methadone analgesic effects. *Conclusion:* Following the ingestion of a toxic dose of a racemic mixture, plasma R- and S-enantiomer concentrations decrease in parallel. Despite large inter-individual variability in methadone TK and TD, TK/TD relationships would be helpful to provide quantitative data regarding the respiratory response to methadone in poisonings.

146. Persisting Tachycardia and Late Onset Seizures in two Non Fatal Cases of Quetiapine Intoxication

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Objective: Quetiapine is an atypical antipsychotic drug belonging to the class of dibenzothiazepine derivates. In contrast to typical antipsychotics fewer extrapyramidal side effects are reported (1). In the following two cases late onset seizures were observed. *Case Series:* A 17-year-old female presented to the emergency department following ingestion of a large quantity of quetiapine tablets (Seroquel®). The patient was conscious but a little drowsy, responded well to verbal stimuli and was hypotensive. Electrocardiogram showed sinus tachycardia but no QTc prolongation. Toxicological analysis revealed a serum quetiapine level of 5596 ng/mL. 12 hours post ingestion, the patient's Glasgow coma scale (GSC) decreased below 8/15 without responsiveness to pain. Physical findings included low blood pressure, mydriasis and tachycardia (150 beats/min). When an arterial line was installed, the patient suddenly began to have seizures which were immediately treated with diazepam. At this very moment the serum quetiapine concentration had reached its top level of 7264 ng/mL. The decision was made to intubate the patient. 18 hours post ingestion the patient regained consciousness but was still tachycardic (140 beats/min). Now the serum quetiapine level was 2162 ng/mL. Three and a half hours later the patient extubated herself. 33 hours after ingestion the serum quetiapine level dropped to 423 ng/mL and the heart rate decreased to 113 beats/min. In a second case report a 16-year-old female was admitted to the emergency department 14 hours after the ingestion of 3600 mg quetiapine. She had vomited, was agitated, had fixed pupils and a blood pressure of 107/46. GCS was 8/15 and the electrocardiogram showed sinus tachycardia of 145 beats/min. The serum quetiapine level was 2398 ng/mL. One hour later our patient exhibited seizure activity and lorazepam was administered. Sinus tachycardia lasted for approximately 40 hours post ingestion. *Conclusion:* In both cases the ingestion of large amounts of quetiapine necessitated a strict follow-up in the ICU. Low blood pressure, reduced consciousness and persisting sinus tachycardia was seen. No QTc prolongation was observed. In both patients generalized seizures developed only after 12 to 15 hours. Emergency physicians should be aware of the occurrence of late onset convulsions in quetiapine overdose. *References:* 1. Misra LK, Erpenbach JE, Hamlyn H, Fuller WC. Quetiapine: a new atypical antipsychotic. S D J Med 1998; 51:189–193.

147. Successful Endoscopic Removal of Slow Release Clomipramine-Bezoars in Two Cases with Acute Poisoning

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Objective: To illustrate that acute gastroscopy can be of clinical usefulness in selected cases of drug overdose. *Case 1:* A 28-year-old woman ingested 60 slow release tablets containing 75 mg clomipramine (4.5 g). The ambulance arrived 30 minutes afterwards and the patient was given activated charcoal during transport to hospital. She was asymptomatic on admission. Gastric lavage was performed but no sign of tablet recovery was seen. The PIC recommended an acute x-ray since slow release clomipramine has been shown radio opaque. An abdominal x-ray four hours after ingestion indicated the presence of a large tablet conglomerate in the ventricle. It was decided to anaesthetize and intubate the patient in order to remove the presumed pharmacobezoar endoscopically. A large bore gastric tube intended for lavage was taped side to side to the gastroscope. The conglomerate was identified, crushed and sucked out through the tube. Big lumps were grabbed with a wire basket or pliers and extracted by withdrawing the whole instrument. It was estimated that 40–50 tablets were removed this way. The patient was wakened and remained asymptomatic during 24 hours of ICU observation. Laboratory tests and ECG were normal and there was no complication attributable to the gastroscopy. *Case 2:* A 25-year-old woman was taken to hospital four hours after intake of 6 g clomipramine (80 depot-tablets of 75 mg) and 120 mg oxazepam. On admission she was rousable on strong stimulation. The ECG displayed sinus tachycardia with normal QRS-complexes. The patient was intubated before gastric lavage. However, it proved impossible to pass the esophagus with the tube. It was therefore decided to perform a gastroscopy. Approximately ten cm below the larynx the gastroscopist noted lots of tablet residues and granular material which was extracted through the endoscope. In the distal part of the esophagus an initially impenetrable, cement-like obstruction was observed. With great efforts including the use of pliers, flushing and suction, it was possible to remove this conglomeration and enter the ventricle. Some tablet residues were noted there, and these could be sucked out. A gastric tube was inserted and activated charcoal instilled. The patient was transferred to the ICU for mechanical ventilation and further observation, but never displayed any significant signs of cardiovascular disturbances. Extubation was performed 20 hours post ingestion. Routine laboratory tests were normal. *Conclusion:* These cases confirm that slow release clomipramine can form radio opaque pharmacobezoars. The favourable outcomes support the use of gastroscopy as a diagnostic and therapeutic tool in cases of poisoning where clinical findings or x-ray have raised suspicion of a conglomerate containing highly toxic tablets.

148. Determination of Olanzapine Plasma Levels in Patients with Acute Poisoning

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Objective: Olanzapine is an atypical antipsychotic commonly used in many psychiatric disorders. Although acute olanzapine poisonings are sometimes severe in their clinical course, the determination of olanzapine plasma levels is not performed routinely and its diagnostic evaluation is not well-defined. Our purpose was to evaluate the clinical course of acute olanzapine poisoning in relation to blood concentration of the drug and to characterize some toxicokinetic parameters. *Methods:* The study group consisted of 8 patients (4 men, 4 women; mean age 42.2 years, SD = 17.4) hospitalized in our Department from August 2005 to May 2006 because of acute olanzapine poisoning. The data relating to clinical course of poisonings (consciousness disturbances, level of psychomotor agitation, blood pressure, pulse rate, temperature, blood glucose, creatine phosphokinase (CPK)) were obtained from the retrospective analysis of medical records. The plasma olanzapine determinations were performed using HPLC-DAD. Blood samples were taken at admission and several times through the first 72 h of hospitalization. Considering these measurements, the initial olanzapine concentration (Co) (possible in 6 cases) and biological half-life (t1/2) were calculated and then compared with the clinical data. *Results:* The ingested doses were in the range of 80 to 600 mg, exceeding the maximum single dose 8 to 60 times. Maximum olanzapine concentrations measured at admission (on average 4.5 h after ingestion) ranged from 207.7 to 768.5 ng/ml. The relation of Co with ingested dose showed increasing tendency (R2 = 0.72). The calculated t1/2 was 25.0 to 77.8 h (mean 42.6; SD=17.4) and it was higher in men than women (48.1 vs. 37.1 h) and in nonsmokers than smokers (45.9 vs. 39.3 h). All the patients had consciousness disturbances lasting on average 32.6 h (SD = 20.4), longer in patients (n = 2) with SSRI coingestion (63.0 vs. 22.5 h). The positive correlation between Co and the duration of consciousness impairments were observed (R 2 = 0.65). The mean olanzapine concentration at the time of total regression of consciousness disturbances was 163.9 ng/ml (n = 6; SD = 85.6) and it was lower in patients (n = 2) with GI decontamination (143.2 vs. 205.5 ng/ml). The mean Co in patients with Glasgow Coma Scale (GCS) score ≤8 was 546.2 ng/ml and 250.5 ng/ml with GCS >8. Positive correlations between Co and blood glucose level (R2 = 0.78) or CPK activity (R2 = 0.63) were found. No relation between Co and other studied parameters were observed. The mean Co in patients with moderate poisoning (Poisoning Severity Score – PSS2) was slightly less than in severe poisoning (PSS3) (431.5 vs. 463.7 ng/ml). *Conclusion:* Our preliminary studies showed that plasma olanzapine measurements can be a useful diagnostic tool in acute olanzapine poisoning.

149. Collaborative Poison Center Management of Rabies Encephalitis in a Patient Treated with a Novel Anti-Excitotoxic Regimen

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Objective: To describe the rare diagnosis and ongoing management of human rabies encephalitis by a tertiary-care pediatric hospital in collaboration with a regional poison control network. *Case Report:* On receiving an acutely ill, 11-year-old male child with symptoms of combativeness, hyper-kinesis, and sialorrhea, a primary treatment team at Oakland Children's Hospital called the San Francisco Division of the California Poison Control System (CPCS-SF) for consultative management. Given the epidemiologic and symptomatic similarity between this child, a recent immigrant from the Philippines, and a 1987 CPCS-SF case of a 13-year-old Filipino male immigrant with rabies (1), testing for rabies was recommended as part of the patient's initial toxicological work-up. Corneal Impression Testing (2) for rabies viral inclusions in the child's neuro-corneal tissue was positive, confirming active rabies encephalitis. Based on the successful, and unprecedented, treatment of human rabies with a high-dose, long-term combination of anesthetics and anti-virals (amantadine, ribavirin, ketamine, and midazolam) in 2005 by a team at the Medical College of Wisconsin (3), the decision was made to treat the current patient with a similar regimen. The patient has begun treatment and remains stable as of today, the abstract submission deadline date. *Conclusion:* The diagnosis of rare toxidromes is enhanced by the phenomenon of "institutional memory," which may be augmented by poison-control center consultation. Poison-center consultation may also help minimize the harm and enhance the efficacy of emergent, experimental therapies. *References:* 1. [Authors Unlisted]. Human rabies-California, 1987. Morbidity and Mortality Weekly Report 1988; 37:305–308. 2. Zaidman G, Billingsley A. Corneal impression test for the diagnosis of acute rabies encephalitis. Ophthalmology 1998; 105:249–251. 3. Willoughby R, Tieves K, Hoffman G, et al. Survival after treatment of rabies with induction of coma. The New England Journal of Medicine 2005; 352:2508–2514.

150. Change in the Use of Depilatory Creams as a Cause of Dermal Lesions. Role of the Poison Centre in Toxic Surveillance

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Objective: Various dermal reactions have been described after the use of depilatories solutions. Many of them were the result of misuse, overuse, or sensitization to the ingredients of these products. Irritation and burns may result from increased concentration or prolonged exposure times. In Spain depilatory creams contain thioglcycolic acid (1–5%) and concentrations below 4.75% should not cause dermal lesions. Nevertheless at our PCC an increasing number of consults due to dermal lesions after the exposure to depilatory creams were detected. Therefore we decided to analyse the circumstances of exposure in order to find the aetiology and propose preventive measures. *Methods:* Study of consults related to exposure to depilatory creams registered in the Spanish Poison Control Centre from January 2005 to October 2006. Data including aetiology, sex, age of patients, part of the body, duration of contact, and type of dermal lesions were analyzed. *Results:* 367 cases of human exposures to depilatory creams were registered during the study period. Sensitization reactions were observed in 18 cases (4.9%). 72 cases (19.6%) were due to accidental exposure to the product and 5 (1.4%) were intentional ingestion as a suicidal attempt. A high number of cases, 272, (74.1%) were due to the adverse effects after the use of these products. 94.9% of these cases were adults with 40.8% of them being male, 45.2% were female and the rest unknown. Males used the cream on the thorax (back, shoulders, or chest) 36.8%, genitals 23.7% and armpit 18.4%, whereas female used them on legs 29.6%, groin and genitals 29.6%, upper lip 18.5%, and armpits 7.4%. In 59.6% of the consults the time of exposure was equal or less than the directions for use (6 minutes). Dermal lesions were as follows: blisters, 44.1%; erythema, 20.6%; irritation, 15.1%; non-specified lesions, 16.9%. *Conclusion:* Depilatory creams were the cause of dermal lesions after an exposure time inferior to the one recommended by the manufacturer. The lesions were especially observed in males, and often in areas of the body in which the product should not be applied (chest, genitals, face, etc.). We contacted the health authorities and the manufacturer and there has been an agreement so that in 2007, the label data will be extended, and an advertising campaign will focus on the correct use of these creams.

151. Do the Callers Understand and Follow our Advice and are they Satisfied with the Service?

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Objective: In a previous study (1) we found that 83.5% of the callers to the Finnish Poison Information Centre would have called or visited another health care unit if a centre had not been available, indicating that a poison information centre could reduce utilisation of other resources. The aim of this study was to investigate whether the callers understand and comply with our instructions, refrain from using other health care resources, and to measure customer satisfaction. *Methods:* All calls from the public received during one week (43) in 2005 were eligible for the study. At the end of a call the caller was asked for informed consent to participate. A structured telephone interview was made by an independent person within 1–2 days. Interview results were compared with PIC call records. *Results:* During the study period, 350 calls from the public concerning human poisoning exposures were received. 120 callers were excluded (86 consent not asked, 24 not reached for interview, 10 other reasons). 230 persons were included in the study and successfully interviewed. Most of the calls (176, 76.5%) concerned children under 10 years of age, and the caller was most often the mother (148, 64%) or the father (30, 13%). The recommended place of treatment was recorded as home in 194 (84%) PIC call records, and 194 (84%) callers gave, in the interview, home as the place of treatment recommended for them. There was also complete agreement in recommended place of treatment in the remaining calls. The other instructions were reported by the caller identically to the records for 90.4% of the 230 instructions. 225 (97.8%) callers indicated they had followed the instructions given, 4 (1.7%) followed partly and 1 (0.4%) had not followed. 134 callers were very satisfied with the outcome of the call (80.0%), 40 were satisfied (17.4%), and 1 (0.4%) was undecided. When asked if the call had changed their anxiety felt at the time of the call 77% indicated it had been relieved very much and 21% it had relieved slightly while 1.7% were undecided. *Conclusion:* The instructions given by the PIC were correctly understood and complied with by the great majority of the lay callers. When in the advice given treatment at home was considered adequate, the caller did not seek other medical services. *References:* 1. Hoppu K, Forsell M. What would the caller have done, if the poison information centre had not been available? (Abstract). J Toxicol Clin Toxicol 2000; 38:239–240.

152. Poisons Centre Enquiries from Prisons

Lawler JM, Thomas SHL. *National Poisons Information Service (Newcastle), Regional Drug and Therapeutics Centre, Newcastle upon Tyne, UK*.

Objective: To identify the incidence of poisons centre enquiries originating from prisons and describe the epidemiology of associated poisonings. *Method:* Details of all enquiries

received by the National Poisons Information Service (Newcastle) from prisons between April 1, 2003 and June 30, 2006 were retrieved. *Results:* Of the 34,229 enquiries received during the study period, 672 (1.96%) originated from prisons. Most enquiries from prisons were made during the afternoon or evening with 53% (n = 356) being received between 3pm and 10pm. Prison nurses made 557 (83%) enquiries, 625 (93%) enquiries involved actual exposures, and 554 (88.6%) of which were intentional. 71 (11.4%) cases involved accidental exposures or were of unknown motivation. Of the 47 remaining enquiries, 21 (45%) were to assess the potential toxicity of medication and 16 (34%) were for tablet identification. Of the 625 actual exposures 436 (70%) involved males and 184 (30%) females. 172 (28%) of these cases were referred to hospital and 405 (65%) were advised that the patient could be managed in prison. Age was known in 446 (71%) cases of actual exposure and was recorded as "adult" in an additional 170 (27%) cases. The mean age was 29.3 years for males and 25.3 years for females. The agents involved were known in 622 of the 625 cases of actual exposure. 442 (71%) cases involved a single agent, 110 (18%) involved 2 agents, 46 (7%) involved 3 agents and 27 (4%) involved 4 or more agents. Pharmaceuticals were implicated in 574 (91.8%) of actual exposures, 30 (4.8%) involved household products or cleaning agents, and 13 (2%) involved drugs of abuse. 93% (n = 510) of the 554 intentional exposures involved ingestion of pharmaceuticals. 739 specific pharmaceutical agents were recorded, some patients ingesting multiple agents. The most frequently ingested agents were paracetamol (15%), antidepressants (15%), NSAIDs (23%) and antipsychotic medications (9%). It was known that prisoners overdosed on their own medication in 92 (18%) of the 510 deliberate ingestions. *Conclusion:* Fewer than 2% of all enquiries during the study period originated from prisons. Enquiries more frequently involved males. Whilst this is not consistent with reported trends in hospital admissions (1), it may be indicative of the gender demographic within the UK prison population. Age range and the use of antidepressant and antipsychotic medication in overdose is consistent with trends in hospital admissions following intentional overdose, although NSAIDs may be more frequently ingested by prisoners and paracetamol used less frequently (1). Discussion with a poisons centre may help to prevent unnecessary referral of prisoners to hospital. *Reference:* Lawler JM, Thomas SHL. Patterns of intentional self-poisoning in adults. Clin Tox 2005: 43;493.

153. Six Years of Thiazolidinedione Exposures Reported to the TESS Database

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Objective: To better elucidate the toxidromes associated with thiazolidinedione (TZD) ingestion and assess the incidence of severe clinical effects. *Method:* A review of all thiazolidinedione ingestions reported to the TESS database for the years 2000 through 2005. Included were TZD combination products, as well as the TZD removed from the market early in 2000. *Results:* 8,807 patients were reported of which 6,551 were acute exposures, 1,943 were acute on chronic and 230 were chronic exposures. The three main reasons were unintentional (n = 3,920), therapeutic error (n = 31,630) and suspected suicidal (n = 1,180). 4,318 (49%) patients were managed at home. Of those patients referred to or already in a HCF, 2002 (45%) were treated and released. 3,954 patients (45%) were determined to have no effect, 690 (7%) had a minor effect, 819 (9%) had a moderate effect, and 139 (2%) had a major effect. There were 11 deaths; 5 were acute, 5 were acute on chronic and 1 was a chronic. Hypoglycemia occurred in 505 (6%) of the patients. Transaminase elevations of >1000IU was seen in 1 patient, and >100, but <1000IU in 6 patients. All of these patients were chronic or acute on chronic exposures. Of the 8,807 patients, 3,417 (39%) were ≤6 yrs., 1,458 (43%) were managed at home, and 1,036 (30%) were referred to a HCF. Of those referred or already in an HCF 1,203 (50%) were treated and released, 385 (16%) were admitted to a non-critical unit, and 158 (7%) were admitted to an ICU. 2,256 patients (66%) were determined to have no effect, 122 (4%) had a minor effect, 108 (3%) had a moderate effect, and 8 (<1%) had a major effect. There was 1 pediatric death. Hypoglycemia occurred in 98 (3%) of all pediatric exposures, and no alterations in transaminases were observed. *Conclusion:* Hypoglycemia was a rare occurrence in TZD overdoses/exposures, and elevations in transaminases are not seen with acute exposures only. The incidence of transaminase elevation or death in acute on chronic was also rare, occurring in 3, and 5 of 1,943 patients respectively. The high incidence of HCF referrals in pediatric patients less than 6 years old we believe is due to the lack of good data on the incidence of adverse effects for this class of drugs, and the understandable practice of cautious management.

154. Has Increased Availability of Paracetamol had any Effects on Inquiries Received by the National Poisons Information Centre in Norway?

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Objective: Paracetamol poisonings are considered the major acute poisoning problem among pharmaceuticals in Norway (1). In November 2003, a change in legislation allowed certain medicines, including paracetamol, to be sold outside pharmacies in Norway. The aim of this study is to ascertain whether there is an increase in the number and severity of paracetamol poisonings presented to the national Poisons Information Centre (PIC) after 2003. *Methods:* The PIC database was retrospectively searched for the years 2000 to 2006 (November/December 2006 extrapolated). Inquiries received by PIC regarding acute and chronic exposures in general, and acute and chronic exposures to paracetamol in particular, were recorded. The number of paracetamol inquiries in which the exposures were considered potentially severe by PIC were also extracted from this material. *Results:* The mean increase in inquiries to PIC regarding acute and chronic exposures from 2000 to 2006 was 6% (SD = 1.3%) per year. For paracetamol this increase was respectively 5.5% (2001), 13.2% (2002), 7.5% (2003), 30.1% (2004), 7.7% (2005), and approximately 13.2% (2006). Over a three-year period prior to the change in legislation the total increase in inquiries regarding acute and chronic exposures to paracetamol was 28.3%. Over the last three years this increase has been 61.6%. In the period from 2000 to 2003, exposures to paracetamol were considered to be potentially severe in 30% of the inquiries. This number is consistent with the years 1996 to 2001 (1). From 2004 to 2006, 37% of the inquiries regarding paracetamol exposures were considered to be potentially severe. The number of severe paracetamol exposures presented to PIC has nearly doubled from 2003 to 2006. *Conclusion:* In November 2003, paracetamol was made available in non-pharmacy outlets in Norway. In 2004, there was a considerable increase in inquiries to PIC regarding acute and chronic paracetamol exposures, and the number continues to increase. The number of inquiries regarding severe exposures to paracetamol is also increasing. PIC data should always be interpreted cautiously. It is too soon to draw definite conclusions, but these results indicate that easily accessible paracetamol may lead to an increase in the number and severity of paracetamol poisonings. *References:* 1. Bøe GH, Haga C, Andrew E, et al. Paracetamolforgiftninger i Norge 1990–2001. Tidsskr Nor Lægeforen 2004; 124:1624–1628.

155. Do European Guidelines Diminish Poisonings? The Lamp Oil Story

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Objective: In 1997, a European guideline concerning the viscosity and surface tension of coloured and fragranced paraffin was adopted to limit the number and the severity of these intoxications. However, after an initial decrease between 1997 and 2002, the number of requests for information has increased since 2002 at the Dutch National Poisons Information Centre. The question arises whether the guideline is still adequate. We aimed to characterize the current intoxications with lamp oils and to determine whether these intoxications differ in frequency and in severity from the intoxications reported before the guideline was adopted. *Methods:* Data on all cases of possible lamp oil intoxications reported to our poisons centre from April 1, 2005 until December 31, 2005, were collected prospectively. Physicians and patients (or caregivers of the involved child) were interviewed using a standardized enquiry form. Information concerning exposure, symptoms and treatment was obtained. These data were statistically compared to data from a previous study performed in our centre in 1996 (1). *Results:* In 2005, 152 cases were included. The majority of the intoxications consisted of ingestion of 1–2 sips of liquid hydrocarbon paraffin out of an oil lamp by children younger than 5 years of age. In 63% of the cases colored paraffin or a colored oil lamp was involved. The intoxications were compared to 165 paraffin intoxications from the 1996 study. In 1996 and 2005, respectively 77% and 72% of the patients had symptoms subsequent to ingestion. In both years, cough and vomiting were the most frequent symptoms. The number of cases with aspiration, the number of cases diagnosed with pneumonitis and the number of admissions did not differ significantly between both years. X-ray of the thorax was less often performed in 2005 than in 1996. The risk of abnormalities on X-ray did not differ. *Conclusion:* The severity of lamp oil intoxications did not differ between 1996 and 2005. This is disappointing since a guideline was adopted in 1997 to limit the number and the severity of lamp oil intoxications. New actions to check compliance with the current guideline, to improve the packaging and labelling of paraffin and oil lamps, and the education of parents should be considered, to reduce the frequency and severity of these intoxications. *References:* Zoelen GA van, Vries I de, Meulenbelt J. Acute intoxicaties met lampolie in 1996. Rapportnummer 348802015, April 1997, RIVM, Bilthoven.

156. Intoxications in Senior Patients: Review of Data From a Poison Centre and Toxicological Analysis

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Objective: Aging is a common feature in most western European populations. In Germany, 19.25% of the inhabitants are at least 65-years-old with an annual increase of 0.62%. Therefore, poison information centres will be challenged by an increasing number of poisoned elderly patients. However, only a few studies have been published addressing this issue. *Methods:* To elucidate the circumstances of intoxication, substances, and risks emerging from altered kinetics in the aged patient, two different approaches were followed. A) A retrospective study based on inquiries to the Berlin Poison Information Centre was focussed on patients > 60 years (n = 5774) covering the years 2001 to 2005. Data were analyzed for modes of intoxication, frequency of substances and basic treatment advice. They were compared to the results of younger adults (age 15–59 years; n = 45486), serving as control group. B) Results from toxicological analyses in acutely poisoned inpatients > 60 years of age (n = 2604) from years 1996 to 2005 were reviewed for the spectrum of detected substances and individual pharmacokinetics parameters. Data were compared to those from younger in patients (age 15–59 years; n = 14165) and population kinetics to detect potential differences. *Results:* A) In aged patients accidental intoxication occurred more frequently (35.1%) than in control group (28.8%), whereas suicidal exposures were less common (37.1% vs. 44.2%). Errors in administration of medication were twice as likely, and incidence of unwanted drug effects was approximately three times more likely to cause poisoning in senior patients than in the control group. Household products were ingested by aged patients six times more frequently than by younger patients. Approximately 32% of these products contained detergents encompassing the substantial risk of aspiration. Suicidal ingestions of nonbenzodiazepine hypnotics and benzodiazepines were more frequent in aged patients. In contrast, suicidal intoxications with paracetamol or SSRIs were less common than in younger adults. Intoxicated seniors were approximately three times more likely to need inpatient treatment than younger adults. B) Pharmacokinetic analysis revealed prolonged elimination half-life in senior patients which significantly exceeded population kinetics: e.g. doxepin (130%), clozapine (211%), thioridazine (354%) and verapamil (885%). Comparing the half-life between aged individuals substantial variations were observed: e.g., individual half-life of nitrazepam was 48 hrs and 26 hrs, respectively in two senior patients. *Conclusion:* Aged people have a different risk profile in getting intoxicated and were exposed to a different spectrum of substances. In addition, the clinical course and prognosis may be influenced by altered pharmacokinetics. Nevertheless, information about these issues is still incomplete and quite hypothetical. In order to improve prevention and clinical management of elderly intoxicated patients, scientific efforts are required.

157. The Leonardo Da Vinci Programme – Increased Collaboration between Poisons Centres

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Objective: The Leonardo Da Vinci programme is a European Community programme launched to support funding of transnational partnership projects aimed at improving quality, fostering innovation and promoting the European dimension in vocational training. Information about the programme is available at the Da Vinci national websites. Within this programme a bilateral exchange has started with the following countries: Bulgaria, Lithuania, Romania, Slovakia and Sweden. The objective is to create opportunity for further education and promote exchange of experience between poisons centres in Europe. *Methods:* The Swedish Poisons Information Centre (SPIC) has received a grant for nine persons to facilitate visits to these countries. Expenses for administration, travel and accommodation during two weeks each are covered. This project will be running during the period 2006–2008. The initial phase started with a visit by two participants from the Swedish centre to the Toxicology Clinic (TC) in Sofia, Bulgaria. Organization and function of the TC were studied and the poisoning patterns in the two countries were compared. *Results:* Both centres started their activity around 1960. The main organisation of the TC is concentrated on treatment of acute poisoned patients in two treatment wards (adults and children) in contrast to the SPIC where the main responsibility is a 24-hour telephone service to both medical professionals and the general public. 2,617 patients (adults 75%, children 25%) from the Sofia area (1.5 million inhabitants) were treated in the TC during 2005 because of poisonings by pharmaceuticals (45.6%), chemical products (36.6%), pesticides (11.2%), and plants/mushrooms (6.6%). The most common groups of pharmaceuticals were combined preparations (30.1%), benzodiazepines (23.5%), and antidepressants (12.3%). Corresponding data for chemicals were ethanol (59.8%), sodium hydroxide (23.1%) and gases (5.7%). In 2005 the SPIC answered 76,996 inquiries from Sweden (9 million inhabitants) and of these 61,821 were acute poisoning incidents in humans. Chemical products were present in 41%, pharmaceuticals in 39% and plants/mushrooms in 13% of these episodes. The most frequent pharmaceuticals, among patients advised to seek medical attention or treated in hospital, were neuroleptics, sedatives and hypnotics (23.7%), analgesic drugs (19.8%) and psychoanaleptics including antidepressants (12.8%). Corresponding data for chemicals were detergents (24.4%), fuels (12.3%) and gases (10.2%). *Conclusion:* The initial phase of the funding programme Leonardo Da Vinci has taken place. Increased collaboration between poisons centres will enhance the exchange of experience and knowledge and also create a basis for the development of poisons centres.

158. Participation of Poisons Centres in a Pilot Project for Common Data Collection

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Objectives: The EAPCCT has launched a pilot project for common data collection in European Poisons Centres in order to create a proof of principle of the technical feasibility. The aim of the first stage of the project was to determine which Poisons Centres fulfil the necessary minimal requirements for participation. *Methods:* All Poisons Centres on the EAPCCT Poisons Centres directory have been invited to participate in the pilot project. A questionnaire was sent to the Poisons Centres in order to investigate the willingness to contribute to the project, to measure the degree of data compatibility, and the local information technology (IT) requirements. The questionnaire consisted of 40 questions covering the topics of availability of IT support, structure of data regarding patients, exposure, agents, symptoms and outcome. *Results:* Until November 21, 2006, 24 Poison Centre directors from 14 countries from all parts of Europe replied. Four wished not to participate, five would like to participate at a later stage, and 15 were interested to join the project, 14 of these were also willing to develop local software at their own expense. All 15 have an electronic database of cases. Nine have in-house IT support, 10 have an external technician. Most have experience with the xls (n = 20) or the xml data formats (n = 8). All record the sex of the patient as controlled term. Nineteen record the patient's age or date of birth, while 2 record age groups only. Nineteen record date and time of exposure as controlled terms. All record the circumstances of exposure (19 as controlled term), all distinguish at least between accidental, intentional and occupational exposures. 12 have data about confirmation of exposure as controlled term, 5 as free text. Nineteen distinguish single acute exposures from other ways of exposure. 21 record the route of exposure, 20 as controlled term. All Poisons Centres use a classification system for toxic agents, 19 with a hierarchical structure. Eighteen record active ingredients (16 with classification system with hierarchical structure). All record symptoms at the time of the call (16 as controlled terms). Eighteen record symptoms from medical follow-up (8 as controlled terms). Nineteen do a severity grading (14 using the Poisoning Severity Score). Seventeen assess severity at the time of the call, 10 from medical follow-up. Fifteen assess causality. *Conclusion:* A significant number of Poisons Centres from all parts of Europe are ready to contribute data to a common electronic data collection. As most important data fields are in the Poisons Centre's databases as controlled terms, automated data export and upload in a central database seems feasible.

159. New Development of Illegal Use in France of Iboga (*Tabernanthe Iboga*)

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Objective: The aim of this presentation is to alert the European clinical toxicologists about the new development in Southern France of Iboga (*Tabernanthe iboga*) extract use. *Methods:* Several cases of illegal use of iboga have been collected by the "Centre d'Evaluation et Information sur les Pharmacodépendances" system in France. This alert is based on a bibliographical synthesis of pharmaco-toxicology studies about ibogaine and references reporting international use of iboga extracts. *Results:* Iboga (local name: sacred wood, Choka) is a shrub with yellow flowers and orange fruits which grows in the tropical rain forest of equatorial Africa. This plant is traditionally used during shamanic meetings in Gabon. The roots, which are the main part used, contain about ten different kinds of alkaloids including ibogaine which is a psychoactive and hallucinogenic molecule. This substance is a partial agonist (or agonist / antagonist) of 5HT2 serotonin receptors with interactions with dopaminergic and cholinergic systems. In France, iboga is currently used during "discovery seminaries" for personal near-death experiences, but also for its supposed efficacy as an anti-addictive medication especially for fighting heroin dependency. This indication of ibogaine as a miracle medicine is totally illegal in our country. Clinical trials are currently being performed in USA and Netherlands in order to evaluate this activity. Authors emphasize that deaths have been reported during this uncontrolled use (1). *Conclusion:* The French health system proposes to give to ibogaine the status of a stupefying substance as in USA, Belgium and Switzerland in order to avoid or to limit the Internet business concerning iboga (more than 800 Internet site selling this shrub). *Reference:* 1. Maas U, Strubelt S. Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction. Med Hypotheses 2006; 67:960–4.

160. Trends in Poisoning with Drugs of Abuse in Wales (2000–2004)

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Objective: This retrospective study aims to identify trends in poisoning with Drugs of Abuse and methods of information provision in Wales. The spectrum of agents was limited to include; amphetamine, cannabis, cocaine, ecstasy, heroin; ketamine and LSD and were combined for the purposes of this study. *Methods:* Enquiries received by NPIS (Cardiff) concerning poisoning with drugs of abuse in Wales, Welsh hospital admissions and TOXBASE accesses (from Wales) were analysed. *Results:* Enquiries received by NPIS (Cardiff) from Wales regarding Drugs of Abuse were compared to total telephone enquiries for the same period. Enquiries decreased during 2000–2004. In 2000, NPIS (Cardiff) received 480 enquiries directly relating to drugs of abuse. This figure fluctuated annually with 533 calls received in 2001, 497 in 2002, 301 in 2003, and 295 in 2004. The percentage of telephone enquiries directly relating to drugs of abuse remained roughly constant (3.14%). The total number of enquiries received by NPIS (Cardiff) declined annually during the same period in line with the national strategy to promote TOXBASE, an internet database run by the NPIS, as the first source of information for managing poisoned patients. NPIS (Cardiff) received 16,254 calls from Wales in 2000, 15,892 in 2001, 13,261 in 2002, 11,476 in 2003, and 9,674 in 2004, a decrease of 40% between 2000 and 2004. TOXBASE access data demonstrated that TOXBASE hits for drugs of abuse increased from 340 in 2000, 587 in 2001, 1,099 in 2002, 1,514 in 2003, and 2,194 in 2004. Increased TOXBASE access was not limited to drugs of abuse. Total TOXBASE access in 2000 accounted for 6781 logons from Wales and increased annually: 14,048 in 2001, 17,197 in 2002, 18,789 in 2003, and 20,838 in 2004. The proportion of TOXBASE logons for drugs of abuse rose from 5% in 2000 to over 10% in 2004. Hospital admissions data in Wales for drugs of abuse showed admissions totalled 961 in 2000, 1,126 in 2001, 1,280 in 2002, 1,249 in 2003, and 1,329 in 2004. *Conclusion:* Enquiries concerning drugs of abuse are increasing, as are admissions. This retrospective analysis demonstrates the mean percentage of telephone enquiries received by NPIS Cardiff regarding drugs of abuse in Wales remains roughly constant, whereas the proportion of TOXBASE logons for drugs of abuse has doubled. Total telephone enquiries received by NPIS (Cardiff) decreased by 40% during the same period whilst TOXBASE has become an increasingly popular tool in managing the poisoned patient. The national strategy for promoting TOXBASE is working in Wales.

161. Acute Alcohol Intoxications: Analysis of Ethanol and Acetaldehyde Concentrations in Patients with Focus on Low Ethanol Blood Levels

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In recent years alcohol is the most often detected agent (35%) and a tendency to increasing mixed intoxications by alcohol and drugs was demonstrated in our previous studies. Epidemiological studies have established a relationship between excessive alcohol intake and liver disease, although there seems to be a weak relationship between the extent and duration of alcohol intake and severity of liver injury. Acetaldehyde (the first and most toxic poison created by alcohol metabolism) has long been suspected to be a causative agent of alcohol liver disease. *Objective:* The objective of this study was to measure the levels of acetaldehyde in social and chronic drinkers with acute alcohol intoxications with focus on low ethanol concentrations. *Methods:* The study population included 28 acutely poisoned patients with low alcohol levels, admitted to the Clinic of Toxicology: Ten social drinkers; 10 pediatric patients, and eight patients with well-documented histories of chronic alcoholism. In samples collected from the patients the alcohol and acetaldehyde levels in whole blood were measured using headspace gas chromatography. *Results:* The mean acetaldehyde levels (±SD) in the first group of social drinkers with ethanol concentrations 1.0–2.0 g/l were: 3.53 ± 0.77 mg/l. In the blood samples from children (ethanol 1.00–2.00 g/l) the mean acetaldehyde was: 1.83 ± 0.89 mg/l. In the chronic alcoholics higher levels of acetaldehyde were measured: 7.30–12.44 mg/l, the blood ethanol concentrations determined in them were very low: 0.26–1.00 g/l. *Conclusion:* The data obtained demonstrate higher acetaldehyde levels together with low blood ethanol in alcoholic users compared to that in non-alcoholic users also with low ethanol concentrations. This could be used as prognostic evaluation for chronic alcohol abuse. There is substantial evidence that acetaldehyde contributes to the reinforcing effects of ethanol and is therefore involved in alcohol consumption and abuse but further studies are necessary to clarify especially the role of brain acetaldehyde in humans.

162. Poisonings with Street-drugs in the City of Lodz (1993–2002)

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Objective: Substances of abuse have been known in many cultures and geographic zones, and they were used for different reasons, from religious to hedonistic purposes. Poland, a region of Central Europe, has never been an area of religious use of narcotics, but lately the number of drug abusers has been increasing. *Methods:* Our material consists of patients treated for poisonings with street-drugs in the Department of Acute Poisonings, Lodz, Poland during the

period 1993–2002. *Results:* During the analyzed period (10 years) the number of patients treated for street-drugs intoxication has grown 12 times. The type of substance of abuse has also changed. In the early 90s opiates dominated (over 84% all poisonings with street-drugs). In 2002 all groups of drug abuse were noted, from natural or synthetic opiates, amphetamine, cocaine, LSD to *Cannabis sativa* derivatives (THC). We also discovered intoxications with hallucinogenic mushrooms (containing psilocybin or psilocin) and the plant *Datura stramonium* (containing tropine alkaloids). The most common street-drugs used were amphetamine and opiates; THC derivatives were the third. Amphetamine and THC derivatives were the most frequent sources of intoxication in young people 15–20 years of age. Amphetamine and opiate poisonings were the commonest in young males, 21–30 years old. We discovered a fast growing number of youngsters between 15–20 years of age (in 1993–1994 - 7 patients, in 2001–2002 - 135 patients). Suicidal attempts were noted in less than 13% of patients, more than 82% of intoxication cases were the result of overdose in drug-dependent patients, over 5% were accidental and 0.2% criminal poisonings. In this period of time (1993–2002) 4 persons died. *Conclusion:* Drug abuse is a serious problem in Poland, it has expanded in recent years and it is likely to expand further in the years to come. The treatment of drug addicted people needs to be improved and a suitable prevention program should be developed. The drug addicted treatment system should comprise a network of units where patients could be detoxified and would receive psychiatric treatment and a network of rehabilitation units preparing the patients for their new life.

163. Is Caffeine Abuse a Growing Problem? Review of Edinburgh Hospital Admission Data and TOXBASE Enquiries from Scotland between 2000–2005

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Objective: Ingestion of caffeine may cause significant toxicity, including metabolic disturbance, agitation, arrhythmia, seizures and, rarely, death. Its potential for misuse has previously been recognised (1), and a recent report suggests that caffeine abuse is a growing problem among young adults (2). We sought to establish patterns of caffeine ingestion as indicated by hospital admissions and enquiries to TOXBASE for information about caffeine poisoning. *Methods:* Hospital admissions due to ingestion of caffeine-containing products and caffeine-only products were examined retrospectively for the Royal Infirmary of Edinburgh between 2000–2005. TOXBASE is an internet-based resource adopted as the common platform for provision of poisoning management advice throughout the United Kingdom. TOXBASE enquiries from healthcare professionals in Scotland about caffeine were examined during 2000–2005. Data were compared between years using Chi-square proportional tests with Yates' correction. *Results:* 499 patients were admitted to hospital due to ingestion of caffeine-containing products, including 26 who ingested caffeine-only products. Annual data for hospital admissions in Edinburgh and TOXBASE enquiries from Scotland are presented in Table 1. The proportions of hospital admissions in Edinburgh and TOXBASE enquires in Scotland related to caffeine products are small, and have remained constant between 2000–2005. *Conclusions*: These data show that only a small proportion of poisoning cases involve caffeine products. In contrast to data reported elsewhere, the present data from Scotland do not suggest any change in patterns of caffeine misuse. *References:* 1. MacFadyen L, Eadie D, McGowan T. Community pharmacists' experience of over-the-counter medicine misuse in Scotland. J R Soc Health 2001; 121:185–92. 2. McCarthy D, Mycyk MB, DesLauriers C. Hospitalization for caffeine abuse is associated with concomitant abuse of other pharmaceutical products. Ann Emerg Med 2006; 48(Supplement 1):S101.

Table 1. Admissions to the Royal Infirmary of Edinburgh and TOXBASE enquiries from Scotland related to ingestion of caffeine-containing products and caffeine-only products between 2000–2005, expressed as the absolute number and, in parentheses, the proportion of all toxicology admissions and enquiries from Scotland, respectively

	Caffeine-containing products	Caffeine-only products
Hospital admissions		
2000 (n = 2735)	86 (3.1%)	1 (0.0%)
2001 (n = 2782)	101 (3.6%)	9 (0.3%)
2002 (n = 2752)	98 (3.6%)	3 (0.1%)
2003 (n = 2455)	69 (2.8%)	5 (0.2%)
2004 (n = 2108)	80 (3.8%)	3 (0.1%)
2005 (n = 1864)	65 (3.5%)	5 (0.3%)
Total (n = 14696)	**499 (3.4%)**	**26 (0.2%)**
TOXBASE enquiries		
2000 (n = 27654)	437 (1.6%)	48 (0.2%)
2001 (n = 36003)	555 (1.5%)	73 (0.2%)
2002 (n = 44240)	716 (1.6%)	68 (0.2%)
2003 (n = 65280)	1135 (1.7%)	140 (0.2%)
2004 (n = 65817)	1200 (1.8%)	169 (0.3%)
2005 (n = 72086)	1175 (1.6%)	197 (0.3%)
Total (n = 311080)	**5218 (1.7%)**	**498 (0.2%)**

164. High Mortality Rates among GHB Abusers in Western Sweden

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Background: Acute poisoning with GHB has been an increasing medical problem during the last decade in Sweden. GHB is a drug of abuse that causes euphoria, anxiolysis and hypnosis. *Objectives:* The aim of this study was to document all in-hospital cases of GHB poisonings during 1995–2004. It was also our aim to record deaths due to GHB abuse during one year to be able to compare the toxicity of GHB with other illicit drugs such as heroin and amphetamine. *Methods:* The number of GHB-poisoned patients treated at the Sahlgrenska University Hospital in Gothenburg (Sahlgrenska University Hospital/Sahlgrenska) and the near-by hospital in the city of Mölndal (Sahlgrenska University Hospital/Mölndal) has been recorded with the help of an in-house database. Gender and age could not be recorded at this stage, just statistics. Police seizures of the drugs GHB, 1,4-butanediol and GBL were registered between 1996 and 2004 by the National Criminal Investigation Department (Rikskriminalen, Stockholm, Sweden) who reported the numbers to the National Institute of Public Health (Folkhälsoinstitutet, Stockholm, Sweden). Number of deaths by illicit drugs during 2004 was recorded by Department of Forensic Medicine, Gothenburg, Sweden. *Results:* The number of poisoned patients admitted to Sahlgrenska University Hospital in Gothenburg during 1995–2004 was 259. The number of seizures by the police in Sweden of GHB was 743, GBL 343 and 1,4-butanediol 236 respectively during the same period. In 2004, the total number of deaths of the western part of Sweden due to poisonings or drug abuse with a positive drug screening was 6 with heroin, 7 with GHB, 32 with amphetamine, 6 with cocaine and one with methadone. One patient with GHB poisoning died after admission to hospital. *Conclusions*: Intoxication by GHB carries substantial morbidity and abuse of GHB carries substantial mortality. There is no indication that one can learn how to deal with this drug safely, even experienced users overdose and die. If the poisoned patient reaches the hospital alive, the acute prognosis is good. The long-term prognosis is insecure with an increased risk for drug dependency and an early death.

165. Lipid Peroxidation in Poisoning - Basic Mechanisms and Clinical Effects

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Objective: To provide an overview of oxidant stress and lipid peroxidation and their role in human physiology and pathophysiology, including poisonings. *Methods and Results:* Increasing attention has focused on free radicals derived from molecular oxygen in a wide variety of pathophysiological processes, including poisonings. Nonetheless, much remains to be understood about their role in normal human physiology and in diseases. Oxidation of lipids (lipid peroxidation) is a major sequela of oxidant stress resulting from free radical-mediated damage to cells and tissues. This lecture will initially discuss basic mechanisms of oxidant stress and lipid peroxidation with a focus on the pathophysiological aspects of these processes and relate what goes on at the molecular level to understanding the role of lipid peroxidation in human poisonings. A major hindrance in the ability to assess the role of lipid peroxidation in human disorders is based on the fact that, until recently, accurate measurements of oxidant stress in vivo were generally not available. A number of methods exist to assess lipid peroxidation as an index of oxidative stress either by measuring loss of fatty acid substrate or by quantifying lipid peroxidation products. No assay is ideal, however, particularly when applied to quantification of lipid peroxidation in complex biological fluids. Assays to quantify lipid peroxidation that will be discussed include 1) fatty acid analysis, 2) conjugated dienes, 3) measurement of lipid hydroperoxides, 4) thiobarbituric acid reacting substances, 5) alkane quantification, and 6) F2-isoprostanes. The relative advantages and disadvantages of each method will be detailed. The F2-isoprostanes are a series of prostaglandin-like products derived from the free radical catalyzed peroxidation of arachidonic acid. Quantification of these compounds to assess lipid peroxidation in vivo is superior to other methods currently available. Thus, portion of this talk will focus on human and animal studies in which isoprostanes have been utilized to assess oxidative stress in vivo. An additional focus of this discussion will be the role of isoprostanes not only as markers of oxidative injury in association with poisonings but also as bioactive mediators of the pathophysiological sequelae of enhanced oxidant stress. Mechanisms by which these compounds exert their bioactivity will also be reviewed. *Conclusion:* The goal of this lecture will be to provide the practicing toxicologist with a basic understanding of lipid peroxidation and its role in normal human physiology and in disease states.

166. Progression of Electrophysiological Abnormalities in Acute Organophosphate Poisoning and the Intermediate Syndrome

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Background: We previously observed that IMS is a spectrum disorder with 4 main patterns of electrophysiological abnormalities; 1) decrement-Increment (DI), 2) combined decrement-Increment and Decrement (Combined DI-D), 3) severe decrement, and 4) progressive decrement (1). All four patterns indicate varying degrees of neuromuscular transmission failure (2) which correlates well with the severity of the intermediate syndrome type muscle weakness. *Objective:* To assess the time course of the progression of electrophysiological abnormalities associated with Intermediate syndrome (IMS) in acute OPP. *Methods:* A prospective case series of 78 consenting symptomatic patients with acute OPP were assessed. Repeated physical examinations with neurological assessments were done. Repetitive Nerve Stimulation (RNS) studies were done on R/ L Median and Ulnar nerves at 1, 3, 10, 15, 20, and 30Hz. *Results:* Serial electrophysiological studies were done in 78 patients. In the first 13 patients serial RNS studies were done at 1, 3, and 10Hz at 24 hourly intervals. Subsequently serial RNS studies were done at 1, 3, 10, 15, 20, and 30HZ stimulations. 3.1% developed Decrement-Increments only at 30HZ. 19.2% developed Decrement-Increments from 10 to 30HZ. 9.0% developed Decrement-Increments from 1–30HZ. 54.8% of patients, who developed Decrement-Increment, recovered to normal patterns within 24 – 48 hours. 45.2% of patients with Decrement-increment progressed to a combined decrement increment and decrement pattern at high and intermediate frequency stimulations. Of these patients 36.8% displayed Severe Decrement at high frequency stimulations. 57% patients with Severe Decrements developed late respiratory failure requiring ventilatory support. Time course of electrophysiological abnormalities at 10Hz level. (see Figure 1) *Discussion:* These results demonstrate the time course of the development of electrophysiological abnormalities in acute organophosphate poisoning. Neuromuscular transmission failure starts mostly within the first 24–48 hrs

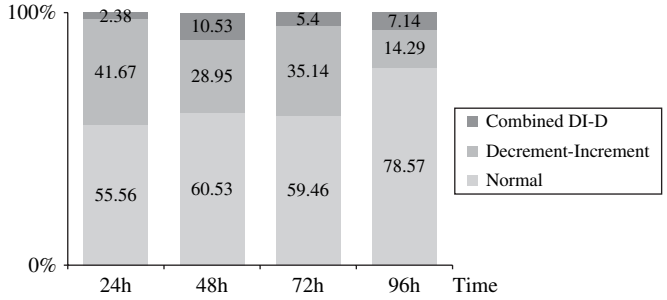

Fig. 1. Time course of electrophysiological abnormalities at 10 Hz.

of poisoning and due to unrecognized reasons a sub-group of patients get progressive transmission failure leading to complete failure at high frequency stimulations and clinical counterpart of this is IMS. Thus IMS may be due to progressive and continuous changes at the Neuromuscular Junction. Severe Decremental pattern may be a useful indicator in identifying the patients who are at risk of developing late respiratory failure. *Conclusion:* Time course of abnormalities clearly demonstrate that IMS is a spectrum disorder with the most severe cases progressing sequentially through the complete spectrum of the RNS findings. *References:* 1. Jayawardane P, et al. Serial neurophysiological studies in 70 patients with organophosphate poisoning: Early prediction of intermediate syndrome. Clinical Toxicology 2006; 44:729 2. Besser R, et al. End-plate dysfunction in acute organophosphate intoxication. Neurology 1989; 39 561–567.

167. Repetition of Acute Poisonings in Oslo - A One Year Prospective Study

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Objective: Repetition of acute poisoning is a well-known phenomenon, especially regarding deliberate self-poisonings. Few studies have focused on these patients, who may be treated in different hospitals or in different levels of the health care system when repeating. Prospective, multi-center and multi-disciplinary studies are therefore necessary to reveal all episodes. Our aims were to study the rate of multiple acute poisonings during one year in Oslo, related to place of treatment, age, gender, intention, psychiatric treatment, and drug abuse. *Methods:* One-year prospective cross-sectional multi-center study including all patients ≥16 years with a main diagnosis of acute poisoning, irrespective of intention, treated by Oslo Ambulance Service, Oslo Emergency Ward (outpatient clinic) or in one of the four hospital emergency departments in Oslo. *Results:* There were a total of 3,775 contacts during one year (947 in hospitals, 958 in the outpatient clinic and 1,870 in the ambulance service). These resulted from 3,025 poisoning episodes by 2,298 persons. 378 (16.4%) patients had more than one episode, 153 (6.7%) had three or more episodes, while the highest number of episodes in one subject was 24. Regarding the first registered episode, there were no differences in the frequencies of later poisonings between patients treated in hospital (17%), outpatient clinic (17%) or ambulance service (16%) as the highest level of care. From Kaplan-Meier calculation, the cumulative proportion of patients without repeated poisoning was 0.74 (95%CI 0.72–0.75), indicating that about ¼ of patients treated for acute poisoning repeat poisoned themselves during the first year. To analyze subgroups for all patients, Cox regression analyzes revealed no differences between genders. Patients aged 20 to 60 years had more repetitions compared to 16 to 20 years, with a peak between 40–50 years, hazard ratio 4.3 (95%CI 2.1–8.4). Patients with pain-unresponsive coma had a hazard ratio for repetition of 1.5 (95%CI 1.1–2.1) compared to conscious patients. Among the hospitalized, Cox regression revealed no differences regarding intention (accidental, suicidal, drug abuse). Daily drug or alcohol abuse had hazard ratio 1.6 (95%CI 1.0–2.4), and known ongoing or previous psychiatric treatment had hazard ratio 3.3 (95%CI 1.8–6.0) compared to no such treatment. *Conclusion:* Multiple poisonings were common, and ¼ of the poisoned patients were estimated to repeat during the first year. Middle-age, deep coma, daily drug-abuse and previous or ongoing psychiatric treatment were markers for the highest risk of repetition. Gender and the physicians' evaluation of the intention of poisoning had no significant impact on repetition.

168. Clinical, Paraclinical, and Electocardiographic Changes of Spider Bite in North East Iran, 2005–2006

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Background: Envenomations involving spider (*L. Treducimgutatus*) bite are relatively common in North East Iran (1,2). The frequency of spider bites varies widely from year to year (3). Envenomation induces local and generalized pain, malaise, chills, sweating, nausea, abdominal pain, confusion, and palpitations (4). However, the pattern and frequency of spider bite-induced clinical, laboratory and electrocardiographic changes have never been studied concurrently. *Methods:* All cases admitted with suspected spider bites between September 20, 2005 and September 20, 2006 were studied prospectively. The patients with known previous cardiac problems were excluded. *Results:* Spider bites accounted for 51 cases (0.5% of all cases). Mean (SD) age was 31.7 (14.9) years. A male predominance (74.4%) was found. Among them 66% were married. On admission, mean systolic and diastolic blood pressures were 126 (21) and 77 (12) mmHg, respectively. Heart rate was 83 (16) bpm, and temperature was in normal range. Mean WBC was 10.9 (3.3) × 10^3, RBC 5.1 (0.5) × 10^6, pH 7.36 (0.04), HCO_3 19.5 (4.0), PCO_2 36.7 (9.1), PO_2 95.2 (13.3), oxygen saturation 97.0 (2.1), creatinine 10.5 (1.8) mg/L, sodium 136 (26), mEq/L, and potassium was 4.2 (0.8) mEq/L. Creatinine phosphokinase was measured for 8 cases and in these had a mean of 721 (835) U/L. The most common signs and symptoms on admission were pain (90%) which was categorized subjectively as moderate to severe in 95%. Patients also complained of pain in their back (43%), stomach (35%), lower limbs (33%), upper limbs (16%), and chest (13%). Sweating (52%), chills (29%), dyspnea (23%), flashing (14%), spasm (12%), headache (12%), nausea (12%), and vertigo (12%) were also recorded. ECG findings included heart rate 87 (26) bpm, QT 0.43 (0.1), QTc 0.38 (0.09) s. ST segments were depressed in 25% of cases in at least two of the pre-cordial leads. None of the cases received specific antitoxin (unfortunately not available in Iran), and all of them were treated conservatively and symptomatically. No deaths were recorded. *Conclusions:* Spider (*L. Treducimgutatus*) bite is relatively common in North East Iran. The spider bite patients presented with a variety of symptoms, which are rates by them as severe, and a high rate of ECG changes. ECG monitoring should be considered in the routine conservative treatment of bites with this spider, particularly if specific antitoxin is not available. *References:* 1. Afshari R, Majdzadeh R, Balali-Mood M. Pattern of acute poisoning in Mashhad, Iran 1993–2000. J Toxicol Clin Toxicol 2004; 42:965–75. 2. Afshari, R. Descriptive epidemiology of intoxication in Mashhad, Iran. 56111. 2001. Tehran University of Medical Sciences (M.P.H. Thesis). 3. Afshari R, Balali-Mood M. Spider bite in North East Iran (2006) proceeding of Asian Pacific association of medical toxicologists, 5th International Congress (APAMT-V), 47:77. 4. Afshari, R. Poisonous spiders and spider bite in north east of Iran. 3352. 1995. Mashhad University of Medical Sciences (M.D Thesis).

169. Study of the Relationship between Seizures and Rhabdomyolysis after Venlafaxine Overdose

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Objective: Venlafaxine ingestion is associated with an increased risk of seizures and rhabdomyolysis. We wished to establish whether acute muscle injury might be a direct effect of venlafaxine or a co-incidental finding in the presence of seizures. *Methods:* Retrospective casenote review of patients admitted to the Royal Infirmary of Edinburgh due to venlafaxine overdose between January 2000 and June 2006. Data are presented as median (95% confidence interval, CI) and compared using Mann-Whitney tests and Yates' corrected Chi-square proportional tests. Correlations were sought using Spearman's coefficient of rank correlation (rho) and 95% CI for rho. *Results:* There were 235 patients with venlafaxine overdose (72.3% women) aged 34 y (33–36 y). Seizures occurred in 8.9%. Abnormally high creatine kinase (CK) values were more prevalent in those with seizures (61.1% versus 25.7%, respectively, p = 0.004). Prevalence of high CK enzymes increased in a time-dependent manner (Table 1). The stated quantity of ingested venlafaxine was positively correlated with CK in the whole group (rho = 0.201, 95% CI 0.045–0.347), and in patients without seizures (rho = 0.174, 95% CI 0.009–0.331). *Conclusions:* Venlafaxine overdose is associated with a high prevalence of acute myopathy in patients who develop seizures and also in those who do not. These data suggest that venlafaxine overdose is associated with muscle injury, independent of seizures. The dose and time-dependent relationships support a causal link between venlafaxine and rhabdomyolysis.

Table 1.

Interval	n	CK	CK > 150 U/L	CK > 1000 U/L
0–4.0	43	101 (73–114)	7 (16.3%)	0 (-)
4.1–8.0	58	80 (66–97)	10 (17.2%)	0 (-)
8.1–12.0	28	121 (76–185)	11 (39.3%)	3 (10.7%)
12.1–24.0	59	169 (122–278)*	32 (54.2%)†	7 (11.9%)
>24.0	33	393 (119–922)**	20 (60.6%)†	10 (30.3%)†

*p < 0.005, **p = 0.001 by Mann Whitney tests, and † p < 0.001 by Yates' corrected Chi square proportional tests compared to 0–4 h group.

170. Experimental Study in Rat of the Variability of the Methadone-induced Respiratory Effects Using a Pharmacokinetic/Pharmacodynamic (PK/PD) Approach

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Objective: Methadone may be responsible for intoxications resulting in acute respiratory failure and deaths. Circumstances of poisonings are multiple, including methadone overdoses, psychotropic drug co-ingestion (like benzodiazepines), metabolic induction or inhibition as well as inter-individual genetic variability. Thus, to better characterize the variability of methadone respiratory effects, we studied in rat the pharmacokinetic/pharmacodynamic (PK/PD) relationships between the ventilation depression and the concentrations of both methadone enantiomers, in various conditions of methadone administration. *Methods:* Analysis in Sprague-Dawley rat of the level of sedation and the respiratory effects by the measurement of the respiratory rate (RR), the arterial blood gases (N = 8 rats /group), and the plethysmographic patterns (N = 6 rats / group); determination of the area under the curve (AUC) for each parameter; measurement of plasma methadone and its enantiomer concentrations using HPLC-mass spectrometry (limit of quantification: 1 ng/ml); modelling of the PK/PD relationships. *Results:* We first determined the kinetic parameters of intraperitoneal 1.5 mg/kg methadone: elimination half-life 140 min, clearance 23 ml/min/kg, and distribution volume 5,100 ml/kg for both enantiomers. Methadone (1.5, 5 and 15 mg/kg) induced a rapid but transient onset of marked respiratory depression, associating significant decrease in respiratory rate (p = 0.05), decrease in PaO_2 (p = 0.0009), increase in $PaCO_2$ (p = 0.025), and decrease in pH (p = 0.02). The plethysmographic study

showed that the respiratory depression is due to an increase in the inspiratory and the expiratory time while the tidal volume remained constant. Pre-treatment of animals with sub-cutaneous diazepam (20 mg/kg) induced a significant increase in $PaCO_2$ ($p = 0.05$) in comparison to controls receiving 5 mg/kg methadone. This pre-treatment resulted in a significant increase in R-methadone concentrations (AUC determination, $p = 0.05$). Cytochrome P450 3A-induction using dexamethasone resulted in a significant decrease in methadone effects on PaO_2 ($p = 0.005$), with a significant delay in plasma methadone peak concentration. *Conclusion:* In rats, the PK characteristics of both methadone enantiomers are equivalent at 1.5 mg/kg methadone. Methadone is responsible for a significant dose-dependent respiratory depression. There is a significant increase in methadone-related respiratory effects following diazepam pre-treatment and a significant decrease following dexamethasone pre-treatment. A PK mechanism for these interactions is hypothesized.

171. Retrospective Clinical Study of an Epidemic of Serious Intoxications caused by Two New Household Products

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Objective: Nanotechnology focuses on the design, synthesis and application of materials on the nanoscale. Information on toxicology of these products is very limited. In March 2006, a supermarket chain in Germany introduced two new sealing sprays based on nanotechnology. The launch of these products started an epidemic of serious intoxications. The German Poisons Centres Toxicovigilance Network reacted fast, so that one day after introduction the sprays were taken off the market. Nevertheless, more than 120 people were affected and one third of them had to be treated in hospitals. To date the exact composition of these products is still unknown. The only specification on the safety data sheet reads: "contains ethanol". Further investigations revealed the products to contain ethanol as solvent, dimethyl ether as propellant gas, reactive silanes and unknown anticorrosive agents. *Methods:* In this retrospective multicentre study we interviewed 91 affected persons. The assessment consisted of demographic data, symptoms, their onset, duration, severity and treatment. *Results:* 77% of the affected persons were female. Major symptoms were dyspnea (92%), coughing (91%), nausea (71%), shivering attacks (60%) and fever (48%). In 50% of the patients onset of the symptoms was within 30 minutes, in 20% they started with a delay of 2 hours or more. The duration of symptoms was up to 3 days in 50%, whereas 20% suffered for more than 2 weeks. Pulmonary symptoms were of the longest duration, while nausea and fever disappeared quicker. More than 30% of the patients were treated in hospitals, the longest in-patient treatment was 5 days. Two patients had to be artificially ventilated. *Conclusion:* New consumer products often raise hopes for an easier household routine. These two sealing sprays promised to develop an extra smooth surface by nanofilm formation so that dirt would not stick anymore. Nevertheless all new products have the risk of poisoning consumers. Here we describe an epidemic of intoxications caused by novel sealing sprays. Since more than three companies were involved in the production process there is no conclusive safety data available to date. So the etiology of these intoxications remains unclear. In this retrospective study we evaluated 91 clinical cases, characterised the typical set of symptoms and described their time course.

172. Genomic, Proteomic, and MRI Investigation of Kidney Injury: Novel Approaches for the Evaluation of Organ Injury

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Objective: The kidney is one of the organs most commonly injured by drug toxicity. However, progress in the understanding of the disease pathophysiology and the management of patients has been limited by a lack of sensitive and specific biomarkers for acute kidney disease (AKD). With advances in genomics, proteomics and imaging come opportunities for the discovery of new biomarkers that can define subtypes of AKD, detect early disease and track the response to novel therapies. *Methods:* Three platforms have produced significant insights into the pathophysiology of AKD: gene microarray analysis, difference in-gel electrophoresis (DIGE) and dendrimer-contrast magnetic resonance imaging (MRI). These techniques have been applied to rodent models of toxic, ischaemic and septic AKD. *Results*: Microarray technology can determine the expression profiles of thousands of genes simultaneously and has been used to demonstrate a distinct gene expression profile for toxic AKD compared with ischaemic AKD (1). The application of microarray technology to biomarker discovery resulted in the discovery of lipocalin, a new urinary biomarker for AKD (2). Lipocalin can detect kidney injury, in rodents and humans, before serum creatinine is elevated (3,4). Whereas gene microarrays describe changes at the level of mRNA, proteomics offers the chance to analyze changes in multiple proteins with disease. Using DIGE we have defined changes in the urinary proteome with AKD induced by toxic and septic insults (5). This approach has produced new drug targets and new biomarkers. MRI is well suited to the study of AKD *in vivo* as it can provide high quality imaging of kidney tissue in multiple planes with rapid acquisition times. Using a new intravenous macromolecular contrast agent (dendrimer-contrast MRI) we can detect early AKD, define different patterns of AKD with toxic and septic insults and track the response to a novel therapeutic agent (6). *Conclusion:* The application of these platforms to toxicology promises to increase the understanding and reduce the morbidity of toxin-induced AKD. *References:* 1. Yuen PS, Jo SK, Holly MK, et al. Ischemic and nephrotoxic acute renal failure are distinguished by their broad transcriptomic responses. Physiol Genomics 2006; 16:375–386. 2. Mishra J, Ma Q, Prada A, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14:2534–2543. 3. Mishra J, Mori K, Ma Q, et al. Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol 2004; 24:307–315. 4. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005; 365:1231–1238. 5. Holly MK, Dear J, Hu X, et al. Biomarker and drug target discovery using proteomics in a new rat model of sepsis-induced acute renal failure. Kidney International 2006; 70:496–506. 6. Dear J, Kobayashi H, Jo SK, et al. Dendrimer-enhanced MRI as a diagnostic and prognostic biomarker of sepsis and sepsis-induced acute renal failure. Kidney International 2005; 67: 2159–2167.

173. Isolation and Characterization of Novel Neurotoxins from the Venom of the Australian Copperhead Snake (*Austrelaps superbus*)

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Background: A. superbus is an Australian elapid snake that may induce significant paralysis in cases of clinical envenomation. However, human cases of envenoming have been infrequently reported and it is unknown whether the venom exerts primarily pre- or postsynaptic neurotoxic effects. Additionally, it is unknown whether direct myotoxicity is also a significant feature of the venom's toxicity. *Objectives:* To isolate and pharmacologically characterize novel neurotoxins and myotoxins from the venom of *A. superbus*. *Methods:* Whole *A. superbus* venom was separated into protein fractions utilizing size exclusion liquid chromatography (LC), anion exchange LC and C2-C18 reverse-phase LC. Purity and mass of isolated proteins was assessed by MALDI-mass spectrometry. At each separation phase, fractions were tested for the presence of neurotoxicity utilizing the indirectly stimulated chick biventer cervicis nerve-muscle preparation (CBCNMP). Pre- or post-synaptic neurotoxicity and myotoxicity were determined. N-terminal protein sequences of isolated toxins were determined by Edman degradation and compared to existing neurotoxins using a Blastp search of the Swiss-Prot/trEMBL database. *Results:* Three novel neurotoxins were isolated from whole *A. superbus* venom. Firstly, α-australexin showed a typical post-synaptic neurotoxic response on the CBCNMP. Neurotoxicity was prevented when the toxin was pre-incubated with Australian monovalent tiger snake antivenom (TSAV) and could be partially reversed by TSAV once neurotoxicity was established. α-Australexin (6645 Da) displayed significant sequence homology with other Australian elapid postsynaptic neurotoxins. Secondly, two monomeric pre-synaptic neurotoxins were also isolated: AS Toxin 1 (13249 Da) and AS Toxin-2 (13197 Da). Both showed typical triphasic presynaptic neurotoxic effects on the CBCNMP. These were inhibited by pre-incubation of the toxins with TSAV but, typical of other elapid presynaptic neurotoxins, the effects of established neurotoxicity could not be reversed by TSAV. Both toxins showed significant sequence homology with the phospholipase-A2 anticoagulant toxin superbin-b, also found in *A. superbus* venom, and other Australian elapid pre-synaptic neurotoxins. Myotoxicity was not evident in any of the venom fractions. *Conclusions:* This is the first report describing the diversity of neurotoxins in the venom of the Australian copperhead snake and adds evidence to the clinical observations that TSAV prevents the onset of neurotoxicity if administered prior to the onset of neurotoxic symptoms. This may lead to a better understanding of the course of clinical envenoming by this species.

174. Cardiac Toxicity of High-Dose Cyclophosphamide in Patients with Multiple Myeloma

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Objective: High-dose cyclophosphamide is a well-known and widely used stem cell mobilisation regimen in patients with multiple myeloma undergoing autologous haematopoietic stem cell transplantation. Highly differing rates of cardiac complications associated with high-dose cyclophosphamide have been reported. To date there has been no systematic clinical study dealing with high-dose cyclophosphamide mobilisation regimen in multiple myeloma patients and evaluating its cardiotoxicity. *Methods:* A total of 23 consecutive patients with multiple myeloma without signs of cardiac disease were given high-dose cyclophosphamide 4 g/m^2 as part of the stem cell mobilisation regimen. The patients were followed for 15 days by serial measurements of cardiotoxicity biomarkers troponin I (TnI), brain natriuretic peptide (BNP) and endothelin-1 (ET-1). Systolic and diastolic left ventricular function was assessed by complete echocardiography prior to, and 6 to 8 weeks after the therapy. *Results:* The group of patients younger than 55 years showed significant differences between basal TnI levels and TnI determined at 15 days after high-dose cyclophosphamide treatment ($p = 0.028$). Significant differences between basal BNP concentrations and BNP levels measured at eight hours after high-dose cyclophosphamide treatment were found in the whole group of patients, as well as in the subgroup of <55-year-old patients and subgroup of >55-year-old patients ($p < 0.0001$; $p<0.001$; $p = 0.001$ respectively). The whole group and the >55-year-old subgroup showed significant differences between basal BNP and BNP determined at 15 days after high-dose cyclophosphamide infusion ($p = 0.004$), as well as between ET-1 measured at baseline and ET-1 determined at eight hours after high-dose cyclophosphamide ($p = 0.004$; $p = 0.018$). Echocardiographic parameters revealed a barely significant decrease in cardiac output after high-dose cyclophosphamide compared to the pre-treatment values ($p = 0.06$), which accords with the increase in echocardiographically detected mild functional mitral regurgitation ($p = 0.025$). TnI levels at 15 days after the completion of treatment correlated with left ventricular diastolic dysfunction indicated by the s/d index ($r = 0.61$; $p = 0.04$). *Conclusion:* Significant neurohumoral activation of heart failure occurring after high-dose cyclophosphamide treatment is manifested by an increase in BNP and ET-1 levels, yet without concomitant cardiomyocyte necrosis. BNP and to a lesser extent ET-1 levels are much more sensitive indicators of myocardial injury than functional tests, such as echocardiography, while diastolic functional parameters are more sensitive predictors of early cyclophosphamide-induced cardiotoxicity. Mild functional mitral regurgitation may develop in patients given high-dose cyclophosphamide therapy.

175. New Drugs of Abuse

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Introduction: In recent years, some trends in drug use have emerged. Besides new agents there are also new ways in which traditional substances are used nowadays. Some problematic trends, based on extent of use and health risk, will be addressed here. Poisons Information Centres (PICs) can contribute to early recognition of trends, by detailed questioning and recording of drug related calls. *New Synthetic Amphetamines:* Quite regularly new amphetamine derivatives are found in drug monitoring programmes. The symptoms and possible complications of overdose with amphetamine derivatives are well documented. It is hard to distinguish between the different derivatives, based on clinical signs in the intoxicated patients. Usually the only information available upon hospitalisation is that the patient has taken some kind of drug of

abuse. Consequently, in calls to PICs, these substances are rarely identified. In 2005 the new drug methylone (methylenedioxy-methcathinone) was sold as a vanilla-scented "room odorizer" in a Dutch smartshop. Methylone is technically a cathinone derivative, the only difference from MDMA in the chemical structure is the substitution of two hydrogen atoms by one oxygen group. Methylone is a new substance on the drug market and clinical effects are not well documented. Symptoms after overdose are expected to be similar to those of MDMA. As methylone is sold in liquid form, it is easier for PICs to identify methylone related calls. Besides overdosing, adulteration with GHB (also a liquid, sold in tubes or small bottles), can be a cause of unexpected effects and anxiety, for which some users might seek medical attention. mCPP (meta-chlorophenylpiperazine) has been mixed with MDMA and sold as "XTC" pills. A drug monitoring project in The Netherlands showed that in the first half of 2006 8.6% of tablets sold as XTC contained mCPP as well. mCPP is a piperazine derivative and a serotonin agonist. Its effect is supposedly slightly more hallucinogenic and less stimulant than that of the amphetamines. In overdose, similar symptoms are to be expected as well as a higher risk for serotonin syndrome. *Stronger Opiates:* An emerging problem for opiate abusers, are highly concentrated forms of heroin on the market due to good harvests in producing countries, like the 2006 harvest in Afghanistan. Even experienced users can overdose if opiate concentrations are (much) higher than expected. A similar overdosing problem can occur when more powerful opiates are mixed in, to improve poor quality products. An example is fentanyl, which is up to 100 times more pharmacologically active than morphine. Last year there was an incident in The Netherlands, with fentanyl (250 mcg) being sold on papertrips (small, stamp-like pieces of paper, blotted usually with LSD). *Ketamine:* is a prescription drug and has been used as a (veterinary) anaesthetic since the 1960s. In recent years it is used mainly by psychonauts (relatively small group of drug users who like to experiment with hallucinogenic drugs in order to gain deeper insights and spiritual experiences). Sometimes ketamine or "K" is sold in party settings. Especially inexperienced users or users who expect to be taking a different drug (appearance is similar to cocaine), who do not expect the effects caused by ketamine, can panic and end up in a clinical setting. *Viagra-analogues:* In the last five years, the illegal Viagra-analogues trade has boomed worldwide. Mostly tablets that resemble the prescription drug closely are sold in the party scene and via the internet. These tablets sometimes indeed contain the real drug (sildenafil in Viagra look-alikes, tadalafil in Cialis look-alikes), but they can contain all sorts of different substances as well. In a Dutch analytical study of 400 illegal Viagra-analogues, more than 10 active pharmaceutical ingredients other than sildenafil-analogues were identified. Even when the pharmacological effects resemble those of sildenafil, there are some health risks mainly for users with underlying cardiovascular disease. Taking into account the erotic setting in which these products are used, simultaneous use with poppers (alkylnitrites) can occur. This combination causes an increased risk of cardiovascular insufficiency. Stackers are used as energizers, weight-loss aids and stamina enhancers. Since the ephedrine containing Ephedra species were prohibited in The Netherlands in 2004, other herbs that contain similar pharmacologically active compounds (like synephrine) are used in the stackers. Most stackers contain substantial amounts of caffeine as well. These products are quite popular amongst truck drivers, fanatic sportsmen and in the party scene. Healthy users that stick to reasonable doses are not expected to develop serious health problems when using stackers. However, people with underlying cardiovascular disease are at higher risk of developing cardiac arrest or intracranial haemorrhage. *High-dose Cannabis:* In the last ten years, especially in the Dutch marihuana, THC (tetrahydrocannabinol) concentrations have substantially risen. In the beginning of the nineties average THC content in Dutch coffeeshop weed ("Nederwiet") was around 10%, in the last years concentrations up to 30% are registered in a Dutch monitoring project. Recently a volunteer study was performed by the Dutch PIC, on the effects of these highly concentrated cannabis products. Cannabis with 0%, 10%, 16% and 23% THC concentration was used to prepare joints that were smoked by the volunteers. On group level, the study showed an increase in serum THC concentrations as well as an increase in adverse effects as tachycardia, hypotension and drowsiness. Performance tests were less adequate with higher mean reaction time and more mistakes. *Recommendations:* Information on drugs of abuse collected by PICs can be shared through participation in drug monitoring projects together with institutions for treatment of drug addiction and projects for on-site drugs testing. The Dutch PIC also takes part in the Coordinating and Monitoring Agency for new drugs of abuse, under the joint responsibility of all the Ministries involved with drug-related issues. Participation in deliberative bodies like these, directly used for policymaking, guarantees a rapid and adequate response to the appearance of new substances of abuse.

176. Piperazine-Based Party Drugs: Case Series of 73 Poisonings

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Objective: Piperazine-based party drugs (PBPDs), including benzylpiperazine (BZP), are marketed as "safe" alternatives to MDMA or amphetamine. They increase monoamine availability (1), and due to increasing concern regarding their potential toxicity, are banned in the USA, Australia and Europe, but remain unrestricted in New Zealand and the United Kingdom. The aim of the present study was to describe toxicity following PBPD poisoning in New Zealand. *Case Series:* Seventy-three reports of PBPD poisoning were received from emergency departments. Ethanol was co-ingested in 63% of cases. Most patients (58%) were under 21 years, and 12% were under 18 years. Symptoms reported were tachycardia (73%), hypertension (70%), vomiting (42%), palpitations (39%), agitation (23%), anxiety (19%), dizziness (15%), mydriasis (15%), seizure (15%), elevated temperature (14%), collapse (11%), tremor (11%), extrapyramidal symptoms (EPS; dystonia, akathisia) (10%), headache (10%), confusion (8%), hyperventilation (8%), insomnia (8%), dry mouth (7%), sweating (7%), CNS depression (5%), dehydration (5%), blurred vision (4%), hallucinations (4%), paraesthesiae (4%), and shortness of breath (4%). There were no fatalities. Using the EAPCCT/IPCS Poisoning Severity Scale (2), 32% of patients had mild, 64% moderate, and 4% severe toxicity. Poisoning requiring admission occurred in 4 cases, all females, and was due to repeated seizure, respiratory failure, possible serotonin toxicity, and choreoathetoid movements. All 4 patients had taken less than 3 tablets. Sixty-nine patients were managed in the ED, and treated with IV fluids, oral benzodiazepines, and antiemetics. Length of stay averaged 6.5 hours (range 1 to 27 hours). Number of tablets ingested averaged 4.7 (range 1 to 40), and 27% of patients had taken the dose recommended on the product packaging (up to 2 tablets or 400 mg). Milligram dose was established in 27% of cases (mean 581 mg PBPD, range 105 to 1500 mg). Of 11 patients with seizure, all had taken less than 5 tablets, and 3 had a prior history of seizure. The minimum dose to cause seizure was 400 mg PBPD. Statistical analysis showed no association between poisoning severity and gender, ethanol co-ingestion, dose, or number of tablets. *Conclusion:* Toxicity following PBPD poisoning is unpredictable; serious effects may occur at recommended doses. Seizure and EPS, if they occur in a non-medical setting, are a significant hazard, especially if ethanol is co-ingested as it may increase the risk of physical injury or aspiration. *References:* 1. Baumann MH, Clark RD, Budzynski AG, et al. N-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or "Ecstasy"). Neuropsychopharm 2005; 30:550–560. 2. Persson HE, Sjoberg GK, Haines JA, et al. Poisoning Severity Score. Grading of acute poisoning. J Toxicol Clin Toxicol 1998; 36:205–213.

177. Inter-Individual Variability in Effects after Acute Exposure to Highly Potent Cannabis

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Objective: Inter-individual variability in maximal delta9-tetrahydrocannabinol serum concentration (THC Cmax) and in psychomotor effects after exposure to cannabis has been reported after low or moderate dose of THC (1). This is possibly due to differences in the depth of inhalation or in previous consumption of cannabis (2–3). In recent years, the THC concentration in cannabis sold on the drug market has increased (4). Inter-individual variability in response to cannabis with a high THC concentration is unknown. Our aim was to investigate this question. *Methods:* In a clinical randomized trial approved by the Hospital Medical Ethical Board, 24 participants smoked four joints containing respectively 0, 29.3, 49.1, and 69.4 mg of THC, on 4 exposure days. Standardization of the smoking procedure was obtained utilizing computer generated instructions during the smoking process. The participants were occasional cannabis users (maximum 9 joints per month). Maximal serum concentrations of THC and of the main THC metabolite (11-OH-THC), and acute effects on motor control were the endpoints. Using analysis of variance with repeated measures, we tested whether inter-individual variability in THC Cmax and in motor control impairment could be explained by differences in Body Mass Index (BMI), previous consumption, smoking duration and metabolism parameters (multivariable models also including the THC dose). *Results:* Inter-individual variability was observed in the relationship between exposure dose of cannabis and maximal THC serum concentration, and in the relationship between maximal THC serum concentration and acute motor control impairment. No significant difference in BMI, smoking duration and previous consumption of cannabis could explain the difference in THC Cmax between participants ($P = 0.50$, 0.18 and 0.57, respectively) but the ratio of THC Cmax to maximal serum concentration of 11-OH-THC differed significantly between participants ($p = 0.002$). The variability in motor control impairment increased with increasing THC Cmax. Inter-individual differences in motor control impairment could not be explained by differences in BMI or previous consumption ($p = 0.34$ and $p = 0.72$, respectively). Some subjects showed no motor control impairment, even at a fairly high THC serum concentration of 75 µg/L at the moment the test was realized, i.e., 70 minutes post-exposure. *Conclusion:* Exposure to cannabis with a high THC content exaggerates inter-individual variability in cannabis response. Inter-individual variability in maximal THC serum concentration seems related to differences in the way the subjects metabolize THC. High THC serum concentration does not always mean motor control impairment. More research is needed to investigate the respective importance of polymorphism in metabolism and in neural cannabinoid receptors, on individuals' response to cannabis. *References:* 1. Barnett G, Licko V, Thompson T. Behavioral pharmacokinetics of marijuana. Psycho-pharmacology 1985; 85:51–56. 2. Perez-Reyes M, Di Guiseppi S, Davis K, Schindler VH, Cook CE. Comparison of effects of marihuana cigarettes of three different potencies. Clin Pharmacol Ther 1982; 31:617–624. 3. Lemberger L, Tamarkin NR, Axelrod J, Kopin IJ. Delta-9-tetrahydrocannabinol: metabolism and disposition in long-term marihuana smokers. Science 1971; 173:72–74. 4. Niesink RJM, Rigter SM, and Hoek J. THC-concentraties in wiet, nederwiet en hasj in Nederlandse coffeeshops (2004–2005). 2005. Trimbos Institute, Utrecht, The Netherlands.

178. Atypical Antipsychotics – Less Toxic than Typical Agents in Acute Poisoning?

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Background: Neuroleptics or antipsychotic agents are used primarily to treat schizophrenia and other psychotic disorders. They are classified by structure, pharmacological properties or whether they are typical (traditional, conventional) or atypical (novel, second generation). Because toxicity results mainly from an extension of pharmacological actions, classification based on receptor binding profiles is clinically useful. Typical neuroleptics bind to and antagonize presynaptic and postsynaptic D2-receptors in different part of the brain. Antagonism to mesolimbic D2 receptors is responsible for their antipsychotic effects, as well as blockade of nitrogastrial D2 produces extrapyramidal side effects (EPS). They are also competitive antagonists at a wide variety of neurorceptors (H1, M1, alfa1). The aliphatic and piperidine phenothiazines have a direct negative inotropic action and quinidine-like antiarrhythmic effect on the heart. Agents are considered atypical if they produce minimal EPS at clinically effective doses, have a low propensity to cause tardive dyskinesias and are effective for treating both positive and negative signs and symptoms of schizophrenia. On the basis of their pharmacologic profile atypical neuroleptics are divided into three groups: 1) the D2, D3 receptor antagonists (e.g., amisulpride, sulpiride); 2) the D2, alfa1, 5-HT2A receptor antagonists, also called serotonin-dopamine antagonists (e.g., risperidone, ziprasidone); and 3) multiple receptor antagonists (clozapine, olanzapine, quetiapine) (1). *Objective:* Since 1990, atypical antipsychotic agents have largely replaced traditional agents as first-line drugs for the treatment of schizophrenia and psychotic disorders. Considering the increase in atypical antipsychotics prescriptions and the risk of suicide in this patient population, the number of reported cases of overdose has increased. The aim of the study is to find out if novel neuroleptics are less toxic than conventional in acute poisoning. *Methods:* Review data from published cases or case series. *Results:* Poisoning by neuroleptics may occur after therapeutic doses or accidental or intentional overdose and primarily manifests as central nervous system (CNS) and cardiovascular toxicity. Similar to typical agents, the majority of patients poisoned with atypical neuroleptics developed mild or moderate symptoms. Death following overdose is a rare outcome and in most cases is associated with co-ingestants (2,3). *CNS Toxicity:* CNS effects range from lethargy, slurred speech, ataxia and confusion in mild poisoning to deep coma with respiratory depression and loss of tendon reflexes in severe poisoning. Anticholinergic central symptoms are common with olanzapine and clozapine poisoning. Unpredictable and transient fluctuations between central nervous

system depression and agitation, frequently associated with miosis, appear to be characteristic findings in moderate to high olanzapine overdoses (1,4). Seizures are more likely to occur after overdose with clozapine, lozapine and quetiapine (1,5). The incidence of neuroleptic malignant syndrome (NMS) is not known, but the frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%. For NMS associated with atypical antipsychotic drugs (clozapine, risperidone, olanzapine, quetiapine) the mortality rate was lower than that with conventional antipsychotic drugs (6). *Cardiovascular Toxicity:* Minor cardiovascular adverse effects from antipsychotic drugs are common. They include ortostatic hypotension and tachycardia due to anticholinergic or alpha1-adrenoceptor blockade, and may occur in the majority of patients at therapeutic dosages and in overdose. The most serious consequences, arrhythmias and sudden death, are uncommon and are most likely to be caused primarily by blockade of cardiac potassium channels such as HERG. Reported data suggests that arrhythmias and sudden death are a particular problem with certain typical neuroleptics (thioridazine and droperidol), high risk populations (elderly, pre-existing cardiovascular disease, inherited disorders of cardiac ion channels or of antipsychotic drug metabolism) or people taking interacting drugs (such as drugs that prolong the QT interval, e.g., tricyclic antidepressants, drugs that inhibit antipsychotic drug metabolism, or diuretics) (7). Prolonged PR, QRS and QT intervals, ST-T segment abnormalities, supraventricular and ventricular arrhythmias have been described following overdose of atypical neuroleptics (8–11), and life-threatening dysrrhythmias - torsade de pointes, after amisulpride overdose (12). *Conclusion:* While new atypical antipsychotics may have a safer therapeutic and overdose profile than first-generation antipsychotics many toxic effects still need to be considered in overdose management. *References*: 1. Burns MJ. The pharmacology and toxicology of atypical antypsychotic agents. J Toxicol Clin Toxicol 2001; 39:1–14. 2. Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual Report of the American Association of Poison Control Centers' National Poisoning and Exposure Database. Clin Toxicol 2006; 44:803–932. 3. Griffiths C, Flanagan RJ. Fatal poisoning with antipsychotic drugs, England and Wales 1993–2002. J Psychopharmacol 2005; 19:667–674. 4. Pelenzona S, Meier PJ, Kupferschmidt H, Rauber-Luethy C. The clinical picture of olanzapine poisoning with special reference to fluctuating mental status. J Toxicol Clin Toxicol 2004; 42:27–32. 5. Balit CR, Isbister GK, Hackett LP, Whyte IM. Quetiapine poisoning: a case series. Ann Emerg Med 2003; 42:751–758. 6. Ananth J, Parameswaran S, Gunatilake S, et al. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 2004; 65:464–470. 7. Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf 2000; 23:215–218. 8. Dubois D. Toxicology and overdose of atypical antipsychotic medications in children: does newer necessarily mean safer? Curr Opin Pediatr 2005; 17:227–233. 9. Harrigan EP, Miceli JJ, Anziano R, et al. A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. J Clin Psychopharmacol 2004; 24:62–69. 10. Czekalla J, Beasley CM Jr, Dellva MA, et al. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. J Clin Psychiatry 2001; 62:191–198. 11. Ciszowski K, Jenner B. Evaluation of some parameters of the circulatory system in acute olanzapine poisoning. Przegl Lek 2006; 63:454–458. 12. Isbister GK, Murray L, John S, et al. Amisulpride deliberate self-poisoning causing severe cardiac toxicity including QT prolongation and torsade de pointes. Med J Aust 2006; 184:354–356.

179. Prognostic Factors of Acute Calcium-Channel Blocker Poisonings

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Objective: Incidence of acute calcium-channel blocker (CCB) poisonings is increasing, representing to date the first cause of toxic death in the US. Our objectives were to describe the CCB-poisoned patients admitted to intensive care units (ICU) and to determine the prognostic factors and the interest of plasma concentration measurement on admission. *Methods:* Retrospective collection of clinical data of CCB-poisoned patients admitted in 2 ICU in 2000–2006; determination of plasma concentration using HPLC (REMEDI); description (median, [25–75% percentiles]); comparisons using Mann-Whitney and Chi-2 tests; multivariate analysis using a step-by-step logistic regression model. *Results:* Eighty-four patients (47M/36F, 44 years [31–56], SAPS II: 15 [8–25]) were included. Verapamil (39/83), diltiazem (13/83), nifedipine (11/83), nicardipin (9/83), and amlodipine (8/83) were involved. On admission, systolic blood pressure was 105 mmHg [86–118], heart rate 76 /min [67–91], QRS duration 85 ms [80–110], and plasma lactate concentration 2.86 mmol/l [1.79–5.98]. Poisoning features included shock (42/83), atrioventricular block (34/83), asystole (8/83), and/or ventricular arrhythmia (4/83). All patients received fluid replacement, 50/83 epinephrine infusion (maximal rate: 3.0 mg/h [1.4–8.0]), and 27/83 norepinephrine (5.0 mg/h [2.9–15.0]). 33/83 were mechanically ventilated. Treatments included: calcium salts (22/83), glucagon (18/83), dobutamine (18/33), 8.4% sodium bicarbonate (16/83), isoprenaline (14/83), insulin+glucose (13/83), terlipressin (4/83), electrosystolic stimulation (2/83), and extracorporeal life support (ECLS, 5/83). Eleven patients (13%) died in ICU. Plasma verapamil concentration was significantly different on admission regarding survival (800 versus 2,522 mg/l, $p<0.05$). If excluding SPAS II from the model, multivariate analysis showed that QRS duration (>100 ms; Odds ratio, 5.3; 95%-confidence interval [1.1–27.0]) and maximal epinephrine rate (>5 mg/h; OR, 27.6; IC, [5.3–144.7]) were the only 2 predictive factors of death ($p = 0.007$). If not, SAPS II was the only predictive factor of death (>60, OR, 97.5; IC, [14.2–665.2], $p = 0.0009$). Shock was refractory if epinephrine+norepinephrine was >8 mg/h with renal (creatinine >150 µmol/l) or respiratory failure (PaO_2/FiO_2 >150 mmHg) (sensitivity, 100%; specificity, 89%). *Conclusion:* Despite optimal management in ICU, CBB poisoning mortality remains high (13%). In case of shock, increasing cathecholamine dosage may be life-saving. In case of bad prognostic factors and especially of refractory cardiac shock, ECLS should be proposed. However, the place of possible new antidotes (2,3-diaminiopyridine) remains to be determined.

180. A Prospective Comparative Cohort Study on the Dosing Pattern of Atropine in Organophosphate Poisoning in Rural Sri Lanka

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Objective: There is wide variation in the recommendation for atropine dosing schedules and subsequent variation in clinical practice. The purpose of this article is to examine the safety and efficacy of atropine in a cohort of patients with acute cholinesterase inhibitor pesticide poisoning. *Method:* A prospective cohort study was conducted in three provincial secondary referral hospitals in Sri Lanka using a structured data collection form that collected details of clinical symptoms and atropine dosing. We compared two hospitals using a titrated dosing protocol for atropine with another hospital using a fixed dose regimen. *Results:* 226 symptomatic patients were recruited in three secondary referral hospitals. Chlorpyrifos was the most common organophosphate in each hospital. The majority of patients were male (158). There was no significant difference in mortality between the three hospitals. Significantly higher doses of atropine were given at the hospital using fixed doses. At this hospital the average rate of atropine infusion was 2.1mg/hr and this was 1.7 times higher than the other hospitals. This hospital also had higher rates of delirium (23%), hallucinations (30%) and need for patient restraint (48%), and longer hospital stay. *Conclusions:* Fixed high dose atropine regimens are associated with more frequent atropine toxicity without any improvement in patient outcome. The need for patient restraint would appear to be a strong indication of excessive atropine use. Atropine doses should be titrated against response and toxicity. Further education and the use of a structured monitoring sheet may assist in more appropriate atropine use. It is likely that fixed dosing schedules are used in other rural hospitals in Asia and causing significant morbidity and unnecessary expense.

181. Toxicity of New Antidepressants

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Objective: To describe the characteristics of new antidepressants when taken in overdose. The most recent drugs in this group to be introduced on the European market are venlafaxine, mirtazapine, reboxetine and duloxetine. *Methods:* Data from SPIC's telephone service and case records obtained from Swedish hospitals have been analysed and compared with published reports. Children were excluded. *Results:* Venlafaxine is a combined serotonin and noradrenaline reuptake inhibitor. SPIC has during the last ten years received 152 copies of discharge summaries describing venlafaxine overdose. The dose range was evenly distributed from 200 mg up to 30 g (unknown in 18 cases). Females dominated (75%). Poisoning Severity Scoring (PSS) was feasible in 138 cases. At doses below 2 g mostly mild symptoms like tachycardia, drowsiness and mydriasis were seen. There were six cases with severe symptoms (PSS 3) and an additional four deaths. Among the serious cases (PSS3) unconsciousness, repeated convulsions and aspiration dominated the picture. The lowest dose that provoked convulsions in this material was 2.25 g, but others have reported this complication above approximately 1.5 g (1). Seizures were observed in 20% of all cases, a number that is similar to what was found in an earlier, comparable Swedish material of 107 citalopram overdose cases. ECG-changes like slightly widened QRS-complexes, QT-prolongation and non-specific ST-alterations were noticed in about 15% of the patients. Malignant arrhythmias were rare but three noteworthy patients died in hospital due to circulatory failure, despite active intensive care measures. These patients had all ingested large doses of slow release venlafaxine and serious symptoms appeared with delay. In one of the lethal cases lamotrigine was co-ingested. In the literature several other cases with serious circulatory effects have been described (2). On the other hand, 36 patients in our survey who ingested >4 g (medium 7.6 g, median 6.0 g) did not develop arrhythmias or clinically significant hypotension. Rhabdomyolysis has been reported and so have features of serotonin syndrome (3). Mirtazapine is a pre-synaptic alpha-2-antagonist that enhances both noradrenergic and serotinergic activity. Overdoses are likely to cause some degree of CNS-depression. Tremor, miosis, agitation, confusion and hallucinations can also occur. Tachycardia is relatively common but otherwise circulatory effects are rare. Convulsions are not reported. Up to 300 mg in adults did not give any significant symptoms and doses between 360 – 2400 mg caused mostly mild and only rarely moderate intoxication in the SPIC-material of 97 case records. Mirtazapine can trigger serotonin syndrome both in mono-therapy and in combination with other drugs (4). Reboxetine is a selective noradrenaline reuptake inhibitor with only minor effects on the 5HT-system; therefore the induction of a serotonin syndrome is not to be expected. In six documented poison centre cases where the dose ranged from 40 to 280 mg the patients were asymptomatic or showed only minor symptoms. In a published case where 200 mg was ingested no symptoms except from drowsiness were seen (5). Data on overdoses with duloxetine, another combined serotonin- and noradrenaline reuptake inhibitor, are so far very limited. Patient records collected by SPIC (n = 7) indicate that only mild symptoms like drowsiness, tremor and tachycardia are to be expected in doses below 3–4 g. In one telephone consultation a patient displayed several features of serotonin syndrome after ingestion of an unknown quantity of duloxetine together with clomipramine. In another case serotonin syndrome was suspected after an overdose of 5.4 g. *Conclusion:* Even though there are differences in toxicity between these new antidepressants, the existing experience indicates that they, like SSRIs, are less cardiotoxic compared to traditional tricyclic antidepressants (6). Seizures are not uncommon after venlafaxine overdoses and arrhythmias may occur with this drug. Very high doses of slow release venlafaxine might occasionally cause serious symptoms that appear with a considerable delay. With the exception of reboxetine, an association with the serotonin syndrome has been identified. *References:* 1. Colbridge MG, Volans GN. Venlafaxine in overdose – experience of the National Poisons Information Service (London centre). J Toxicol Clin Toxicol 1999; 37(abstract):383. 2. Cumpston S, et al. Massive venlafaxine overdose resulting in arrythmogenic death. J Toxicol Clin Toxicol 2003; 41(abstract):659. 3. Daniels RJ. 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182. Is Methylene Blue Safe in Patients with Methemoglobinemia and Glucose 6-Phosphate Dehydrogenase (G6PD) Deficiency?

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Objective: Many standard references caution against the use of methylene blue to treat methemoglobinemia (MetHb) in patients with G6PD deficiency. The purpose of this lecture is to evaluate the validity of that statement. *Methods:* A review of the basic science of G6PD deficiency in relation to MetHb followed by a comprehensive search of available literature will be used to support or refute this position. *Results:* MetHb results when the iron on hemoglobin is oxidized from the Fe+2 valence to Fe+3. The body maintains a relatively low level of MetHb

by two processes; direct reduction of the oxidant prior to the formation of MetHb, and reduction of MetHb. In any individual, overwhelming either of these processes can result in MetHb. G6PD is a critical enzyme in the first step of the hexose monophospate shunt. During this reaction, reducing equivalents are created in the form of NADPH. NADPH is essential for maintaining normal stores of reduced glutathione, which is one of the major defences against oxidizing agents. Thus, it is both expected and observed that patients with G6PD deficiency are at increased risk for oxidant stress (both MetHb and hemolysis). G6PD activity is determined by the X-chromosome. While complete absence of the enzyme is lethal, nearly 1/12 humans expresses some degree of G6PD deficiency. Rather than changing the amount of enzyme produced, or the activity of the enzyme, G6PD deficiency alters the stability (half-life) of enzyme. Thus even in patients with severe variants of G6PD deficiency, young red blood cells and all cells capable of protein synthesis have normal function enzyme. The treatment of choice for MetHb is the administration of methylene blue. Unfortunately, methylene blue is itself a weak oxidizing agent that must be reduced to leukomethylene blue in order to reduce MetHb. An enzyme, NADPH MetHb reductase, performs this conversion. The hypothesis is that because people with G6PD deficiency are deficient in NADPH not only are they at risk for MetHb, but will also have difficulty reducing methylene blue, possibly exacerbating MetHb or provoking hemolysis. Several case reports demonstrate either the failure to reverse MetHb or the development of severe hemolysis when methylene blue is used in patients with known G6PD deficiency (1). Other case reports, however, demonstrate the successful use of methylene blue in patients with G6PD deficiency and MetHb (2). No controlled trials or even large case series exist to specifically address this issue. However, several randomized trials have given methylene blue to malaria patients with known G6PD deficiency without producing hemolysis (3,4). *Conclusions:* Case reports support both success and failure of methylene blue in patients with G6PD deficiency and MetHb. Given the prevalence of G6PD deficiency, its recognized risk for MetHb, and the failure to routinely test patients with MetHb for G6PD deficiency prior to therapy, it is likely that many such patients have received methylene blue without adverse effects. Variations in reported response may relate to variations in: a) the severity of G6PD deficiency in treated patients, b) the dose of methylene blue given, and or c) the type of oxidant involved and the degree of methemoglobinemia. Pending better data it is reasonable to treat people with suspected G6PD deficiency with methylene blue. The lowest effective dose should be used, and other therapies should be available. In patients with known severe G6PD deficiency methylene blue should only be considered when other modalities are ineffectual. 1. Rosen PJ, et al. Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med 1971; 75:83–6. 2. Liao YP, et al. Hemolytic anemia after methylene blue therapy for aniline-induced methemoglobinemia. Vet Hum Toxicol 2002; 44:19–21. 3. Meissner PE, et al. Safety of the methylene blue plus chloroquine combination in the treatment of uncomplicated falciparum malaria in young children of Burkina Faso. Malar J 2005; 4:45. 4. Mandi G, et al. Safety of the combination of chloroquine and methylene blue in healthy adult men with G6PD deficiency from rural Burkina Faso. Trop Med Int Health 2005; 10:32–8.

183. Similar but not Quite the Same: Manganism and Parkinson's Disease

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In 1837, a mere 20 years after James Parkinson described the disease that has come to bear his name, Couper reported five cases of a condition characterized by a movement disorder that had similarities to Parkinson's disease (PD) among manganese ore crushers. Further descriptions of manganese-exposed miners, ore crushers, and smelter workers (1–5) have provided a relatively consistent picture of the clinical features of manganism. These are dysarthria, dystonia, bradykinesia, gait imbalance, and personality disturbances. These workers were exposed to potentially very high levels of manganese, with some documented air concentrations of up to 900 mg/m^3 (2). By comparison, the US recommended limit for airborne concentration of manganese for exposed workers is 0.2 mg/m^3. Given the clinical similarity between PD and manganism, it is natural to consider whether manganese exposure is a cause of PD. This inquiry is currently of heightened interest in the US where large-scale litigation involving allegations of manganese toxicity have been fuelled by the recent publication by Racette *et al.* (6) of a clinical screening program funded by, and participated in, by U.S. Plaintiff Attorneys. The syndrome of parkinsonism consists of one or more of the cardinal signs of tremor, bradykinesia, rigidity, and impaired postural reflexes. PD is a distinct entity of parkinsonism with a rest tremor, no other obvious cause such as repeated strokes or head injuries, responsiveness to L-Dopa, no early or prominent signs of extensive central nervous system involvement. Pathophysiologically, PD is characterized with a degeneration of dopaminergic neurons in a specific anatomical site (the substantia nigra pars compacta [SNPC]) and the presence of Lewy bodies. In contrast, there are many other causes of parkinsonism which are not PD, including a number of chemical substances (e.g., neuroleptic agents, methanol, carbon monoxide, carbon disulfide, and manganese). Manganese toxicity, although associated with a parkinsonian syndrome, does not affect the SNPC. Rather, it primarily affects an area of the basal ganglia known as the globus pallidus. MRIs of heavily manganese-exposed smelter workers show T-1 hyperintensities in the globus pallidus. These are not seen in PD. In contrast, fluorodopa PET scans of the nigral striatal pathway are abnormal in PD, yet are unaffected by manganese exposure (7). Because of these differences in the anatomical loci of manganism and PD, the clinical presentations of these two conditions, although similar, are not identical. In contrast to PD, manganism is associated with the symmetric presentation that would be expected of a toxicologic injury, little or no response to L-dopa, either absence of tremor, or, if present, not a resting tremor, dystonia and an unusual gait. The most compelling demonstration of the difference between manganism and PD is a body of at least 30 epidemiological studies, (8) conducted between 1947 and 2006, that have failed to find a statistically significant association between manganese exposure and the development of PD. These studies were done in a number of different countries, on different populations, and different methodologies (17 case-control, 5 mortality, 4 cohort, and 4 cross sectional studies). Standing virtually alone is the publication by Racette *et al.* (6) reporting a dramatic increase in the prevalence of PD (ranging from 5.8 – 13% depending upon the criteria used) in a population of predominantly manganese-exposed welders. However the evaluation by Racette *et al.* was undoubtedly influenced by a number of flaws. The Racette data was funded by plaintiffs' attorneys who were pursuing lawsuits on behalf of welders who claimed to have manganese-induced injury, and the cases for assessment were chosen by these attorneys. This methodology has a high potential of causing selection bias. That this actually occurred is well documented in the paper by the observation that the majority of individuals chosen for evaluation had symptoms that could be consistent with PD. The evaluation of them was done using a non-validated method of diagnosis by videotape, instead of the traditional physical examinations which generally make up the standard of practice in medicine for the diagnosis of PD. The strong selection bias in this Racette analysis is belied by the finding that only 126 of 14,023 welders screened were found to not have some signs of PD. An attempt by Racette *et al.* to determine if there was a correlation between the degree of exposure to welding fume and the likelihood of developing Parkinson's disease found that there was no dose-response relationship. Thus, pathophysiologic, clinical, and epidemiological evidence indicate that manganese overexposure is associated with a distinct clinical syndrome involving primarily the globus pallidus and having parkinsonian features. However the syndrome is distinct from PD. *References:* 1. Mena I, Marin O, Fuenzalida S, Cotzias CG. Chronic manganese poisoning. Clinical picture and manganese turnover. Neurol 1967; 17:128–36. 2. Rodier J. Manganese poisoning in Moroccan miners. Br J Ind Med 1955; 12:21–35. 3. Schuler P, Oyanguren H, Maturana V, Valenzuela A, Cruz E, Plaza V, Schmidt E, Haddad R. Manganese poisoning; environmental and medical study at a Chilean mine. Ind Med Surg 1957; 26:167–73. 4. Tanaka S, Lieben J. Manganese poisoning and exposure in Pennsylvania. 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184. Rational Strategies for Pre-hospital use of Autoinjectors in Poisoning by Organophosphorus Compounds

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Objective: Risk assessment of public safety has changed during the last years and the international community is faced with increasing proliferation of weapons of mass destruction and terrorist threats (1). Nerve agents, belonging to the group of organophosphorus compounds (OP), are topping the list of substances possibly used for spread of fear and horror. Health care systems have to provide effective methods for medical support in mass casualty scenarios following nerve agent attack. Such scenarios are generally characterised by fast developing, frequently life threatening cholinergic crises in a huge number of victims with limited medical resources, e.g., respirators and specific antidotes. Comparable situations may be seen in developing countries, e.g., in south east Asia, where intentional insecticide OP-intoxication is very frequent (2) and intensive care units are rare. The same holds true for OP-sprayers who may be occupationally intoxicated (3) with the distance to an appropriate medical facility being far. In all three scenarios, the victims are severely threatened by respiratory arrest but neither i.v. administration of drugs is possible nor intensive care is immediately available. Accordingly, the health care system is challenged to provide alternatives to cope with such situations. *Results:* In the military environment, comparable situations are well known as the threat of a nerve agent attack on a battle field has already existed for decades. Here, the concept of i.m. administration of antidotes by autoinjectors for self and buddy aid was developed. Using such devices soldiers are trained to administer drugs intramuscularly as early as signs and symptoms arise, long before qualified medical help can be reached. The concept of this approach is to antagonize signs and symptoms mediated by muscarine receptors with atropine and to reactivate OP-inhibited AChE with an oxime, especially to restore neuromuscular function. Since atropine is ineffective at nicotine receptors, the only possibility to prevent peripheral respiratory insufficiency by pharmacological means is reactivation of inhibited AChE. To this end, the oxime has to be administered as early as possible. Autoinjectors are filled with an oxime, a combination of an oxime and atropine or with atropine alone. One example is the Mark I device (e.g. in US forces; 3 Mark I devices per soldier) with one pralidoxime ComboPen (600 mg pralidoxime chloride) and one AtroPen (2 mg atropine) autoinjector. For children, a special Mark I device with a lower atropine content is commercially available (4). German soldiers are equipped with one ComboPen (220 mg obidoxime chloride and 2 mg atropine) and 2 AtroPens (2 mg of atropine). In healthy adults, doses up to 6 mg atropine (i.m.) are generally well tolerated and central effects are rare. Administration of 3 autoinjectors is regarded safe and recommended for self and buddy aid. For children, the atropine dose has to be carefully adjusted (5). When using conventional i.m. injection maximal pralidoxime or obidoxime plasma concentrations were reached within about 20–30 min and were eliminated with half-lives of 1.4 and 2 h, respectively (6,7). It turned out that oxime plasma concentrations increased slightly faster and reached higher levels, when autoinjectors were used (7). Effective oxime concentrations were reached within a few minutes. Moreover, also atropine effects could be recorded earlier (increase in heart rate) when using autoinjectors. Generally, pralidoxime and obidoxime administered by autoinjectors are well tolerated in man (relevant adverse events, especially of obidoxime are mainly attributed to much higher doses) and were regarded safe (also in children). However, one has to be aware that not every type of OP-inhibited AChE can be reactivated, the main problem being soman. Accordingly, much effort was directed to look for broad spectrum oximes, of which HI 6 turned out to be a hopeful candidate. However, neither this oxime, nor HI 6 autoinjectors are licensed or available on the market at present. *Conclusion:* It appears that introduction of autoinjectors in civil health care could substantially improve the armament against terrorist nerve agent attack. Therefore, it seems rational to stockpile autoinjectors and develop plans for fast distribution to medical first aid responders. These personnel have to be trained and should be able to administer autoinjectors in the earliest phases of medical care. Similarly, in developing countries or rural areas, where the distance to well-equipped medical care facilities or a physician is far, OP-intoxicated patients might profit from autoinjector treatment, as in insecticide OP-poisoning, because therapeutic principles work quite similarly to nerve agent poisoning. Thus, medical personnel on-site or in low-equipped medical facilities should be provided with autoinjectors. *References:* 1. German Ministry of Defence. Weißbuch 2006 zur Sicherheitspolitik Deutschlands und zur Zukunft der Bundeswehr. 2006 www.bundeswehr.de. 2. Eddleston M, Phillips MR. Self poisoning with pesticides. BMJ 2004; 328:42–44. 3. Karalliedde L, Eddleston M, Murray V. The global picture of organophosphate insecticide poisoning. In: Karalliedde L, Feldman S, Henry J, Marrs CT, eds. Organophosphates and health. London:

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185. The Controversy over Serum Paracetamol Protein Adduct in Acute Hepatic Failure of Unknown Cause or Known Alternate Cause-Marker of Exposure or Proof of Causality?

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For policy and litigation purposes it is desirable to determine the causal contribution of paracetamol to individual cases of acute liver failure of undetermined etiology. In the first of three studies by a group of interrelated authors frozen sera from 66 patients with acute liver failure (ALF) and 15 patients with paracetamol overdose without injury were assessed (1). The adduct was detected in all 20 with ALF known to be due to paracetamol overdose/overuse (gold standard positive) and was negative in all 10 patients with liver injury known not to be due to paracetamol (gold standard negative). It was present in 7 of 36 patients with ALF of indeterminate cause and 2 of 15 patients with paracetamol overdose without injury. The authors suggest that the reason for the presence of paracetamol cysteine adducts in patients with ALF known not to be due to paracetamol and in the group with indeterminate cause is that paracetamol actually played a causal role in the toxicity (i.e., that their test is the gold standard for causation as well as a marker for exposure). They argue the 7 patients had other serum values similar to the paracetamol injured patients, in contradistinction to the 29 adduct negative patients of indeterminate cause. They do not consider the alternative hypothesis that some or many patients with preexisting, severe liver injury exposed to therapeutic doses of paracetamol formed intracellular adducts that did not result from pathologic processes, but were subsequently released by other mechanisms of cell death resulting in a positive test. However, in mice poisoned with paracetamol, analysis of homogenized liver for paracetamol protein adduct revealed that levels were high even in NAC rescued mice that did not show other evidence of toxicity (2). This led the authors to conclude that "while formation of paracetamol protein adducts are a prerequisite event in the development of toxicity, covalent binding *per se* does not lead to toxicity." This finding agrees with an earlier finding that when macrophages are inactivated before the addition of paracetamol, adduct formation proceeds but toxicity is attenuated (3). Evidence of the formation of adducts in hepatocytes in non-toxic circumstances, without release into serum, argues against concluding that the presence of paracetamol cysteine adducts implies a causal contribution to injury if other hepatocellular events could cause release of cellular contents (e.g., viral hepatitis). Furthermore, the range of values in these 7 patients overlaps with those 29 patients with ALF of indeterminate cause—in 3 of 7, the peak AST or ALT was lower than and in all 7 cases the peak bilirubin was higher than that of the lowest adduct negative patient. A therapeutic serum concentration of paracetamol was present in one of the adduct positive and at least one of the adduct negative patients, at the same level. Although there are classic clinical patterns of findings associated with various causes of liver injury, none of these is "pure." Thus, it is troubling that in some gold standard positive cases causal attribution was based solely on massive AST and ALT elevation or presence of paracetamol at therapeutic concentrations. Many other agents can cause ALF, including herbal products. In a second study, 9 of 72 patients with fulminant hepatitis A or B had detectable paracetamol cysteine adducts (4). In this series, the adduct positive viral subgroup was different from the adduct negative viral subgroup in injury pattern and was in between the paracetamol-like injury pattern seen in a control group of paracetamol overdose patients. That was taken as evidence of a causal contribution of paracetamol. However, this is a necessary but not sufficient observation to establish causal contribution, particularly with the overlap in serum patterns observed. Importantly, in the Davern study the concentration of adducts correlated with serum transaminase elevation (1). In sera from 51 paracetamol overdosed children and adolescents, adduct was only found in one patient - the most severely injured child (peak AST 6156 IU/L) (5). Thus the presence of intracellular adduct in seronegative mice and absence of serum adduct in lesser injured humans suggests that the presence of adduct in the viral subgroup may have been due to exposure to paracetamol and the degree of cell destruction—whatever the cause. Presence may establish exposure, but not causal association. In the third paper, James *et al.* reproduced the Davern study in pediatric patients (6). The adduct was detected in 9 of 10 patients with ALF attributed to paracetamol (gold standard positive). Testing was also positive in 3 of 30 with liver injury known not to be caused by paracetamol (gold standard negative) and in 8 of 64 whose ALF is causally indeterminate. These last two groups are not different (95% CI for the difference in the proportions is -0.159 to 0.109). The presence of serum paracetamol cysteine adducts by themselves do not provide meaningful etiologic information in a case of pediatric ALF of indeterminate cause. As before, the authors suggest that their test is the real gold standard since, some in the indeterminate group, based on clinical course and liver pathology, resemble those with paracetamol induced hepatic failure. The case is no more compelling in this study. Important questions remain. Might one or two therapeutic doses be enough to form some intracellular adduct? What about in the disordered cell exposed to therapeutic paracetamol? The pathologic role of adducts is not clear in paracetamol toxicity. Even if paracetamol protein adducts represent the final common pathway to cell death in paracetamol overdose, their presence in liver injury of indeterminate etiology has not yet been proven to be meaningful. *References:* 1. Davern TJ II, et al. Gastroenterology 2006; 130:687–94. 2. James LP, et al. Toxicological Sciences 2003; 75:458–467. 3. Michael SL, et al. Hepatology 1999; 30:186–195. 4. Polson J, et al. Abstract from Digestive Disease Week, 2006. 5. James LP. 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186. Recent Developments in the Therapy of Paraquat Poisoning

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Objectives: Paraquat dichloride (methyl viologen; PQ) is an effective and widely used herbicide, desiccant and defoliant in a variety of crops. PQ has a proven safety record when properly used for its intended purpose. Its safety can, at least in part, be explained by its lack of absorption either by inhalation or through the intact skin. This is because the spray droplets generated by agriculture equipment are too larger in diameter (>5 μm) to be inhaled and because the intact skin provides an effective, impermeable barrier to the absorption of PQ. However, over the past 44 years, there have been numerous fatalities following accidental or deliberate ingestion of this herbicide. Deaths from PQ poisoning were first reported in the medical literature in 1966 by Bullivant (1). PQ soon gained a reputation as being one of the most toxic substances available and by the apparent total inability of therapeutic efforts to alter the outcome. Fatality rates are over 50%. The main target organ for PQ toxicity is the lung as consequence of its accumulation through the highly developed polyamine uptake system, and due to its capacity to generate redox-cycle-mediated oxidative stress (2). Since antidotes for human PQ poisonings are still to be identified, the strategies in the management of PQ poisonings have been directed toward modification of its toxicokinetics either by decreasing the absorption or by enhancing its elimination and thus preventing the accumulation of PQ in tissues and include procedures, such as induced emesis or diarrhoea, gastric lavage, administration of oral adsorbents, haemodialysis and haemoperfusion (3). Besides these treatments, additional protective measures have been also adopted, namely those aimed: (i) to prevent the generation of reactive oxygen species (ROS), through the effective control of iron distribution by desferrioxamine; (ii) to scavenge ROS including the maintenance of effective levels of antioxidants, such as vitamin E; (iii) to repair the ROS-induced lesions, particularly the maintenance of effective levels of glutathione by administrating N-acetylcysteine (NAC), and (iv) to reduce inflammation by dexamethasone (DEX), methylprednisolone, cyclophosphamide and NAC. In this presentation, we aimed to collect and describe the most pertinent and significant findings related to PQ toxicity and their implication in the possible treatment measures. It will be described as a pre-clinical treatment study, through the induction of *de novo* synthesis of P-glycoprotein (P-gp) by DEX that leads to a remarkable decrease of PQ lung accumulation, together with an increase in its faecal excretion and a subsequent decrease of several biochemical and histopathological biomarkers of toxicity. Considering that the main target organ for PQ toxicity is the lung and involves the production of ROS and RNS, inflammation, and activation of transcriptional regulatory mechanisms, sodium salicylate (NaSAL) will be also presented as being an adequate therapeutic drug, able to counteract these effects. Finally, the promising treatment by mechanical ventilation with additional inhalation of nitric oxide (NO) will be discussed. *Methods:* For the first approach, DEX (100 mg/kg i.p.) was administered to Wistar rats, two hours after PQ intoxication (25 mg/kg i.p.) and verapamil (10 mg/kg i.p.), a competitive inhibitor of P-gp, was given one hour before DEX to confirm the importance of this transporter in PQ excretion. To test the second hypothesis, NaSAL (200 mg/kg i.p.), was injected to Wistar rats, two hours after exposure to a toxic dose of PQ (25 mg/kg, i.p.). *Results:* The administration of DEX decreased the PQ lung accumulation to about 40% of the group exposed only to PQ and led to an improvement of tissue healing in just 24 hours as a result of the induction of *de novo* synthesis of P-gp. This was evidenced by a significant reduction in lipid peroxidation and carbonyl groups content, as well as by normalization of the myeloperoxidase activity. The involvement of P-gp in these effects was confirmed by Western blot analysis and by the use of a competitive inhibitor of this transporter, verapamil. The sum of these effects was clearly positive since an increased survival rate was observed. In the second study, NaSAL treatment caused a significant reduction in PQ-induced oxidative stress and nuclear factor (NF)-κB activation in lung. In addition, histopathological lesions induced by PQ in lung were strongly attenuated. These effects were associated with a full survival of the PQ treated rats (extended for more than 30 days) in opposition to 100% of mortality, by day 6, in animals only exposed to PQ. *Conclusion:* The induction of P-gp, leading to a decrease in lung levels of PQ and the consequent prevention of toxicity, seems to be a new and promising treatment of PQ poisonings (4,5). Moreover, our studies suggest that NaSAL constitutes an important and valuable therapeutic drug to be used against PQ-induced toxicity. Indeed, NaSAL constitutes the first compound with such a degree of success (100% survival). *References:* 1. Bullivant CM. Accidental poisoning by paraquat: Report of two cases in man. Br Med J 1966; 5498:1272. 2. Rose MS, Smith LL, Wyatt I. Evidence for energy-dependent accumulation of paraquat into rat lung. Nature 1974; 252:314. 3. Dinis-Oliveira RJ, Sarmento A, Reis P, et al. Acute paraquat poisoning: report of a survival case following intake of a potential lethal dose. Pediatr Emerg Care 2006; 22:537. 4. Dinis-Oliveira RJ, Remião F, Duarte JA, et al. P-glycoprotein induction: an antidotal pathway for paraquat-induced lung toxicity. Free Radic Biol Med 2006; 41:1213–1224. 5. Dinis-Oliveira RJ, Duarte JA, Remiao F, et al. Single high dose dexamethasone treatment decreases the pathological effects and increases the survival rat of paraquat-intoxicated rats. Toxicology 2006; 227:73–85.

187. The Efficacy of Veno-Venous Haemofiltraton and Haemodiafiltration for Toxin Removal in the Poisoned Patient

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Introduction: Haemodialysis (HD) has been used for five decades for toxin removal in poisoned patients (1–4). Since two decades, other techniques have been proposed, such as veno-venous haemofiltration (VVHF) and haemodiafiltration (VVHDF). The major advantage is that these techniques are more available than HD because the technical requirements are less important. *Technical and Kinetic Aspects:* HF achieves solute clearance by convection (solvent drag effect) through the membrane, with pore dimensions exceeding those of conventional HD membranes, by removing plasma water which contains dissolved solutes: the removed fluid must be replaced. In HDF, diffuse transport of molecules is added to filtration in order to increase the clearance of solutes. Drugs and chemicals must meet given criteria in order to reach a high extraction ratio: small molecular size, high water solubility, low protein binding (4). Compared to HD, the properties of the membranes used for HF and HDF allow the removal of poisons with higher molecular weight (up to 50000 Daltons for HF and HDF vs. less than 500 Daltons for HD). However, the toxicokinetic requirements for an efficient toxin removal do not differ: small volume of distribution (< 1L/kg), low endogenous clearance and an extraction ratio exceeding endogenous elimination (4). The efficacy of the techniques is measured by the dialysis clearance, the amount of toxin removed and the changes in plasma half-life during the procedure (5). HF and HDF are considered as continuous therapies because they are applied for a longer time (24 to 48 hours) than HD (usually 4 to 6 hours). An advantage of CVVF and CVVHDF is that they are better tolerated than HD in haemodynamically unstable patients. *Results:* The use of CVVF and CVVHDF have been reported in poisonings with salicylates (6), barium (7), lithium (8), carbamazepine (9–10), phenobarbital (11), methanol (12), iodine (13), pilsicainide (14), mercury (15), metformin (16–17), valproic

acid (18–20), and tetramine (21). With CVVHF, the amount of toxin removed is directly dependent on the plasma concentration and the ultrafiltrate flow. The clearances achieved are usually low: for lithium the clearances are respectively 16.6 ml/min and 33.3 ml/min with ultrafiltrate flows of 1 L/h and 2 L/h (8). With CVVHDF, the clearances are lower than with HD (usually five times lower) and depend on the dialysate flux (8–13). In lithium poisoning the clearances are 30 ml/min with a dialysate flux of 1–2 L/H and may reach 60 ml/min with a flux of 4 L/H but, nevertheless, are lower than with HD (100–120 ml/min) (5–8). For methanol and salicylate, the same differences are observed (6–12). In valproic acid poisonings, a significant amount of drug may be removed by extracorporeal elimination techniques when plasma concentrations are high and protein binding is saturated, increasing therefore the free plasma concentration (18). Clnical improvement and decrease of valproic acid plasma half-life during the procedure have been reported (18–20). In the case of barium poisoning, CVVHDF increased barium elimination by a factor of three (7). In a case of inorganic mercury poisoning treated with DMPS, CVVHDF decreased the mercury plasma half-life with an elimination clearance of 10 ml/min (15). Beneficial effects of CVVHDF have been observed in metformin poisonings with severe lactic acidosis (16–17). In these cases it is difficult to relate the clinical efficacy to the increased drug elimination or to the correction of the metabolic disturbances. *Conclusions:* The published experience of CVVHF and CVVHDF in poisonings is scarce. Compared to HD, the efficacy of HDF is lower (about 2–3 times) and in order to achieve the same kinetic effect the procedure has to be applied for a longer period. However, CVVHDF may be used in rare cases when there is an indication for extracorporeal toxin elimination and HD is not available. CVVHD should also be preferred to HD in patient hemodynamically unstable and with severe lactic metabolic acidosis. However, the kinetic and dynamic efficacy needs to be further evaluated. *References:* 1. Winchester JF, Gelfand MC, Knepshield JH, et al. Dialysis and hemoperfusion of poisons and drugs. Update. Trans Am Soc Artifial Organs 1977; 23:762–852. 2. Garella S. Extracorporeal techniques in the treatment of exogenous intoxications. Kidney Intern 1988; 33:735–754. 3. Pond SM. Extracorporeal techniques in the treatment of poisoned patients. Med J Australia 1991; 154;617–622. 4. Jaeger A, Sauder P, Kopferschmitt J, et al. Toxicokinetics in clinical toxicology. Acta Clin Belg 1990; 45:1–12. 5. Jaeger A, Sauder P, Kopferschmitt J, et al. When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. 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188. Emergency Feasibility in Medical Intensive Care Unit of Extracorporeal Life Support for Refractory Toxic Cardiac Arrest

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Objective: To report the feasibility, complications, and outcomes of emergency extracorporeal life support (ECLS) in refractory toxic cardiac arrests in a medical intensive care unit (ICU). *Methods:* Prospective cohort study in a medical ICU in a university hospital in collaboration with the cardiosurgical team of a neighboring hospital. We included twelve poisoned patients admitted over a 2-year period for cardiac arrest (8 extra-hospital and 4 intra-hospital arrests) unresponsive to cardiopulmonary resuscitation (CPR) and advanced cardiac life support, without return of spontaneous circulation. ECLS femoral implantation was performed under continuous cardiac massage, using a centrifugal pump connected to a hollow-fiber membrane oxygenator. *Results:* Stable ECLS was achieved in 10/12 patients. Duration of continuous external cardiac massage was 120 min [45–180]. Early complications included massive transfusions (N = 5) and the need for surgical revision at the cannulation site for bleeding (N = 1). On ECLS connection, plasma lactate concentration was 17.3 mmol/l [5.3–39.3], PaO_2/FiO_2 ratio 271 mmHg [41–557], and serum creatinine concentration 141 µmol/l [83–369]. Deaths resulted from multiorgan failure (N = 5), thoracic bleeding (N = 1), severe sepsis (N = 1), and brain death (N = 1). Massive hemorrhagic pulmonary edema during CPR (N = 3) and major capillary leak syndrome (N = 3) were observed. ECLS duration was 56 h [5–108]. Three cardiotoxic-poisoned patients (18%, CPR duration: 30, 100, and 180 min) were alive at one-year follow-up without sequelae. Two of these patients survived despite elevated plasma lactate concentrations before cannulation (39.0 and 20.0 mmol/l). The ingested toxicants (doses, plasma concentrations, [therapeutic concentrations]) were flecainide (40 mg, 6.0 mg/l, [0.2–0.6])+acebutolol (2 g, 1.8 mg/l, [0.2–1.5]), acebutolol (40 g, 41.1 mg/l), and acebutolol (sustained-release preparation, 34 g, 40.2 mg/l), respectively. ECLS was associated with a significantly lower ICU mortality rate than that expected from the Simplified Acute Physiology Score II (91.9%, p = 0.02) and lower than the maximum Sequential Organ Failure Assessment score (>90%). *Conclusion:* Emergency ECLS is feasible in medical ICU and should be considered as a resuscitative tool for selected poisoned patients suffering from refractory toxic cardiac arrest.

189. Extracorporeal Liver Support for Toxic Hepatic Failure

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Acute liver failure still carries a high mortality. The lack of detoxification, metabolic and regulatory functions of the liver leads to life-threatening complications, including kidney failure, hepatic encephalopathy, cerebral edema, severe hypotension and susceptibility to infections culminating in multiple organ failure. In the most severe cases, the prognosis of liver failure can only be modified by liver transplantation. Due to the current shortage of grafts, the delay necessary to perform liver transplantation is increasing. During this interval, intensive care support is essential, and more particularly the correction of hemodynamic disorders and coagulation, but also the management of cerebral edema. There is an increasing interest in the use of extracorporeal liver support devices in this setting. To date, however, there is no evidence that these techniques are able to decrease the mortality in acute liver failure (in contrast to the data available on acute-on-chronic liver failure). The devices currently under investigation are based on the principle of albumin dialysis (1). These devices are supposed to influence the removal of biological substances and drugs, to modify regional and global hemodynamics, and to protect cerebral function. Among many other functions, albumin is an important transporter of hydrophobic internal and external substances, such as intermediate and end products of metabolism and drugs. Albumin synthesis is markedly decreased during acute liver failure, and on the other hand, the clearance of hydrophobic toxins is also significantly reduced. Two devices were more particularly studied: the recirculating albumin dialysis system (MARS®) and the PROMETHEUS® technique based on plasma separation and adsorption. The MARS® is composed of two dialysers: a conventional one coupled to a bicarbonate buffer, and an albumin dialysate circuit, primed with 600 ml of albumin. The objective is to allow the exchange of protein bound substances between the blood compartment and albumin in the albumin dialysate compartment (and also the diffusion of water-soluble, non protein bound solutes from blood into the albumin compartment). *In vitro* studies reveal that MARS® is removing unconjugated bilirubin, drugs with a high protein-binding ratio, and protein bound toxins. These data were confirmed *in vivo*: free fatty acids as well as aromatic amino acids are eliminated. Comparisons between the two systems remain difficult as MARS® has been more frequently used than PROMETHEUS® (2). The selectivity of MARS® is higher as high flux dialysis membranes are used. Some publications suggest that PROMETHEUS® could produce a higher blood clearance for most toxins. However, the real impact of these differences on the clinical outcome has still to be analyzed. Cytokines are also removed by both devices, and also hepatic growth factors. As cytokines have either pro-inflammatory or anti-inflammatory properties, the benefit of cytokines removal is not really demonstrated (3,4). Concerning coagulation factors, the artificial liver systems do not improve coagulation because there is no effect on liver synthesis. Antithrombin III or factor V are not removed by the system. Heparin is theoretically required during epuration but is seldom used. The technique is usually well tolerated and bleeding is rare. Among the other substances that can be theoretically removed, some sedative drugs from the benzodiazepines family could also be removed. Several publications have also outlined the role of albumin dialysis techniques on cardiovascular dysfunction. Acute liver failure is usually characterized by low systemic vascular resistances (SVR), arterial hypotension and a compensatory high cardiac index. It appears from the limited available data that following MARS®, a significant increase in SVR could be obtained together with an improvement in arterial blood pressure (5,6). It is not certain that this effect is sustained. The effects of albumin dialysis on cerebral function were also investigated either in animal models or in a limited number of observations in humans. In a pig model with acute liver failure induced by hepatic devascularization, MARS® was able to prevent the increase in intracranial pressure (ICP) (7). Interestingly, it seems that this beneficial effect is independent from the epuration of ammonia. In humans, contradictory results have been published but a trend towards an ICP reduction could be noted (5). More than 4500 patients have been treated by MARS®, but the principal indication was acute-on-chronic liver failure. There is no evidence that albumin dialysis epuration techniques could have a significant influence on mortality in acute liver failure. Most of the patients treated by MARS® were effectively transplanted and the demonstration of the benefit of these techniques will remain difficult. We can only conclude at this stage that in a limited number of cases of acute hepatic failure (from toxic origin), albumin dialysis epuration techniques could improve the intensive care management of hemodynamic and neurological disturbances. *References:* 1. Laleman W, Wilmer A, Evenepoel P, et al. Review article: non-biological liver support in liver failure. Aliment Pharmacol Ther 2006; 23:351–363. 2. Evenepoel P, Laleman W, Wilmer A, et al. Prometheus versus molecular adsorbants recirculating system: Comparison of efficiency in two different liver detoxification devices. 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Crit Care Med 2006; 34:158–164.

190. Cesium: Cardiac Toxin and Radiological Threat

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Objective: To describe the clinical presentation, assessment, and treatment of acute cesium poisoning. *Methods:* Comprehensive review of the literature, followed by presentation of clinically relevant basic science, animal and human research. *Results:* Cesium (atomic number 55) is an alkali metal that is chemically related to both sodium and potassium. Toxicity from metallic cesium is limited to thermal injury because of its highly reactive (and explosive) nature when exposed to water. However, several stable cesium salts exist. Both the chloride and carbonate salts are promoted as alternative therapies for terminal cancer despite a lack of clinical or experimental support. Their alleged mechanism of tumoricidal activity is through raising the intracellular pH. People are advised to take about 3 grams/day at a cost of about $3. Unfortunately, at these doses, cesium ions alter cardiac ion channels to produce ventricular dysrhythmias including torsade de pointes. Evidence support both blockade of potassium channels - possibly I (K1) – and enhanced calcium influx as etiologies for this effect. Multiple cases of dysrhythmias are reported in patients taking cesium salts for terminal cancer (1–3). Fortunately, experimental and clinical evidence support a role for magnesium administration to suppress cesium-induced dysrhythmias. Many reported patients had simultaneous electrolyte abnormalities (such as hypokalemia) that could have contributed to the dysrhythmias. It is therefore prudent to check and supplement calcium and potassium as clinically indicated. Magnesium therapy and prolonged observation with continuous monitoring is indicated for any patient with dysrhythmias or QT prolongation. Radioactive isotopes of cesium result from neutron activation of stable cesium (to form Cs-134) and more commonly as a byproduct of nuclear fission reactions (Cs-137). They are potent beta and gamma emitters and as such pose significant risks to human health. In the 1986 Chernobyl incident it was estimated that the total radiation release was on the order of 100 megaCuries (MCi) (or 4 x 1018 becquerels), of which 2.5 MCi were accounted for by Cs-137, with a half-life of over 30 years (4). A year later, a discarded radiotherapy unit was opened in Goiânia, Brazil resulting in radiocesium contamination of an entire community (5,6). More recently, significant concerns have been expressed over the use of radiocesium by terrorists in the production of a dirty bomb. Following external decontamination and local therapy for skin burns (if present), treatment of victims of radiocesium poisoning should include the oral administration of Prussian Blue (9 grams per day in three divided doses) (7). *In vitro* experiments demonstrate that 1 gram of Prussian Blue can theoretically adsorb more than 200 mg of Cs-137. In animal models, oral administration of Prussian Blue significantly reduces the biological half-life of Cs-137. Similarly, in human volunteers, the biological half-live of Cs-134 was reduced from 106 to 44 days with administration of Prussian Blue. Although no controlled clinical trials exist, victims of Chernobyl and Goiânia were treated with Prussian Blue and reduced biological half-lives were reported. *Conclusions:* Although cesium poisoning is uncommon, the potential for significant injury is real. Clinicians should recognize cesium salts as a potential cause of dysrhythmias (especially in oncology patients), and be aware of the role of Prussian Blue following a radiocesium release. *References:* 1. Dalal AK, Harding JD, Verdino RJ. Acquired long QT syndrome and monomorphic ventricular tachycardia after alternative treatment with cesium chloride for brain cancer. Mayo Clin Proc 2004; 79:1065–9. 2. Lyon AW, Mayhew WJ. Cesium toxicity: a case of self-treatment by alternate therapy gone awry. Ther Drug Monit 2003; 25:114–6. 3. Saliba W, Erdogan O, Niebauer M. Polymorphic ventricular tachycardia in a woman taking cesium chloride. Pacing Clin Electrophysiol 2001; 24:515–7. 4. Straume T, Anspaugh LR, Marchetti AA, et al. Measurement of 129 I and 137 Cs in soils from Belarus and reconstruction of 131I deposition from the Chernobyl accident. Health Phys 2006; 91:7–19. 5. Oliveira AR, Hunt JG, Valverde NJ, Brandao-Mello CE, Farina R. Medical and related aspects of the Goiania accident: an overview. Health Phys 1991; 60:17–24. 6. Anjos RM, Umisedo NK, Facure A, Yoshimura EM, Gomes PR, Okuno E. Goiania. 12 years after the 137Cs radiological accident. Radiat Prot Dosimetry 2002; 101:201–4.7. Hoffman RS. Prussian Blue. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, et al., eds. Goldfrank's Toxicologic Emergencies. 8th Edition. New York: McGraw-Hill, 2006:1373–1377.

191. Intentional Thallium Poisoning – Verification and Treatment

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Objective: Intoxication with thallium belongs to rare poisonings. The diagnostics frequently pose a problem, especially after several months' latency (1). There are no data on the excretion of thallium after the antidote treatment in the "unexposed" population, where it originates from environmental sources. Additionally, only rare data exist about the reversibility of changes (2). *Case Series:* A 44-year-old woman experienced in November 2004 severe pain with paresthesiae in lower limbs. Symptoms disappeared within 3 weeks. In March 2005, she suddenly developed a strong muscular pain in the lower extremities. The gait was painful "as on the broken glass." Within 5 days she became bald. She stayed at the neurology department for a month with suspicion of lumboischiadic syndrome and post-traumatic stress disorder due to work overload. The symptoms almost disappeared in June 2005, and she returned to work. In August 2005, a progressive pain in the lower limbs with paresthesiae and blurred vision developed. She could differentiate only dark and light spots in the periphery. After 3 weeks her condition improved a little, however mild pain in the feet and knees, and vision difficulties persisted. In December 2005 her 22-year-old daughter developed strong pain in the lower limbs, with a maximum in the stocking distribution, and paresthesiae. In the following 3 weeks the symptoms deteriorated so much that she was unable to stand up and walk. In the 4th week she lost all hair and developed severely blurred vision so that she could recognize fingers only from 0.3 m distance. Both women thought they had been poisoned by the father/husband, who stored ancient rodenticides. A dog of the family had lost hair about one year before that. In January 2006, analytical measurements by Optical Emission Spectrometer-Inductively Coupled Plasma (OES-ICP) confirmed thallium poisoning (3). The results are shown in Table 1. Starting January 27, 2006, the daughter was hospitalized at our department. She was bald, and unable to walk. Severe senso-motor axonal polyneuropathy in the lower extremities was found (with almost normal finding in the upper extremities). Ophthalmological examination has shown central scotomas in both visual fields, retina appearance was normal. Treatment with antidote Prussian blue, Fe4[Fe(CN)6]3, ferric hexacyanoferrate, was started. After the first dose of 6 g the concentration of thallium in urine increased about twofold. Charcoal 50 g/day was given in the intervals between the antidote (in 4 doses/day), in addition to 10% mannitol and furosemide. Antidotal treatment was continued until the excretion dropped under 5 mcg/l urine. On January 31, 2006 the mother was examined, as she still complained of blurred vision in the centre of the visual field and inability to read. The biological half-lives of thallium in documented cases are in a broad range of 1–30 days (4). Therefore, as an elimination test, the mother was given 6 g of the antidote. Thallium in urine, immeasurable by voltammetry, increased after Prussian blue to 31 mcg/12 h. After the same dose of antidote thallium in urine in a control woman increased only to 4.2 mcg/12 h. Massively lost hair of the mother was not available. In the daughter, sequential analysis of hair has proven that she had been given thallium for 5 months at least. In the light microscopy the proximal end of the hair was tapered and distorted and showed a rough surface with pathological keratinisation. The cortex on the widened club-shaped end appeared dark and disorganized, gaseous inclusions were observed. Until April 2006 the daughter improved a little, she was able to walk with a walker leg support. Atrophy of both optic nerves was noted on the ocular fundus. Magnetic resonance imaging of the brain has shown normal findings including the optic nerves, tracts, chiasma and visual cortex. In August 2006 she could walk without support. Severe polyneuropathic syndrome in the lower extremities, with a pronounced damage to motor fibres (absent compound muscle action potential) was present. EEG still showed abnormal findings (labile background, and sporadic disperse theta activity). Both visual and acoustic evoked potentials were abnormal. The vision slightly improved – she could see fingers from 0.75 m, but could not read, as there were large central scotomas. *Conclusion:* Treatment with Prussian blue increased excretion of thallium in both women, compared with a control subject, which suggests a longer half-life of thallium. However, the clinical effect in the mother was negligible. One year after the last intoxication, her vision remains impaired. Scotomas and severe polyneuropathy persist in the daughter 9 months after the heavy poisoning. The reversibility of symptoms is still questionable. *Acknowledgement:* MSM 0021620807 *References:* 1. Daniel CR, Piraccino BM, Tosti A. The nail and hair in forensic science. J Am Acad Dermatol 2004; 50:258–2612. 2. Pau PWI. Management of thallium poisoning. HKMJ 2000; 6:316–318. 3. Das AK, Chakraborty R, Cerevera ML, et al. Determination of thallium in biological samples. Anal Bioanal Chem 2006; 385:665–670. 4. Hoffmann RS. Thallium toxicity and the role of Prussian Blue in therapy. Toxicol Rev 2003; 22:29–40.

Table 1. Thallium measurements in both women

	Units	Daughter	Mother	Normal values (ref.3)
Days of treatment with Prussian blue		22	5	
Estimated latency from exposure		6 weeks	5 months	
Initial measurement OES-ICP analysis				
Blood	mcg/l	770	8.5	0.049–0.130
Urine	mcg/l	580	0.3	0.018–0.021
Hair	mcg/g	6.8	–	0.007–0.650
Peak with antidote*				
Urine	mcg/l	1170	21	4+
Urine	mcg/12 h	1750	31	4.2+
Faeces	mcg/g	55	5.5	?
Measurement after the end of treatment*				
Urine	mcg/l	2.0	5.4	Negative
Urine	mcg/12 h	2.4	4.0	Negative
Faeces	mcg/g	0.9	0.6	Negative
Last measurement*		August 2006	April 2006	
Urine	mcg/l	Negative	Negative	Negative
Urine	mcg/12 h	Negative	Negative	Negative

- not measured, ? not known, *voltammetric analysis, and +measurement in control subject.

192. Epidemiology of Psychotropic Drug Poisonings in Slovakia

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Objective: Psychotropic drugs (anxiolytics, antidepressants, neuroleptics) are among the most common causes of health injury from self poisoning. Every year psychotropic drugs make up more than 30% of all drug intoxications. To obtain more information about psychotropic drug overdoses in Slovakia, we performed a retrospective analysis of all case records sent to the National Toxicological Information Centre (NTIC) in Bratislava. *Methods:* Case records concerning overdoses with psychotropic drugs sent to the NTIC from Slovak hospitals were studied for the period 2003–2005. The following data were analysed: age, sex, intent of exposures (suicidal or accidental), substances ingested and clinical severity. All intoxications were classified in accordance with the Poison Severity Score. *Results:* During the 3-year period 2780 drug intoxications were reported to the Slovak NTIC of which 906 (32.6 %) involved psychotropic drugs. Suicidal poisonings (87.5%) were more common than accidental poisonings. Female exposures (57.9%) were more prevalent than exposures involving males (40.3%). Suicidal intoxications predominated in females. The majority of cases (71%) were adults; the most frequently involved age group was those aged 19–30 years. The most frequently ingested anxiolytic drug was alprazolam. Citalopram predominated in antidepressants and risperidone was the most often ingested neuroleptic. Mild toxicity developed in the majority of patients (58.3%). Moderate or

severe symptoms occurred in 27% of all exposures, 4 cases resulted in death. *Conclusion*: Intoxications involving psychotropic drugs are among the more common enquiries to the Slovak NTIC. In our experience children are more sensitive to the toxic effects of these agents. Clinical symptoms occur early and are usually of mild to moderate severity.

193. Adverse Drug Reactions as a Cause for Hospitalization

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Objective: To evaluate the main characteristics of adverse drug reactions (ADRs) of patients hospitalized in the Clinic of Toxicology. *Methods:* The study of drug-related hospital admissions of 4,590 adults (over 18) was conducted in the period 2003–2005. Suicide attempts were excluded. We compared the age, sex, the main diagnoses in adverse drug events and the main drugs which induced ADRs. *Results:* 332 hospital admissions were registered as ADR related. The most frequent ADRs were: allergic dermatosis (n = 135), edema (n = 63), combined (n=90), and allergic shock (n=37). There was 1 fatal outcome from asphyxia. The drugs most often associated with ADR were antibiotics (n=86), and ACE inhibitors (n = 52), and non-steroidal anti-inflammatory drugs (n = 20). Female gender was overwhelming and the group of 50–65 years of age had the higher number of ADRs. 33% of those hospitalized for ADRs have had previous allergic disease. *Conclusion:* There is need of careful benefit-risk assessment for the practical decision making. The number of ADRs among middle aged patients receiving ACE inhibitors in treatment of hypertonic disease is increasing.

194. Retrospective Survey of Acute Poisoning Admissions in an Irish General Hospital

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Objectives: To determine the number of adult poisoning admissions to a major Irish general hospital between January 1 and December 31, 2004 inclusive, to describe patient demographics and to identify the agents involved in poisoning. *Methods:* Acute poisoning admissions (accidental, intentional and of undetermined intent) were retrospectively identified from the hospital in-patient enquiry system. Data on patient age and gender, length of admission and International Classification of Disease (ICD9) diagnostic codes were obtained. Patient charts were reviewed to confirm and supplement the information on the hospital system. The study was approved by the hospital Ethics (Clinical Research) Committee subject to compliance with data protection legislation. *Results:* 108 patients had 119 admissions due to poisoning during the study period. Seven of these patients were admitted twice during the study period and one patient had five admissions. The female:male ratio was 1.45:1. The youngest patients were 14 years old (both females) and 34% of patients were under 30. The agents most frequently ingested were aromatic analgesics, mainly paracetamol, (36 admissions), antidepressants (25 admissions), and benzodiazepine tranquillisers (20 admissions). The average length of stay was 5.3 days (range 1 to 98 days). *Conclusion:* The poisoning admissions in this study were similar those reported in other Irish hospitals (1,2). A similar pattern is also evident in enquiries to the National Poisons Information Centre (3). Females outnumbered males while paracetamol, antidepressants and benzodiazepines were most commonly ingested. *References:* 1. Malone K, McCormack G, Malone JP. Non-fatal deliberate self-poisoning in Dublin's North Inner City – an overview. Ir Med J 1992; 84:132–135. 2. McMahon GT, McGarry K. Deliberate self-poisoning in an Irish county hospital. Ir J Med Sci 2001; 170:94–97. 3. National Poisons Information Centre Annual Report 2005.

195. Adult Respiratory Distress Syndrome in Patients with Acute Poisoning in Department of Toxicology in Niš, Serbia

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Objective: Adult respiratory distress syndrome (ARDS) is the syndrome of acute, severe and progressive respiratory insufficiency, occurring during the course of various diseases, and characterized by severe hypoxia, decreasing lung compliance, and diffuse pulmonary infiltrates. The aim of the study was to determine the frequency of ARDS occurrence in the patients with acute poisoning (AP), to determine the mortality rate of the patients with ARDS during AP and to assess the factors that increase the mortality rate in patients with ARDS. *Methods:* Basic criteria used for diagnosis of ARDS: 1. Analyze the alkaline-acid status in AP patients (pH, BE, HCO_3, pO_2, pCO_2, $SatO_2$); 2. Difficult clinical picture; 3. Diffuse pulmonary infiltrates in lung rentgenography; 4. Adequate previous history of the disease; and 5. The absence of heart failure (EKG, EHO-cardiography). *Results:* During the period 2001–2005, 1139 toxic cases have been attended in the Department of Toxicology in Niš, Serbia. 29 (2.54 %) patients with ARDS were treated as a complication of AP. The majority of poisoning were caused by medicaments – 15 (51.72%), opiates- 6 (20.69%), organophosphorus compounds – 5 (17.24%), ethanol – 2 (6.89%), acetic acid – 1 (3.46%) patient. Out of 29 patients with ARDS in AP 18 died (62.06%). In patients with AP and ARDS, lethal outcome can be influenced by: 1. The amount of toxic substance taken and the velocity of its elimination (gastric lavage, forced diaresis or hemodialysis); 2. The stage of distress in which intensive care of patients was started; and 3. Timely applied cardiopulmonary resuscitation and correction of cardio circulatory and metabolic disturbances, and to a smaller degree the state of cardiovascular system before the development of distress and the patient's age. *Conclusion:* ARDS is a frequent complication during the course of AP which demands timely application of intensive care in specialized departments aiming to decrease still very significant mortality rate.

196. Availability of Psychotropic Medicines and Agrochemicals in Patients with Suicidal Attempts During an Investigation Period of Six Months

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Objective: The purpose of this study is to come to a conclusion about the kind of the toxic substance, the gender and the timing of suicidal attempts, mainly investigation of the availability of medicines and agrochemicals. *Material and Methods:* In a period of six months (May-October 2006), 3,060 suicidal attempts from all over the country were reported to PIC and epidemiologic data, clinical state, amount of the toxic substances and the outcome were evaluated. *Results:* From the 3,060 incidents that were studied, 75.5% were females while the remaining 24.5% were males. High frequency of suicidal attempts was observed during leisure days. Most of the calls came from the capital area. Two groups of patients have been investigated thoroughly. A group: psychotropics, because of the high frequency (47.7%) in suicidal attempts and B group: agrochemicals, because of the severity of intoxication. From the A group, 75.7% occurred with psychotropic medicines alone, while 24.3% occurred by combining them with other substances. 49.8% of the suicidal attempts were under medical treatment with psychotropic medicines. In addition, 25.2% had at least one previous suicidal attempt. 46 cases had received a highly toxic dose of psychotropic substances. In those history revealed the reason for the large supply of medicines at home. In 56.5% of these cases, there were prescriptions which involved more medicines than the patient needed per month, while 37% were due to the saving of the medicines by the patient and 6.5% of the cases had obtained the medicines from the pharmacy without a prescription. 2.6% of the total number of attempts occurred from agrochemicals with the highest frequency in males and in rural areas, while a proportion of them were not even occupationally involved with these substances. From the 3,060 attempts 7 deaths were reported, which had been caused by agrochemicals. The attempts with agrochemicals appear to cause the most severe clinical states and demand the longest hospitalization. *Conclusion:* A. The method of prescription and the supply of psychotropic drugs must be strictly controlled by physicians and the families of the patients under psychotropic therapy. B. State authorities and PICs must organize steps for restriction in the use of agrochemicals and their commercial delivery from agriculturalists, in order to reduce the number of fatal suicidal attempts.

197. Retrospective Study of Drug Overdoses in a Suburban Emergency Department

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Objectives: To describe attendances at the Emergency Department of a major Irish general hospital following drug overdose, the agents ingested and patient disposition. *Methods:* The Emergency Department notes of all patients who attended the department between January 7 and June 12, 2004 were reviewed and those who had taken an overdose were identified. *Results:* There were 20,000 attendances at the ED during the study period. 287 of these were identified as drug overdoses, with an average of 1.8 overdoses per day during the study period. 15 people had repeated attendances, which represents 5.9% of those attending with overdoses: 10 patients attended twice during the study period, 2 presented 3 times, 2 presented 5 times and 1 presented 9 times. Each presentation was counted as one case for the purposes of this study. Most cases were 20–29 years old (23.3%). The youngest patient was 14 (the youngest age treated by the hospital) and the oldest was 78 years old. 152 out of 287 presentations were by women (52.9%). However, 53% of the cases who presented repeatedly were male. The majority of patients had taken more than one drug. Benzodiazepines were a component of 147 overdoses, diazepam being the most commonly used (49 cases). 123 presentations involved antidepressants or antipsychotics, particularly venlafaxine or escitalopram. Paracetamol/paracetamol-containing products were the most commonly ingested analgesics (69 cases). 40 patients had taken other analgesics, including 14 who had taken aspirin. 33 cases were admitted to the hospital, including 8 who were admitted to ICU/CCU, 64 did not wait to receive treatment or discharged themselves against medical advice, and the remaining patients were treated in the ED and discharged, with further care by the acute psychiatric unit, their GP or social services if appropriate. No patient died in the ED during the study period from drug overdose. *Conclusion:* 1.5% of attendances to this ED during the study period were due to overdoses. These were mostly women aged between 20 and 29 years. However, of those who repeatedly overdosed the majority were male.

198. Acute Poisonings Admission to a General Intensive Care Unit: A Five-Year Report

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Objective: The correct management of some poisoned patients may require admission to the Intensive Care Unit (ICU). We studied the ICU admission criteria in poisoned patients and the related features of poisonings. *Methods:* Five-year (July 1 2001- June 30 2006) observational study including all patients older than three years admitted to our general ICU with a main diagnosis of acute poisoning. We defined three criteria for ICU admission: the presence of an actual organ system dysfunction (group 1), the perception that significant organ dysfunction could appear in asymptomatic patients on the basis of toxicokinetics or toxicodynamic (group 2), and a clinical judgment for intensive observation in mildly symptomatic patients (group 3). *Results:* There were 49 poisoned patients (2.72% of admitted patients) and 63.3% were caused by miscellaneous agents. All toxic agents were confirmed by toxicological laboratory analysis. The number of patients was 39 for group 1, 4 for group 2 and 6 for the third group. The average length of ICU stay (in days) was 2.5, 1.1 ($P<0.05$ compared to group 1 with Wilcoxon test) and 1 ($P<0.05$ compared to group 1), respectively. Six patients died: three for massive paraquat ingestion, three due to a delay between ingestion and first aid (two 85-year-old patients for neurodepressant brain injury and one for ethylene glycol). For group 1 the poisons were mainly benzodiazepines (32.8%), tricyclic antidepressants (14.1%) and antipsychotics (10.9%). The main causes of vital function impairment were: respiratory failure (26: one patient required non-invasive ventilation and 23 intubation and ventilation), severe cardiovascular toxicity (4) and neurological dysfunction (9) with a Glasgow Coma Score <10. Group 2 included two fatal paraquat poisonings, a paracetamol ingestion successfully treated with N-acetylcysteine and an intentional digoxin IV injection. The last case was admitted asymptomatic with sinus rhythm to the ICU, after a digoxin-Fab treatment started in the Emergency Room for severe electrocardiographic changes. Forty hours post-injection, an atrioventricular dissociation appeared, probably due to a rebound in free digoxin levels. Group 3 included six patients, discharged after good recovery, poisoned by: benzodiazepines and tricyclics, phenobarbital and orphenadrine, ammonia, ethanol, digoxin, olanzapine. No ventilatory support was used in this group. *Conclusion:* A five-year experience based on a rational approach to ICU admission in poisoned patients is described. Many poisonings (79.6%) presented an immediate life-threatening nature, while for patients who were asymptomatic or minimally symptomatic at admission, ICU stay was chosen for observation and treatment due the unpredictable clinical course.

199. Acute Poisoning in Infants - Epidemiological Study in a Period of 5 Years

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Objective: To describe the clinical and epidemiological characteristics of acute poisoning in infants admitted to a Paediatric Toxicology Department in a period of 5 years. *Methods:* We analyzed all cases of acute poisoning concerning children less than 1 year old admitted to our department between 2001–2005. The following criteria were used in order to obtain a complete description: patient age, sex, type of substance, route of exposure and symptom severity. Infants were divided according to the age into three groups: neonates (0–1 month old, 2–6 months old and 7–12 months old). *Results:* 176 infants with acute accidental poisoning were admitted to our department between 2001–2005. The repartition by age was the following: neonates: 39 cases (22.54%); 2–6 months old: 89 cases (50.56%); and 7–12 months old: 48 cases (27.27%). There were 94 boys (53.40%) and 82 girls (46.60%). The substances involved were the following: nitrites (contained in water used for preparing food) 78 cases (44.31%), nasal decongestants (naphazoline and ephedrine) 28 cases (15.9%), carbon monoxide 27 cases (15.34%), medicines 22 cases (12.50%), caustics 8 cases (4.54%), pesticides 5 cases (2.84%), colored substances 3 cases (1.70%), Dentocalmin 2 cases (1.13%), chloramine 2 cases (1.13%), and mushrooms 1 case (0.56%). The routes of exposure were represented by: ingestion 125 patients (71.59%); inhalation 28 cases (15.34%); and nasal administration 23 cases (13.07%). According to the poisoning severity score (PSS) we noted the following repartition: 0 no symptoms 7 cases (3.97%); 1 minor 9 cases (5.11%); 2 moderate 42 cases (23.86%); 3 severe 114 cases (64.22%); and 4 fatal 4 patients (2.84%). The fatal cases were caused by: caustics 2 cases, mushrooms 1 case and nitrites 1 case. *Conclusion:* The majority of infants with acute poisoning presented with severe symptomatology. Nitrites from water still remain the most common agents in poisoning at this age. Therefore acute poisoning in infants must receive special attention in toxicologists, general public and authorities. *References:* 1. Bedry R, Lians B, Daniel V, Fayon M. Guide Pratique De Toxicologie Pediatrique-Arnette 2002. 2. Bates N, Edwards N, Roper J, Volans G. Paediatric Toxicology 1997.

200. The Patern of Acute Poisonings in Poland During the Period 1997–2001

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Objective: In 1967, the Ministry of Health decided to set up a network of toxicological centres. Toxicological centres (T.C.) send data on the treated patients to the National Poison Information Centre (N.P.I.C.). The data are analysed at the N.P.I.C. In 1996 N.P.I.C. decided to collect data on patients treated at T.C. and those treated at other health care units but who consulted a T.C. specialists. *Methods:* Data from the Polish T.C. (Gdansk, Krakow, Lublin, Lodz, Poznan, Rzeszow, Sosnowiec, Szczecin, Tarnow, Warsaw, Wroclaw) for 1997–2001 were collected to prepare our current analysis. The collected data refer to patients hospitalized in 1997–2001 at the regional Polish T.C. and patients for whom a consultation (in 1997–2001) was made to specialists of those centres but treated at other health care units (over 113,000 patients). *Results:* The analysis shows that drugs constituted the most frequent cause of the poisonings (over 45% all poisonings), in particular sedative-hypnotic drugs (mainly benzodiazepine derivatives), anticonvulsants, and psychotropic drugs (mainly phenothiazine derivatives). Poisonings by alcohols accounted for 16.9 - 20.2%, by gases (primarily by carbon monoxide) 4.7–6.2%, by street drugs 3.5–5.9%, by pesticides 3.1–5.1%, and by organic solvents 3.3–4.5% of total poisonings. Suicidal poisonings constituted nearly 34% of total poisonings, accidental 25%, poisonings resulting from street-drugs, and alcohol abuse over 23%. Chemical accidents or fire has been considerably reduced from 1% in 1997 to 0.4% in 2001. Suicidal poisonings dominated in the 15–30 age group. Accidential poisonings were most frequent among children below 15, while abuse-related poisonings dominated in the 30–50 age group. The highest numbers of deaths were recorded after intake of drugs (212), alcohols (166), and *Amanita phalloides* (26). The highest fatality was recorded for the intake of ethylene glycol (over 28% all treated ethylene glycol cases). *Conclusion:* Results of this analysis enable observation of the trends in poisonings by various chemicals. The results are useful in planning steps to be taken in order to prevent the poisonings.

201. Epidemiology of Acute Renal Failure in Toxicology Centre

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Objective: Acute renal failure is a frequent complication of acute poisonings, which may cause high mortality and difficulties in treatment. *Methods:* The acute renal failure incidence in poisoned patients in a Regional Toxicology Centre in the period 2003–2006 was analyzed retrospectively. Therapy included intermittent haemodialysis treatment in all cases. *Results:* 4,726 patients with acute poisonings were admitted to our Centre in the period of 3 years and 10 months. 124 patients (2.6%) with acute renal failure requiring haemodialysis treatment were included in the study. There were 103 men and 21 women, mean age - 41.4 years (range 16 to 76 years). Haemodialysis treatment was carried out in all cases - 812 procedures, mean 6.5 procedures per case. The mortality rate was 29.8% (37 patients). The causes of the acute renal failure were the following: acute poisoning with 70% acetic acid - 25% (31 patients), ethylene glycol poisoning - 6.5% (8 patients), other alcohol poisonings - 21% (26 patients), rhabdomyolysis - 43.5% (54 patients), mushroom poisoning - 0.8% (1 patient), and hemorrhagic fever with renal syndrome - 3.2% (4 patients). The greatest mortality rate was in the cases with acute 70% acetic acid poisoning - 54.8% as a result of gastrointestinal bleeding. In other cases of acute renal failure the mortality was 21.5%. The number of patients with acute renal failure increased from 51 in 2003–2004 to 73 cases in the period of 2005–2006: patients with acute poisoning with 70% acetic acid - from 11 to 20 cases, and rhabdomyolysis from 20 to 34 cases, but the mortality decreased from 33.3% to 27.4%. Factors decreasing mortality were early haemodialysing treatment and anticoagulation with 4% sodium citrate in extracorporeal circuits. We have had some good results in the patients with severe complications such as shock and bleeding by using lowflow haemodiafiltration. *Conclusion:* Presence of a haemodialysing service in the toxicology centre permits us to treat patients with acute poisonings and acute renal failure early and more selectively.

202. Different Levels of Care for Poisoned Patients in Oslo - A One-year Prospective Study

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Objective: Many acute poisonings in Oslo are treated by ambulance personnel or in an outpatient clinic (Oslo Emergency Ward) as the highest level of care. Our aim was to study this group, and compare with poisonings treated in hospitals. *Methods:* One-year prospective cross-sectional multi-center study including all patients >16 years with a main diagnosis of acute poisoning, treated by Oslo Ambulance Service, Oslo Emergency Ward (outpatient clinic) or by one of the four emergency hospitals in Oslo. Each episode (case) in this study was represented by contact from the highest level of care (hospitals > outpatient clinic > ambulance service). Cases transferred from one level of care to a higher without registration from the latter ("lost to follow-up") were excluded from the calculations. *Results:* There were 3,775 contacts as a result of 3,025 poisoning episodes. Among the 1,870 ambulance cases, 743 (40%) were treated and left at the scene, 15 (0.8%) died at the scene, and 1,112 (59%) were transferred to a higher level of care where 650 (35%) were registered, while 462 (25%) were lost to follow-up and excluded. Among the 958 outpatient clinic cases, 802 (84%) had this as the highest level of care, 156 (16%) were transferred to hospital where 94 (10%) were registered, while 62 (6%) were lost to follow-up and excluded. In hospital, a total of 947 admissions of 941 episodes were recorded, of which 10 died. Median age was 38 years in outpatient clinic and 37 years in hospital, slightly more than 35 years in the ambulance group (p=0.017). Male majority in ambulance (70%) and outpatient clinic (69%) differed from male minority in hospitals (46%, p<0.001). Ethanol poisonings were mainly treated in the outpatient clinic, n=439 (ambulance n=167, hospital n=161). Opiates were most commonly treated by the ambulance service, n=542 (outpatient clinic n=189, hospital n=68), while poisonings by medicines were most commonly treated in hospitals, n=549 (outpatient clinic n=83, ambulance n=22). Coma (GCS<8) were more frequent in ambulance (37%) than in hospital (24%, p<0.001), than in the outpatient clinic (10%, p<0.001). Naloxone was given to 49% in ambulance (the only ambulance antidote), and naloxone or flumazenil were given to 4% in outpatient clinic and to 27% in hospital. *Conclusion:* More than half of all acute poisonings were treated outside hospital. They were often related to drug- or alcohol abuse and with a male dominance. A large proportion of opiate overdoses, frequently comatose, were treated with antidote by ambulance service without admission to hospital.

203. The Impact of Menstrual Period of Women in Committing Intentional Poisonings

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Background: Intentional poisonings are more common in women in northeast Iran (1). There is much information on the effect of hormonal changes on biological and psychological changes during the menstrual cycle (2). However, the frequency and association of suicidal attempts in regard to menstrual cycle has not previously been evaluated in Iran. *Methods:* All eligible female cases with intentional suicidal attempts were studied prospectively from the first of July 2006 to September 31, 2006. All subjects with irregular menstrual period (less than 21 and more that 28 days), menopausal, use of oral contraceptive, and accidental overdoses were excluded. All cases were interviewed by a psychiatrist. The menstrual cycle was divided into 4 phases: 1) menstrual follicular, 2) late follicular, 3) early luteal, and 4) late luteal. *Results:* Overall, 134 cases were included. Mean (SD) age was 22.6 (6.8). Among them, 51% were married and 67% had no previous suicidal attempts. Figure 1 shows the frequencies of suicide attempts in relation to the four phases of mensutration. As can be seen in menstrual follicular and late luteal phases the frequencies are higher. These together are significantly more common than late follicular and early luteal phases (P<0.001). Being married or previous suicidal attempts had no effect on the results. *Conclusions:* Self harm using poisons was more common in the early follicular and late luteal phases of the menstrual cycle. These findings were independent of marital status and history of previous self harm attempts. These findings are also consistent with previous studies (2) and compatible with low estrogen and progesterone levels in these phases. High risk

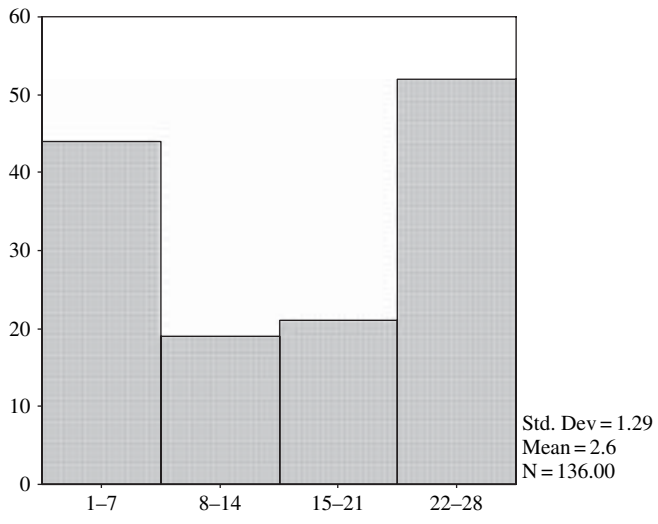

Fig. 1. Frequency of suicidal attempts in relation to the menstrual period.

patients should be advised to be aware of potential impulsive behavior in these menstrual phases. *References:* 1. Afshari R, Majdzadeh R, Balali-Mood M. Pattern of acute poisoning in Mashhad, Iran 1993–2000. J Toxicol Clin Toxicol 2004; 42:965–75. 2. Caykoylu A, Capoglu I, Ozturk I. The possible factors affecting suicide attempts in the different phases of the menstrual cycle. Psy Clin Neurosci 2004; 58:460–4.

204. Beware: National Epidemics can Cross International Borders - The Need for Toxicovigilance

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Objective: In September 2006, diethylene glycol (DEG) was used inappropriately in Panama as a cough preparation diluent instead of glycerine, and came to international attention after 34 fatalities were publicized (1,2). Although dispensing of this product was limited to Panama, the ease of international travel raises the spectre of multinational epidemics. Since its initial use as an industrial solvent in 1928, DEG has been increasingly used outside of industry because of its low cost of production (3). Multiple DEG poisoning epidemics have been reported and patients usually present initially with gastrointestinal symptoms followed by flank pain, anuria, coma and occasionally seizures (4). *Case Report:* A 47-year-old woman presented to her primary care doctors office with complaints of generalized weakness, easy fatigability, nausea, and vomiting. Two weeks earlier, while on vacation in Panama, she started using a cough preparation obtained from a local pharmacy for a presumed viral syndrome. Her physical examination was unremarkable other than coryza and an occasional cough. Her laboratory studies and chest radiograph were normal. She mentioned to her doctor that her sister reported that a cough preparation in Panama had been making people sick, which prompted a call to our center. The patient had consumed about 40mL. The medication manufacturer, name, lot number, and manufacture date matched the Panamanian product according to CDC information. The bottle, 'Expectorante sin Azucar' was sent to our center for testing by GC. It contained 6.8% DEG. She never developed other manifestations of poisoning. *Conclusion:* This case illustrates how epidemics can cross international borders and highlights the critical role of the clinical toxicologist and poison center in toxicovigilance and the need to inquire about travel history. The excellent outcome of this patient may not have occurred if the toxic product was not rapidly identified and its use discontinued. *References:* 1. Lacey M, Grady D. Panama Journal: A killer in a medicine bottle shakes faith in government. New York Times – October 5th, 10th, 13th, 15th & 16th, 2006; World News. 2. Roig-Franzia M. Intended tainting suspected in 21 deaths in Panama. Washington Post – October 13th, 2006; Page A18. 3. Alfred S, Coleman P, Harris D, et al. Delayed neurologic sequelae resulting from epidemic diethylene glycol poisoning. Clin Toxicol *2005*; 43:155–9. 4. Wax PM. It's happening again- another diethylene glycol mass poisoning. J Toxicol Clin Toxicol 1996; 34:517–20.

205. Accidental Paraquat Poisoning: A Severe Case with Successful Management

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Objective: Paraquat (P) poisoning is a potentially serious event that could require, in the absence of a specific antidotal treatment, the use of invasive procedures and aggressive pharmacological therapies. Among 218 cases of exposure to pesticides referred to Pavia Poison Control Centre over a 5-month period in 2005, 5 (2.3%) were of P exposure. Among these, 2 were fatal voluntary ingestions and 2 accidental non toxic exposures: we describe the fifth case in which all the available treatments were applied. *Case Report:* A 46-year-old man affected by chronic obstructive bronchopneumopathy (COPD) was admitted to emergency room 1.5 hour after accidental ingestion of about 80 ml of a 11.7% P and 5.9% diquat solution. At admission the patient was asymptomatic; neither pharingodinia nor vomiting was reported. Arterial blood pressure and gas analysis were normal. Gastric lavage, activated charcoal and cathartics were immediately practised. Fuller's earth solution every 2 hours for one day, forced diuresis, N-acetylcysteine (NAC, 150 mg/kg i.v. followed by 300 mg/kg/day for 10 days), and vitamin C (4g/day for 15 days) were promptly administered. P blood level at 8 hours after ingestion was 1.9 mg/L, so three charcoal hemoperfusion (HPc) sessions were carried out. At the end of HPc, a pulsed cyclophosphamide-methylprednisolone therapy (cyclophosphamide 15 mg/kg/day for 2 days and methylprednisolone 1g/day for 3 days) was started. Vitamin E (600 mg/day for 30 days) was started by day 4. P blood levels at day 4 and 8 results were undetectable. Pulmonary function tests, gas analysis, and chest radiographs during hospitalization were compatible with the patient's disease (COPD). The patient remained always asymptomatic and was discharged at day 15 with dexamethasone 30 mg/day for 45 days, followed by 12 mg/day for 3 months. At follow-up, pulmonary and liver function tests, gas analysis (repeated one time a week up to 3 months after discharging) and repeated chest radiographs resulted without abnormalities: at 8 months the patient's follow-up was stopped. *Conclusion:* P poisoning is often associated with a dramatic clinical course. HPc can reduce P plasma level and NAC, antioxidants and corticosteroids, especially combined with cyclophosphamide may offer some benefits by preventing oxidative damage and pulmonary fibrosis. In this case, the mortality rate related with patient's plasma level was about 80–90% (1); early diagnosis, decontamination and subsequent treatment may have played a discriminant role for the successful management. *Reference:* 1. Proudfoot AT, Stewart MS, Levitt T, et al. Paraquat poisoning: significance of plasma-paraquat concentrations. Lancet 1979; i:330–332.

206. Metabolic Acidosis in Prometryn Poisoning

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Objective: Prometryn is a triazine herbicide, which is one of the most extensively used groups of herbicides. The mechanism of acute triazine herbicide toxicity in humans is not known. We report a first case of acute prometryn poisoning. *Case Report:* A 62-year-old male ingested 50 g of prometryn and ethanol in a suicide attempt. On arrival two hours after ingestion, he was somnolent and vomited. Seven hours after ingestion laboratory tests showed metabolic acidosis with a calculated anion gap of 47.5 mmol/L and lactate of 23.4 mmol/L. Gas chromatography/mass spectrometry revealed serum prometryn concentrations of 48.1 mg/L. Hemodialysis corrected metabolic acidosis, but the serum prometryn concentration increased to 67.7 mg/L. The lactate level after hemodialysis was 11.7 mmol/L and returned to within normal limits 47 hours after ingestion. The patient was discharged without any sequelae after psychiatric evaluation. *Conclusion:* In high anion gap metabolic acidosis we should consider poisoning with prometryn and other triazine herbicides. Hemodialysis corrects metabolic derangements, but it does not lower serum prometryn concentration.

207. Enhanced Monitoring of Paraquat Exposures by TOXBASE. The NPIS Pesticide Surveillance Project 2004–2006

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Objective: To describe paraquat exposures during the first two years of the NPIS TOXBASE pesticide surveillance project. *Methods:* All patient related accesses to pesticides of interest on TOXBASE between 1 April 2004 and 1 April 2006 were automatically notified electronically to NPIS Edinburgh. Enquirers were asked to complete an on-line questionnaire or paper questionnaire printed at the time or sent subsequently. All pesticide telephone enquiries to NPIS Edinburgh were also followed up. Enquiries from outside the UK, and those involving animals were excluded. Paraquat exposures were analysed for circumstances and symptoms in adults and children. *Results:* Data on 92 cases of exposure were captured. 75 exposures were accidental (50 male, 24 female, 1 not reported) and 17 deliberate self-harm (11 male, 6 female). Of the accidental exposures, 58 were adults, 10 children (<13yrs), in 7 age was not reported. 19 patients were exposed via ingestion, 16 by inhalation, 14 by skin contact and 4 from eye contact. A further 19 were exposed from multiple routes of exposure. 3 questionnaires did not record a route of exposure. Severity was graded by respondents as 1 major, 9 moderate, 22 minor, 5 uncertain. In 38 cases no severity score was offered. To record circumstances of exposure the respondents were offered various options of which they could mark any or none. Where reported, 32 patients were exposed whilst using the product themselves, 4 whilst the product was in use by another person, 6 were exposed after the pesticide was applied and 13 were exposed due to unsatisfactory storage. 13 were occupational exposures. One death was recorded following accidental ingestion. Of the 58 adults accidentally exposed 28 were using the product themselves, 2 whilst in use by another person. 2 were exposed after the pesticide had been applied. 9 were exposed due to unsatisfactory storage. 45 (77.6%) were symptomatic. Of 10 childhood exposures 1 occurred whilst someone else was using the product, 3 after the pesticide had been applied and 3 were exposed due to unsatisfactory storage. 4 (40.0%) were symptomatic. All 17 deliberate self-harm exposures were ingestions. Respondents graded severity as 6 major, 1 moderate, 4 uncertain and 6 were not marked. Two deaths were recorded. *Conclusion:* More males than females were exposed to paraquat in both accidental and deliberate self-harm cases. Adults were nearly twice as likely as children to be symptomatic. Respondents graded deliberate self-harm exposures as being more severe than accidental exposures. Deaths occurred from both accidental and deliberate ingestions. In adults most accidental exposures occurred during product use. Most children were exposed due to unsatisfactory storage or after the pesticide had been applied.

208. Colorimetric Detection of Urinary Diquat: In Vitro Demonstration

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Introduction: Bipyridyl compounds (e.g. paraquat and diquat) are commonly used as herbicides, and have the potential for severe toxicity after ingestion (1). Diquat is associated with acute renal failure in addition to mucous membrane and GI irritation (2). The addition of sodium dithionite to alkalinized fluid specimens can help detect the presence of paraquat or diquat if these compounds are present in sufficient concentrations. The test sample turns blue to deep purple in the presence of paraquat and yellow-green in the presence of diquat. The intensity of the color change is dose-dependent and well described for paraquat. *Objective:* Using a test kit for paraquat containing sodium bicarbonate and sodium dithionite, we were able to demonstrate the dose-dependent color changes associated with different concentrations of diquat in urine specimens. *Methods:* Roundup Herbicide Weed and Grass Killer (Monsanto Corporation) with active ingredients diquat dibromide (0.73% by weight) and glyphosate (18% by weight) was obtained from a garden-supply store in the United States. Quantities of diquat-containing solution were added to the urine specimens to yield ten different concentrations of diquat (730 mg/L, 365 mg/L, 219 mg/L, 73 mg/L, 51.1 mg/L, 36.5 mg/L, 21.9 mg/L, 7.3 mg/L, 3.65 mg/L, 0.73 mg/L) in a total volume of 10 mL. Samples of unadulterated urine served as negative control specimens, and Roundup Herbicide with only glyphosate (2%) was diluted 1:1 v/v to control for the possible confounding effect of glyphosate. Dry powder formulations of sodium bicarbonate and sodium dithionite were obtained from paraquat test kits (Syngenta, UK). Sodium bicarbonate (1 gram) was added to each specimen. After approximately 2 minutes, sodium dithionite powder (1 gm) was added and gently agitated. Plastic vials were used to prevent adsorption of the compound to glass. This procedure was repeated with urine specimens from three healthy adult males. *Results:* A green color with dose-dependent intensity was detected in all of the diquat containing specimens, but not in the urine and glyphosate-only controls. Similar results were obtained with two other urine specimens from different individuals. This green tint was transient, fading after approximately 30 minutes in the specimens with the two lowest concentrations of diquat. *Conclusions:* This qualitative technique is not intended to replace quantitative measurement of diquat levels in urine or blood specimens. However, in situations where more formal testing is not readily available and the diagnosis of diquat is suspected, the use of this simple test may aid in rapidly confirming the diagnosis of exposure. *References:* 1. Vale JA, Meredith TJ, Buckley BM. Paraquat poisoning: Clinical features and immediate general management. Hum Toxicol 1987; 6:41–7. 2. Jones GM, Vale JA. Mechanisms of toxicity, clinical features, and management of diquat poisoning: A review. J Toxicol Clin Toxicol 2000; 38:123–8. *Acknowledgements:* Syngenta Corporation (UK) provided the

Fig. 1. Addition of sodium bicarbonate and sodium dithionite to urine specimens containing decreasing concentrations of diquat. Numbers represent: 1: urine control; 2: 730 mg/L, 3: 365 mg/L, 4: 219 mg/L, 5: 73 mg/L, 6: 51.1 mg/L, 7: 36.5 mg/L, 8: 21.9 mg/L, 9: 7.3 mg/L, 10: 3.65 mg/L, 11: .73 mg/L, and 12: glyphosate-only control.

bicarbonate/dithionite testing kits. Roundup Herbicide Weed and Grass Killer is a product and registered trademark of Monsanto Corporation (USA).

209. Analysis of Organophosphate Insecticides Poisoning in an Emergency Department

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Objective: The use of organophosphate insecticides (OFI) without suitable safety measures implies a risk of poisoning. The purpose of the study is to describe the poisonings caused by OFI attended in the Emergency Department in the last three years (1,2). *Methods:* Retrospective study of OFI poisonings from 2003 to 2005. From each case, epidemiological data have been collected (day and time of visit, profession), toxicological (type of toxin, route of exposure, exposure time), clinical (symptoms and physical examination), analytical (cholinesterase plasma activity - CPA), treatment and discharge. *Results:* Data for 36 patients have been collected, average age 46 years, 35 of whom were males. The annual distribution was: 13 cases 2003, 14 cases 2004 and 9 cases 2005. As for the monthly distribution, 17 cases were seen in spring and 15 in the summer months. 85% of the patients were farmers, so the poisoning was a work accident. The route of exposure was skin and respiratory, but 2 suicide attempts were detected through the consumption of OFI orally. The more frequent clinical signs were nausea, vomiting and/or diarrhoea in 24 cases, sickness in 13, general feeling of discomfort in 10 and muscular weakness in 3 cases. The average heart rate was 65+/-16 bpm (extremes of 30 to 90). The average levels of CPA were of 4.112 U/L (extremes 0–10.543, normality 5.300–14.500 U/L). Half of the patients needed atropine and 33% pralidoxime. We proceeded to discharge patients from the Emergency Department in 22 cases, requiring their admission to the Internal Medicine room in 9 and Intensive Care Unit in 5. No lethal case was recorded. *Conclusion:* Poisoning caused by OFI has a seasonal distribution, it is an entity typical in males who work as farmers and it is caused by inhalation and skin contact with the agent. Nearly half of the patients require antidotal treatment and admission to hospital although in our experience, no lethal case was recorded. *References:* 1. Peter JV, Cherian AM. Organic insecticides. Anaesth Intensive Care 2000; 28:11–21. 2. Martin JC, Yelamos F, Laynez F, et al. Poisoning caused by organophosphate insecticides. Study of 506 cases. Rev Clin Esp 1996; 196:145–149.

210. A Simplified Acute Physiology Score in the Prediction of Acute Organophosphate Poisoning Outcome in an Intensive Care Unit

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Objective: To study the impact of the Simplified Acute Physiology Score (SAPSII) in the prediction of mortality in patients with acute OPP requiring admission to ICU of Loghman-Hakim Hospital Poison Center over a period of 24 months. *Methods:* This was a retrospective, case-control study of records of patients with acute OPP admitted to the ICU between January 2005 and December 2005. The demographic data were collected and SAPSII score was recorded. *Results:* During the study period, 24 subjects were admitted to the ICU with acute OPP. All 24 patients (15 male) required endotracheal intubation and mechanical ventilation in addition to gastric decontamination and standard therapy with atropine and oximes and adequate hydration. Of these 24 patients, 8 (5 male) died. SAPSII score was significantly higher in non-survival group than survival group. *Conclusion:* Mortality following acute OPP remains high despite adequate intensive care and specific therapy with atropine and oximes (1–3). One-third of the subjects needing intensive care die within the hospitalization period. SAPSII scores which were calculated within the first 24 hours were recognized as a good prognostic indicator among patients with acute OPP who required ICU admission. SAPSII score above 11 within the first 24 hours is a predictor of poor outcome in patients with acute OPP requiring ICU admission. *References:* 1. Jalali N, Pajoumand A, Abdollahi M, Shadnia Sh, Pakravan N. Pesticides poisoning: One-year report of Loghman-Hakim Hospital Poison Center. Progress in Medical Research 2003; 1:52. 2. Abdollahi M, Jalali N, Sabzevari O, Nikfar S, Fallahpour M. Pesticide poisoning during an 18-month period (1995–1997) in Tehran, Iran. IJMS 1999; 24:77–81. 3. Jalali N, Pajoumand A, Abdollahi M, Shadnia Sh. Epidemilogical survey of poisoning mortality in Tehran during 1997–1998. Toxicol Lett 2000; 116:309.

211. Pesticide Poisoning in Mashhad from 1997 to 2005

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Objectives: Despite regulation, pesticides are very easily available in Iran. Therefore, acute pesticide poisonings, either as intentional or accidental are common (1,2). The aim of this study was to determine the pattern change of pesticide poisonings in Mashhad over a six year period. *Methods:* All files from 2000 to 2005 and a systematic randomly selected 10% of all hospital-referred poisoned patients from 1997 to 1999 from Imam Reza University Hospital of Mashhad were studied retrospectively. *Results:* Pesticide poisoning cases were identified between 2000 and 2005, accounting for 4,118 (6.3% of all acute poisonings). These poisonings are gradually declining in Mashhad (see Table 1). Patterns of age, female preponderance, intentional mode, time of ingestion, and month of the year taken were stable during this period. Table 1 summarizes the pattern of pesticide poisoning in this centre. *Conclusions:* Acute pesticide poisoning is common in Mashhad, Iran. It is mainly intentional and most common in women. A decrease in prevalence of these poisoning in Iran, however, needs to be investigated and might be the result of replacement by other poisonings or new restrictive laws have been enacted. *References:* 1. Afshari R, Majdzadeh R, Balali-Mood M. Pattern of acute poisoning in Mashhad Iran 1993–2000. J Toxicol Clin Toxicol 2004; 42:965–975. 2. Afshari, R. Descriptive epidemiology of intoxication in Mashhad, Iran. 56–111. 2001. Health Faculty, Tehran University of Medical Sciences. Ref Type: Thesis/Dissertation.

212. Pattern of Pre-Hospital Treatment Received by Cases of Pesticide Poisoning

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Objective: Pesticides particularly organophosphates are commonly used as agricultural insecticides worldwide. Easy availability makes them a popular method for self-harm in the developing countries like Bangladesh. The aim of the study was to investigate the pattern of prehospital treatment received by the patients following pesticide poisoning and to assess the outcome. *Methods:* It was a prospective study, descriptive in nature conducted in one adult Medicine unit of Dhaka Medical College Hospital over a period of nine months from October 2005 to June 2006. Sixty patients enrolled consecutively during this period with definite history and clinical features of acute pesticide poisoning were the study subjects. Data were collected in an individual case record form. *Results:* The largest part of the patients came from the rural area (80%) with mean age of 24.7±8.8 years and 50% were married. Most of them (40, 66.7%) were male. 91.7% poisoning was intentional and familiar disharmony (45%) was the key underlying cause. Thirty five (58.3%) patients were educated and 41 (68.3%) patients purchased the pesticide themselves for self destruction. The brand of the poison could be identified in 32 (53.3%) cases: the most commonly used compound was malathion (31.2%) and chlorpyrifos (25%). 75% patients sought treatment in a public hospital before coming to the present place for management. 98.3% patients received stomach washout. Only 22 (36.7%) patients received first aid before arrival to hospital: 19 (31.7%) patients received induced vomiting by ingestion of tamarind water or lemon water or soap water or introduced finger or other substances like cowdung. 5% patients received a home remedy made from milk or raw eggs etc. The overall mortality rate was 16.7%. The majority of the patients (80%) died within the first 24 hours of admission and mostly due to acute cholinergic crisis (80%). *Conclusion:* Prehospital treatment following acute pesticide poisoning is not optimal and mortality following such poisoning is high in Bangladesh. Prompt recognition and early treatment is mandatory in acute poisoning. Measures

Table 1.

	Location	97	98	99	00	01	02	03	04	05
Insecticides[1]	Mashhad	340	200	240	436	387	337	236	247	163
Rodentocide[1]	Mashhad	60	80	80	39	44	60	23	30	23
Herbicides[1]	Mashhad	–	–	–	11	6	3	6	11	0
Overall[1, 2]	Mashhad	630	590	610	587	491	492	307	295	267
Female (%)	Mashhad	68.2	60.0	78.3	57.9	56.2	52.5	59.0	62.5	66.4
Accidental (%)	Mashhad	36.4	50.2	37.0	36.7	34.6	23.5	26.6	22.8	20.9
Ingestion (%)	Mashhad	84.8	94.2	90.9	82.1	90.2	94.3	92.5	95.6	95.7
Age mean (SD)	Mashhad	25.3 (14.7)	22.4 (12.2)	20.1 (13.4)	22.3 (14.4)	26.3 (15.5)	25.4 (14.2)	24.1 (13.9)	23.8 (13.9)	25.1 (13.3)
Time (mean (SD))	Mashhad	15.6 (7.0)	16.4 (5.7)	14.7 (6.9)	14.1 (6.4)	14.3 (6.8)	14.6 (6.0)	14.5 (6.0)	14.5 (6.9)	14.4 (6.0)
Month (mean (SD))	Mashhad	6.4 (3.7)	6.4 (3.6)	5.5 (2.6)	8.7 (2.0)	6.5 (5.9)	6.0 (2.6)	4.8 (2.0)	7.7 (1.6)	8.6 (0.8)

[1]Frequency of cases in each year.
[2]Fungicides, moluscocides, combination, and unknown in addition to the above ones.
–Data not available.

should be taken to increase the awareness among the general population regarding the first aid following pesticide poisoning. Immediate correct first aid and pre hospital treatment could reduce the mortality. *References:* 1. Faiz MA, Rahman MR, Ahmed T. Management of Acute Poisoning with organophosphorus insecticide. J Bang Coll Phys Surg 1994; 12:59–62. 2. Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. QJM 2000; 93:715–731.

213. A Clinico-Epidemiological Study on Pesticide Poisoning

Anwar S, Alam MS, Quddus MR, Majumder MMA, Khan ZM, Rahman M, Arif SM, Faiz MA. *Department of Medicine, Dhaka Medical College & Hospital, Dhaka, Bangladesh.*

Objective: To investigate the clinico-epidemiological aspects and to evaluate the immediate outcome of patients admitted with pesticide poisoning. *Methods:* Over a period of one year between January 2004 and December 2004, victims of pesticide poisoning admitted to one medical indoor department of Dhaka Medical College Hospital, Dhaka were enrolled. The diagnosis was based on history of pesticide ingestion and clinical features or with evidence of a brought specimen. The age, sex, marital status, occupation, cause of intoxication, poison consumed, time elapsed between ingestion and admission to the hospital, signs and severity of intoxication on admission, treatment and outcome were recorded on a pre-designed case record form. A total of sixty patients with pesticide poisoning were enrolled. After giving gastric lavage in the emergency department, all patients with suspected OPC poisoning were managed with atropine, pralidoxime and other supportive treatment also given. *Results:* The number of pesticide poisoning cases was 60 (1.37%) out of 4,378 admitted patients. The mean age was 23.38 ± 1.16 years. There were 24 (40%) males and 36 (60%) females, with male: female ratio being 2:3. 26 (43%) patients came from urban area and 34 (56%) patients from rural area. Incidence was high among students 21 (35%) and housewives 18 (30%). The most common reason for poisoning was suicide - 56 patients (93.3%). Sudden anger was the cause of suicide in 32 (53.3%) patients. 22 patients (36%) purchased poison over the counter and 28 (46%) patients used prior purchased poison for household use. The brand of poison was identified in 50% cases. The most commonly involved compound was malathion 15 (50%) patients. Only 15 (25%) patients presented within 2 hours of ingestion. All patients were managed with intravenous atropine. Pralidoxime was used in 38 (63.4%) cases. The mean amount of atropine used was 245.22 ampoules. The duration of hospital stay among the survivors was more than 5 days in 30 (63%) cases. The overall mortality was 21.7%. Majority of patients (9, 69.23%) died within the first 24 hours of admission. *Conclusion:* Acute pesticide poisoning is one of the commonest causes of death in the medical ward. To reduce this mortality proper management guidelines, proper training of physicians and other healthcare workers could be sought. More research work should be performed to determine the best therapy and improve survival. *Reference:* 1. Karim SA, Faiz MA, Nabi MN. Pattern of poisoning in Chittagong Medical College Hospital. JCMCTA 1993; 4:10–14.

214. The Recovery of Erythrocyte Acetylcholinesterase Activity in Patients Intoxicated with Dichlorvos

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Objective: As it has been known that every organophosphate insecticide has different toxicity in humans, a study in a single agent may have an important meaning for understanding organophosphate intoxication. We investigated the recovery of erythrocyte acetylcholinesterase (AChE) activities in patients intoxicated with dichlorvos in order to see whether their recovery patterns are similar or not. *Methods:* The medical records of 34 patients who ingested dichlorvos in suicidal attempts were retrospectively reviewed. Their erythrocyte AChE activities were measured more than twice during the treatment period. For all patients, orogastric lavage was performed and activated charcoal was administered on arrival at the emergency room. One gram of 2-PAM was administered every 6 hours and continued until the patients became clinically free from cholinergic symptoms and signs. Atropine doses were adjusted according to their severity of intoxication based on the erythrocyte AChE levels. The AChE levels of all patients were measured on arrival and on the next day, and thereafter the follow-up levels were measured twice a week in 17 patients. *Results:* The initial mean AChE level of patients at the time of admission was 13.1 (SD 1.4) U/gHb. The changes of AChE activities were remarkable over the first 24 hours after the ingestion of dichlorvos. Nineteen patients showed rapid increase of AChE the rate of which is higher than 3.0 U/gHb/day and their mean increase rate was 11.3 (SD 1.7) U/gHb/day. Another 6 patients showed slow increase at the rate of 1.0 (SD 0.2) U/gHb/day. The AChE levels in the rest of the patients decreased at the rate of 3.0 (SD 0.8) U/gHb/day. However, the increase rates of AChE after the first day were very slow and the mean rate was 0.5 (SD 0.1) U/gHb/day. The mean time intervals between the ingestion of dichlorvos and the administration of 2-PAM was 3.1 (SD 0.6), 5.3 (SD 1.9) and 1.8 (SD 0.3) hours in patients with rapid increase, slow increase and decrease of the AChE levels respectively. *Conclusion:* The AChE of patients intoxicated with dichlorvos seems to be reactivated when treated within about 3 hours after the ingestion. A decrease of AChE level during the first day of the ingestion may be seen when the blood sample is obtained too early or the amount of dichlorvos is large, even though the 2-PAM is administered early.

215. Forecast Factors for Admission or Discharge in the Acute Organophosphate Compounds Poisoning

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Objective: The toxic effects of the organophosphate insecticide (OFI) have been known for more than 50 years. In spite of this, there are no objective parameters that allow us to forecast which are the most severe poisonings or those which can develop late complications (1,2). *Methods:* Retrospective study of OFI poisonings from 2003 to 2005. From each case, epidemiological data have been collected (day and time of visit, profession), toxicological (type of toxic, route of exposure, exposure time), clinical (symptoms and physical examination), analytical (cholinesterase plasmatic activity - CPA), treatment and discharge. A comparison has been made between those patients who needed admission to hospital against those who were discharged from the Emergency Department (ED). *Results:* Data for 36 patients have been collected and three groups of patients have been detected: Group A or discharge from ED (n = 22), Group B or admission to Internal Medicine room (n = 9) and Group C or admission to an Intensive Care Unit (n = 5). From the clinical manifestations, differences regarding the existence of muscular effects (weakness) were found: 4% in Group A, 33% in Group B (p = 0.06) and 60% in Group C (p = 0.01); syncope history: 0% in Group A, 22% in Group B (p = 0.07) and 60% in Group C (p = 0.003); and in the heart rate, which was significantly lower in Group C (50+/-23 bpm) than in the rest (Group A 67+/-12 bpm and Group B 66+/-12 bpm, p = 0,04). The administration of atropine was necessary in 30% of patients in Group A, 66% in Group B (p = 0.11) and 100% in Group C (p = 0.009) and pralidoxime in 9%, 55% (p = 0.01) and 100% (p = 0.0003) respectively. The CPA was 6.281 U/L in Group A, 2.701 U/L in Group B (p = 0.004) and 232 U/L in Group C (p = 0.0001 and p = 0.021 respectively). *Conclusion:* The combination of syncope or weakness, the existence of bradycardia, the need for a treatment with antidotes and lower CPA are factors that forecast the admission to hospital due to OFI poisoning. *References:* 1. Nouira S, Abroug F, Elatrours S, et al. Prognostic value of serum cholinesterase in organophosphate poisoning. Chest 1994; 106:1811–1814. 2. Aygun D, Doganay Z, Altintop L, et al. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. J Toxicol Clin Toxicol 2002; 40:903–910.

216. Time-series Analysis of Cholinesterase Levels in Patients with Organophosphate Poisoning

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Purpose: Previous studies have reported that plasma cholinesterase (AchE) measurements could be one of the useful parameters for prognosis of acute organophosphate (OP) poisoning. However, there has been considerable disagreement regarding the prognostic usefulness of AchE in OP poisoning. Earlier studies were plagued with cross-sectional and one-point time methodological flaws making it difficult to interpret their results. The purpose of this study was to investigate the prognostic value of time-variable cholinesterase levels and their relationship with clinical outcomes in OP poisoning. *Methods:* We reviewed medical and intensive care records of patients with acute OP poisoning admitted to the emergency department between March 1998 and September 2006. We collected patient information regarding poisoning, clinical, and demographic features. Patients were assessed according to clinical outcomes and their AchE levels on days 1, 2, 3, 5, 7, and the last day. *Results:* During the study period, 58 patients were enrolled in this study. There was a significant difference between the AchE levels on days 1 - 3 of the patients requiring mechanical ventilation and of patients with moderate poisoning ($p<0.005$). Also, decreased logarithmic AchE levels correlated with longer durations of mechanical ventilation ($r = -0.411$, $p = 0.002$) and the development of intermediate syndrome. The decline of AchE levels on days 1 - 3 was recognized as a poor prognostic factor by Log-rank survival analysis ($p<0.005$). *Conclusion:* In acute OP poisoning, measurements of time-variable AchE levels could be helpful in the prediction of development of intermediate syndrome, duration of mechanical ventilation and the patient's survival.

217. Fatality After a Single Dermal Application of Lindane

Sudakin DL. *Veritox Inc., and Oregon State University, Corvallis, Oregon, USA*.

Objective: Lindane is an insecticide used for the treatment of scabies in the United States. The US FDA has approved lindane as "second-line" therapy, when less toxic alternative treatments have failed or are contraindicated. Seizures and neurological complications have been reported from the therapeutic use and misapplication of lindane. The product labelling instructs to wash lindane off the skin after 8 to 12 hours, and to not apply to open wounds, cuts, or sores. This case report describes a 66 year old male who developed progressive neurological symptoms and severe hypoxic encephalopathy after a single dermal application of lindane. *Case Report:* An adult male was admitted to a hospital for a urinary tract infection and mental status changes. Scabies was clinically diagnosed. An order was written to apply lindane 1% to the skin from the neck to the toes. An order was not written to wash lindane from the skin after its application. Fresh scratch marks were documented throughout the patient's body. At the time of application, the patient was awake and conversant. Eight hours after the application, family members reported an acute worsening in the patient's mental status. Hypoxemia (oxygen saturation of 87%) was documented. 9.5 hours after the application, the patient had a seizure. Within another hour, the patient was non-conversant, diaphoretic, tachycardic, and hypoxemic (oxygen saturation 88%) on supplemental oxygen. 11 hours after application, the patient became hypotensive (73/48). He was transferred to a critical care unit where he remained severely hypotensive for several hours, despite the use of pressors. Repeated seizure activity was observed. Arterial blood gases after admission to the ICU revealed severe respiratory acidosis (pH 6.94, CO_2 84, O2 196). Blood cultures were obtained and a lumbar puncture was performed. The results did not confirm bacteremia or meningitis. He was afebrile, with no significant abnormalities in the white blood cell count. Lindane toxicity was not considered in the differential diagnosis. Within several hours after admission to the ICU, the patient's blood pressure returned to baseline. Persistent myoclonic jerking movements were noted. An MRI did not reveal an acute infarct, hemorrhage, or other structural CNS abnormality. An EEG showed severe generalized cerebral dysfunction. The patient's mental status never returned to baseline. He remained intubated in the ICU, and later developed infectious complications. He expired 50 days after admission. Blood testing for lindane was never performed. The diagnosis at autopsy was hypoxic ischemic encephalopathy from lindane poisoning. *Conclusion:* Health care professionals should be aware of the risks associated with lindane, and comply with product instructions when prescribing this medication.

218. Pesticide Exposure in the Czech TIC from 1997 to 2005

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Objective: To describe the development of the frequency and severity of exposures to pesticides, based on calls to the Toxicological Information Centre (TIC) for a population of

Table 1. Pesticide exposure in the Czech TIC from 1997 to 2005.

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Insecticides	224	291	335	189	198	217	192	183	153
Rodenticides	102	140	105	142	136	150	105	118	164
Herbicides	–	–	–	83	109	117	78	77	89
Other*	326	431	440	524	565	675	492	473	479
Female %	38.7	42.0	37.5	40.8	38.1	37.7	42.8	40.9	41.8
Accidental %	82.4	85.6	91.3	88.0	93.3	92.4	89.2	92.0	88.3
Ingestion %	81.7	86.0	82.5	83.8	85.8	85.2	82.1	81.5	86.0
Age (mean, SD)	22.9 (14.4)	21.8 (20.4)	23.0 (19.9)	22.9 (14.4)	25.7 (27.6)	26.6 (30.9)	29.9 (20.3)	27.6 (24.6)	24.6 (27.1)
Time (mean, SD)	15.5 (7.0)	16.4 (5.7)	14.7 (6.8)	13.9 (7.7)	14.1 (8.3)	14.6 (10.7)	14.1 (6.6)	14.1 (6.6)	14.5 (7.9)
Month (mean, SD)	6.9 (4.2)	6.5 (5.3)	6.3 (4.8)	6.8 (6.6)	6.6 (7.7)	6.6 (9.1)	6.4 (5.8)	6.4 (6.1)	6.4 (5.6)

*Fungicides, moluscocides, combination, or unknown pesticides.
–Data not available.

approximately 10 million. *Method:* Data taken from TIC database from periods 1997–2005 were evaluated retrospectively using electronic evidence system. *Results:* Overall there were 4,405 pesticide poisonings in this period and accounted for 6.3% of total calls to TIC. 48% of calls concerned adults, 40% children, and 12% animals. These calls slowly decreased from 7.8% in 1997 to 5.0% in 2005. The detailed data is given in Table 1. About 79% of all exposures occurred in the growing period from April to October, and only 21% calls in the other months. Pesticide poisoning was predominantly accidental overdose. Ingestion accounted for 84%, inhalation 13% and skin contamination 3%. There were 91% unintentional exposures, 6% suicidal, 2.3% occupational and 0.7% due to aggressive behaviour. A total of 0.3% of exposures were lethal. In 2005, only 14.4% of subjects were recommended for hospitalisation with 1/3 of them demonstrating symptoms. Antidotal treatment was recommended only in 1.6% of calls; 0.8% patients were given atropine, and other 0.8% phytomenadione. In 2005, only one lethal case was registered. It concerned post-mortem consultation due to suicide with pirimicarb. *Conclusions:* Acute pesticide exposure in our country is mainly accidental and has good prognosis in general, due to low toxicity of commercial products used. *Acknowledgement:* MSM0021620807

219. Non-specific Reporting of "Other" Pesticide Classifications in Annual Poison Control Center Statistics

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Objective: Annual reports of the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS) are an important source of epidemiological data for pesticide exposures in the U.S. Many researchers and regulatory agencies utilize TESS data, and its value depends upon obtaining and reporting the most accurate and specific information about chemicals in pesticide formulations. Pesticide incidents can be difficult to categorize due to multiple active ingredients and classifications. In addition, new pesticides have been introduced, some with different chemistries and modes of action. In some cases, TESS annual reports classify the pesticide implicated in exposure incidents into a non-specific category of "other." When reported in TESS reports in such a format, this presents challenges in interpreting the data from an epidemiological perspective. The purpose of this study was to review TESS annual reports and assess the trend of pesticide incidents reported to U.S. poison centers categorized into and reported as a non-specific classification of "other." *Methods:* Pesticide exposure data were extracted from TESS annual reports for the years 2001–2005. The proportion of the exposure incidents classified into the non-specific classification ("other") was determined annually for pesticides including fungicides, fumigants, herbicides, insecticides, repellents, and rodenticides. The data were also stratified by medical outcome (none, minor, moderate, major, death). *Results:* During the five-year period, the proportion of all pesticide exposure incidents classified and reported into the non-specific category of "other" was 11.5%. There was an annual increase in the proportion of pesticide incidents reported to U.S. poison centers classified as "other" from 2001 (9.8%) to 2005 (12.3%). Fungicides were the class with the highest proportion (40%-57%) of incidents categorized and reported as "other" in TESS data tables. Incidents involving herbicides and insecticides were also frequently (12.9%-17.3%) classified into the "other" category. Fungicides were the pesticide class where incidents reported as "other" in the data tables comprised the highest proportion of incidents associated with moderate, major, and death outcomes. For some fatal incidents reported in the data tables to have been caused by "other" classifications of pesticides, the subsequent abstract section of the TESS report provided the identify of the specific active ingredient in the formulation. *Conclusion:* The tabular data presented in the annual TESS reports frequently categorized pesticides into a non-specific classification. This presents challenges in the epidemiological interpretation of the data, particularly for incidents associated with significant clinical outcomes. The annual TESS reports would have enhanced utility if the data tables were expanded to include more specific information about the active ingredient implicated in pesticide exposure incidents.

220. High Dose of Permethrin Ingestion: A Case Report

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Introduction: Pyrethroids are synthetic derivatives of natural pyrethrins. These insecticides are highly effective contact poisons, and their lipophilic nature allows them to readily penetrate insect chitin (exoskeleton) and paralyze their nervous systems through Na^+ channel blockade. Pyrethroids are typically less toxic to mammals than to insects but systemic poisoning may occur. The most common symptoms are gastrointestinal (dysphagia, epigastric pain, vomiting), confusion, coma and seizure. (1) We present a case report of high dose ingestion of permethrin. *Case Report:* A 35-year-old man ingested 250 ml of an insecticide with 25 g permethrin in a suicide attempt. After 30 minutes he arrived in the emergency department, without any signs or symptoms. Vital signs were blood pressure 140/80 mmHG, heart rate 108 beats/min, an electrogardiogram demonstrated sinus tachycardia. An arterial blood gas reported pH 7.382, pCO_2 35.4 mmHg, pO_2 82.8 mmHg. After clinical evaluation, the patient was decontaminated with gastric lavage and activated charcoal administration and admitted to the intensive care unit where multiple-doses of activated charcoal (15 g every 4 hours) were administered. He developed diarrhoea (7 hours after ingestion) that persisted for 1 day. No clinical neurotoxicity such as tremor, hyper excitation, ataxia, convulsions or paralysis occurred, though these have been reported in permethrin-intoxicated animals. Blood and urine samples were obtained for evaluating permethrin's metabolite (3-phenoxybenzoic acid) levels using gas chromatography-mass spectrometry. The plasma concentrations of 3-phenoxybenzoic acid at 6, 18, and 30 hours were 22.147 mcg/ml, 8.863 mcg/ml and 1.848 mcg/ml respectively (first-order kinetics of elimination with a half-life of 4.22 h. Urine concentrations of 3-phenoxybenzoic acid at 6 and 30 hours were 1.784 mcg/l and 55.457 mcg/l. *Conclusion:* This case report confirms that permethrin is typically less toxic to humans than to insects, and the most common effects are gastrointestinal. *References:* 1. Yang PY, Lin JL, Hall AH, Tsao TC, Chern MS. Acute ingestion poisoning with insecticide formulations containing the pyrethroid permethrin, xylene, and surfactant: a review of 48 cases. J Toxicol Clin Toxicol 2002; 40:107–113.

221. Enhanced Monitoring of Pyrethroid Exposures by TOXBASE. The NPIS Pesticide Surveillance Project 2004–2006

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Objective: To describe pyrethroid exposures during the first two years of the NPIS TOXBASE pesticide surveillance project. *Methods:* All patient related accesses to pesticides of interest on TOXBASE between 1 April 2004 and 1 April 2006 were automatically notified electronically to NPIS Edinburgh. Enquirers were asked to complete an on-line questionnaire or paper questionnaire printed at the time or sent subsequently. All pesticide telephone enquiries to NPIS Edinburgh were also followed up. Enquiries from outside the UK, and those involving animals were excluded. Pyrethroid exposures were analysed for circumstances and symptoms in adults and children. *Results:* Data on 266 cases of exposure were captured. No deaths were recorded. 254 exposures were accidental (118 male, 134 female, 2 not reported) and 12 deliberate self-harm (5 male, 7 female). Of the accidental exposures, 124 were adults, 115 children (<13yrs), in 15 age was not reported. 92 patients were exposed via ingestion, 61 by inhalation, 26 by skin contact, 15 from eye contact and 1 "other route." 52 were exposed from multiple routes of exposure and 7 questionnaires were not marked. Severity was graded by respondents as 0 major, 9 moderate, 79 minor, 8 uncertain, 158 not recorded. To record circumstances of exposure the respondents were offered various options of which they could mark any or none. Of the 124 adults accidentally exposed 75 were using the product themselves, 9 were in use by another person, 22 were exposed after the pesticide had been applied and 4 were exposed due to unsatisfactory storage. 24 were occupational exposures. 91 (73.4%) were symptomatic. Common symptoms: mouth/throat – pain/irritation (21), nausea/vomiting (15), eye irritation (13), paraesthesia (13), skin irritation (8), headache (8), and shortness of breath (7). Of 115 childhood exposures 17 occurred whilst someone else was using the product and 29 after the pesticide had been applied. 18 were exposed due to unsatisfactory storage. 18 (15.7%) were symptomatic. Common symptoms: nausea/vomiting (5), eye irritation (3), abdominal pain (3), fever (2), diarrhoea (2), mouth/throat – pain/irritation (2), skin irritation (2). Of 12 deliberate self-harm exposures 10 were ingestions, 1 multiple routes, 1 unknown. Respondents graded the severity as 1 major (also ingested *Atropa belladonna*), 1 moderate, 3 minor, 1 uncertain. 6 not recorded. *Conclusion:* More females than males were exposed to pyrethroids in both accidental and deliberate self-harm cases. Adults were 4 times more likely to be symptomatic than children. The majority of respondents that answered the question considered the severity of the exposure to be minor. No deaths occurred from either accidental or deliberate exposures. In adults most accidental exposures occurred during product use.

222. Death after Ingestion of Surfactants: A Particular Risk for Patients Suffering from Dementia

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Case Report: In a state of mental confusion, a 79-year-old male ingested ca. 200 mL of a detergent containing surfactants at his home. Despite cardiopulmonary resuscitation (CPR), the patient died at the hospital within 60 minutes, from lung oedema. *Manifestations/*

Course: The mentally disabled patient had been staying at home alone during daytime. He had been attended once a day by a home care service and, in the mornings and evenings, by his relatives. He was found in the evening on his couch by his son, who noticed a "strange manner of speaking." The open bottle of the detergent and a cup with remains of the detergent were found on the floor. The quantity ingested amounted to about 200 mL. On his immediate admission to hospital, the patient was awake but did not show any adequate reaction. He suffered from pronounced dyspnoea and bubbling crepitation over the lung fields. Respiratory and circulatory arrest set in within ten minutes. The patient died in spite of CPR including suction, intubation and adrenaline (epinephrine) administration. No post-mortem was performed. *Measures:* Measures taken so far. On account of a considerable number of accidents involving surfactant-containing products as well as other household products and disinfectants, the BfR Documentation Centre for Poisonings (BfRDocCentre) conducted an expert hearing involving representatives of nursing and consumers' associations, of the industry and the Poison Control Centres in November 2001 under the responsibility of the predecessor institution of the BfR, the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV). The aim of the hearing was to point out the background of such accidents and to develop strategies for their prevention. We therefore placed special emphasis on the problem of accidental ingestion by elderly and disoriented persons. In parallel, corresponding press releases were issued. In the context of the press releases, 12,000 information leaflets in the German, Turkish, Russian, Serbian/Croatian and Polish languages were distributed to hospitals and day-care institutions. *Conclusions:* Since 1995, in the age groups over 65 years, the number of the documented cases of severe health impairment after ingestion of products containing surfactants in the BfRDocCentre has increased to 16, including as many as 14 deaths. In 2003 and 2004, however, no severe cases were reported to the BfR, possibly as a consequence of appropriate instructions given to nursing and cleaning staff. In 2005 and 2006, there were unfortunately two additional serious cases of aspiration in elderly people. The BfR will place special emphasis for a second time on the problem of accidental ingestion by elderly and disoriented persons.

223. Poisoning by Domestic Solvents in Children under 7: One Year Prospective Study in the Marseille Poison Centre

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Objective: Domestic solvents are present in various products at home, leading to numerous childhood poisonings. *Methods:* In order to evaluate the systemic toxicity including the respiratory tract disturbances of domestic solvent ingestion, a prospective study was performed in the Marseille Poison Centre between January and December 2005. Each young patient (child under 7 years old) was followed during 2 weeks after the accident. *Results:* 202 cases of solvent ingestion were included during 2005. The patients were mainly boys (60%) and the average age was 2 years (5 months to 7 years). The most frequently implicated products were Stoddart solvent/white spirit (55% of the whole series), with or without acetone (40%), motor oil and gas (26%), and barbecue lighter products (22%). No clinical symptoms were observed in most cases (73%), and only 3% had immediate respiratory symptoms. All of these developed in 6 to 9 hours a real aspiration pneumonia with fever up to 39°C, and abnormalities on chest X ray radiography. These cases of direct pulmonary toxicity were very different from the only one case of delayed pneumonia observed after the ingestion of a complete solid barbecue lighter product by a 21-month-old boy. *Discussion:* The results of this study confirm that ingestion of liquid solvents with no respiratory symptoms in few minutes have a good prognosis, but the presence of immediate respiratory symptoms will always lead to aspiration pneumonia in about 9 hours. The delayed development of "elimination" pneumonia is rare and should be considered when a child eats large quantities of solvents.

224. Risk of Aspiration Carried by Colourless Liquids for Grill Lighting and Other Petroleum Distillates/Paraffins Table

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Objectives: Due to their physicochemical properties low-viscosity paraffinic hydrocarbons, like fuels containing paraffins and petroleum distillates may enter the lungs in ingestions and can cause severe chemical pneumonia. Even very low quantities, often only a little sip, may result in aspiration and severe health damage. In Germany, already five deaths in infants and young children have been recorded since 1990, two of them with colourless liquids. In Germany, the use of such petroleum distillates in coloured and/or scented lamp oils sold to the private end consumer has been banned since 1 January 1999 and in the EU, since 1 July 2000. However, the use of such low-viscosity paraffins is still permitted in colourless liquids such as those used in grill lighting aids, in colourless lamp oils etc. Again and again, severe health impairment has resulted from their ingestion. Observations made by different parties have indicated that the unbanned uncolored and unscented products containing paraffins/petroleum distillates, are more aggressively advertised and sold, with increasing market shares, by wholesalers and retailers. *Assessments:* During the period between 1 January 1999 and 31 December 2005, the BfR Documentation Centre for Poisonings (BfRDocCentre) received reports on 66 cases involving grill lighting aids, 104 cases involving colourless lamp oils and 28 other cases with kerosene and fire-breathing liquids. Pneumonia was developed in 38% of cases caused by grill lighting aids and in 45% of cases caused by colourless lamp oils. Chemical pneumonia also resulted from the aspiration of pure kerosene and with a very high frequency for liquids for fire-breathing (see table). As in the past, the BfR continues to strongly advocate that the ban on the selling of colored and/or scented lamp oils containing low-viscosity paraffinic hydrocarbons to the private end consumer be extended to other products such as grill lighting aids and colorless and unscented lamp oils. Based on the BfRDocCentre data and extrapolations of the German Poison Centre inquiries between 1 January 1999 and 31 December 2005, these colorless liquid products could be involved in more than 1,300 aspiration cases in Germany. Cost assessments of the financial burden caused through physician consultations, hospital admittance, diagnostic and therapeutic costs, and rehabilitation measures, will exceed the level of 10 Million Euros in this period of 6 years. *Results and Activities:* Based on BfRDocCentre reports the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety has again taken up the problem. Thus, the German Federal Minister for the Environment has demanded more stringent regulations for the marketing of such chemicals on the EU level.

Table 1. Products containing low-viscosity paraffinic hydrocarbons vs. documented cases of pneumonia

	Total 1999–2005	Thereof pneumonia
Grill lighting aids	66	25 (38%)
Colorless lamp oils	104	47 (45%)
Kerosene	19	6 (32%)
Liquid for fire-breathing	9	6 (67%)

225. Chemical Injuries from Laundry Detergents

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Introduction: For some years laundry detergents have become more concentrated and as a consequence more irritating. In order to evaluate the risk associated with the detergents we have conducted an epidemiological study of emergency room visits brought about by exposure to these products. *Methods:* The study was based on data from the Danish Accident Registry, which includes information from 5 emergency rooms covering a representative sample of 15% of the Danish population (1). Information on all visits to the emergency rooms is recorded according to the Nordic Accident Classification (2). In the present study all patients with exposure to laundry detergents as causal agent in the years 1998–2001 were included. Information on individual characteristics, type and localisation of the injury, treatment, cause and circumstances of the accident and referral from the emergency room was obtained. *Results:* In the 4-year period, 34 patients were treated for injuries caused by exposure to laundry detergents. Five patients exposed to spot-cleaners were excluded, leaving 29 patients for further analyses, corresponding to an incidence rate of 0.9 injuries per 100,000 person years. Thirteen patients had been exposed to fluid detergents, 15 to washing powders and 1 to an undetermined product. Five exposures occurred at work and the rest in the home environment. Twenty-one patients had eye exposure, 1 skin exposure and 7 – all children – had ingested the detergent. The only effect was irritation in 24 patients, 19 of these with eye exposure. For the rest of the cases no effect could be established. Three patients were referred for follow up visits while the majority of the patients were discharged without further action planned. *Conclusions:* Given the widespread use and anticipated frequent exposure to laundry detergents treatment in emergency rooms occurs very rarely. Consequences from exposure to laundry detergents are at worst irritation of the eyes which in the majority of cases can be treated at the emergency room without further follow up. *References:* 1. Laursen B, Møller H, Tranberg KAM, Frimodt-Møller B. Annual report for the Danish Accident Registry 2002. The Danish Institute for Public Health 2003. Available at www.folkesundhed.d. 2. NOMESCO. Classification of external causes of injuries. 3rd rev. ed. NOMESCO (Nordic Medico-statistical Committee) 48:1997.

226. Neutralization Capacity of Limescale Removers

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Objective: Study of factors influencing severity of limescale remover ingestion. *Methods:* Data on kettle limescale remover ingestion obtained in years 2000–2006 were collected from the Toxicological Information Centre (TIC) database. The neutralization capacity (NC) reaction was measured for 4 of the most common kettle limescale removers with a time interval of up to 24 hours. For comparison, NC of 1% acetic acid was measured. NC was defined as mmol NaOH required to titrate 100 ml of test product to achieve pH 6.00, expressed as the mean of 3 determinations (pH 6.00 being same as tap water). *Results:* Between 2000–2006, TIC answered approximately 50 enquiries per annum following limescale remover ingestion. 79% patients experienced no symptoms, 21% only mild symptoms (mostly burning in oral cavity or retrosternally but rarely causing digestive difficulties). In 73% the remover solution was consumed as tea, 11% as coffee or milk, 10% as a plain remover solution, and 6% concentrated remover. During the last 12 months 45 calls was received in total: only 3 patients ingested concentrated remover. Subsequent oesophagoscopy was performed: 2 cases revealed no pathological findings and one patient presented with hyperaemia only. Nineteen subjects were examined otorhinolaryngologically, no pathology was found. NC of the remover (A and C solutions) differed only mildly throughout the time intervals; however, combination with tenzides influenced NC differently. NC of 1% acetic acid was 11.1 mmol per l00 ml. *Conclusion:* Neutralisation capacity of limescale remover solutions is relatively low; it is comparable with vinegar (9% acetic acid) in 3 fold dilution with water. Furthermore NC slightly decreases with time, as part of the remover is consumed by the reaction with limescale. Measurement of pH values and neutralization capacity were affected by presence of active compounds e.g., surfactants. Partially the remover is buffered by the consumables buffering capacity (coffee, tea, soup, etc.). This could explain why the mucous membranes are not seriously injured post-contact with removers. *Acknowledgement:* MSM0021620807, MIT1H-PK/42.

Table 1. Neutralization capacity measurements at time intervals (hrs) up to pH = 6

	Initial pH	NC (mmol NaOH/100 mL of tested solution)				Percentage change of NC			
Composition of removers:		0	2	4	24	0	2	4	24
A) Amidosulfonic acid 100%	1.3	33.1	30.2	29.5	29.1	100	91.2	89	87.9
B) Amidosulfonic acid 5–15%, ortophosphoric acid 5%, tenzides 2%	2.3	12.0	11.0	10.9	10.7	100	91.7	91	89
C) Citric acid 100%	2.8	36.0	34.5	33.5	32.5	100	95.9	93.1	90.4
D) Citric acid>30%, tenzides 2%	2.3	88.0	92.1	83.6	46.0	100	104	95	52.3

227. Liquid Detergent Capsules: A New Risk

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Objective: To highlight the increased risk of injury by liquid detergent capsules, in particular, the risk to children. *Methods:* All cases of exposure to liquid detergent capsules identified from 1 January 2001 to 30 October 2006 by the Poison Centre and regional network of emergency departments were analysed. *Results:* 438 exposures to 17 different washing machine liquid detergent capsules. Children were involved in 99% (n = 433). Route of exposure was ingestion (n = 382, 87%), ocular (n = 35, 8%), ingestion+ocular (n =17, 4%), and cutaneous (n =4, 1%). After ingestion, 257 patients (66%) were symptomatic and 6 (2%) developed severe symptoms (PSS [3] 2). Two children aged 1 and 3 years developed ARDS and were intubated and ventilated (PSS = 3). After ocular exposure, 35 patients (67%) were symptomatic. Among them 9 cases of keratitis were found in follow up. *Conclusion:* Incidents with liquid detergent capsules are less frequent than traditional detergents. This has to be correlated with the small share of the market (0.8%). There is a relatively high risk of toxicity with 3% of severe cases (ARDS, caustic lesion) after oral exposure and 17 % of keratitis with risk of sequelae after ocular exposure. We highlight the problem of lack of knowledge of the risk by parents and physicians. Proper information should be emphasized.

228. Medication Error Inquiries by Health Care Professionals – A 6-Year Study

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Objective: This study was carried out to analyze the extent and type of medication errors by health care professionals (HCPs) leading to a call to the Finnish Poison Information Centre. *Methods:* All telephone inquiries concerning actual or suspected medication errors made by HCPs between 1 June 2000 and 31 May 2006 were included. Exclusion criteria were inquiries involving animals and general questions on poisonings. *Results:* A total of 237,828 inquiries were received during the survey period. The number of inquiries concerning acute poisoning exposures was 160,767, of which 969 (0.6%) concerned medication errors by HCPs. These included a total of 973 administration errors. Females were involved in 484 (50%) and males in 361 (37%) exposures, with gender unknown in 116 (12%). Eight (1%) inquiries concerned more than one patient. The main types of errors were administration of a wrong drug (588; 57%), wrong dose (331; 32%), and erroneous route of administration (54; 5%). Most of these errors occurred in nursing homes for the elderly, for mentally retarded and for dementia patients. The number of inquiries concerning medication errors doubled during the survey period. Most of the calls were received in summer months and in December. The calls came from nursing staff in 648 (67%) and from physicians in 217 (22%) cases. The Centre was usually contacted rapidly, within 1 hour after the error in 644 (66%) and 1 to 4 hours in 150 (15%) calls. The medication error was repeated in 66 (7%) patients. The elderly between 80 and 89 years of age (151; 16%) and children under the age of 10 (108; 11%) were most often the victims of medication errors. The most common error in adults was administration of a wrong drug, in children of a wrong dose. Approximately 75% of the patients did not require referral, and 25% were recommended to be referred to a health centre or a hospital. *Conclusion:* Medication errors occur in nursing home type facilities especially during the holiday seasons. The most serious medication errors are due to erroneous route of administration in hospital setting. The elderly are usually exposed to different type of error than children.

229. Classification of Medication Errors: Clues for Prevention

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Introduction: In previous years worldwide many poison prevention programmes have been set up to reduce the number of accidental drug poisonings. The focus of these programmes was greatly on rising public awareness, and on parents of young children with messages to keep medicines out of their reach. Fewer programmes were directed towards diminishing the number of accidental drug poisonings due to medication errors. As a first step, the following study was undertaken to evaluate the medication errors reported to our poisons information centre. *Methods:* From April 2005 – November 2006 consecutive cases of accidental drug poisonings due to medication errors were evaluated with regard to age groups, error types with circumstances of exposure, and drugs involved. *Results:* During the study period, 321 drug poisonings due to medication errors were recorded. In 126 cases (39%) children, mostly up to 5 years of age, were involved, all other cases involved adults. The majority of the medication errors were made at home, involving children (109 cases, 34%) as well as adults (120 cases, 37%). In 49 cases (15%) the medication error was made in a nursing home, in 29 cases (9%) in a hospital or mental institute, and in 14 cases (5%) in a compounding pharmacy. In all of these settings, 45–50% of the mistakes made were dosing errors. In addition, the most notable errors were agent errors: children at home received the wrong medication in over 40% of the cases. In the nursing homes in 30% of the cases the patient received the medication intended for another patient. Especially in hospitals and by adult patients at home, mistakes were made in the delivery route of the drug (20% in both groups). Drug categories most frequently observed were central nervous system agents, such as anticonvulsant medications (often in nursing homes), antidepressants, antipsychotic drugs and analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs). For instance, paracetamol was the main single drug administered wrongly in young children. *Conclusions:* The success of prevention programmes depends highly on tailor-made programmes addressing the right target groups and suggesting adequate prevention measures. This study shows distinctive groups of medication errors, occurring in various settings: at home, at compounding pharmacies, in hospitals, and in nursing homes. Mistakes made by medical professionals ask for a different approach in prevention programmes than mistakes made by patients and caretakers. In each subcategory, the underlying reasons for medication errors, such as failures in procedures, pressure of work, and insufficient knowledge, now need to be clarified. This can lead to tailor-made prevention programmes with the most adequate actions for improving compliance with strict procedures for the preparation, dosing and delivery of drugs.

230. Intravenous Terbutaline Overdose in an Asthmatic Child

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Background: Terbutaline (terb) is a relatively specific β 2 adrenergic agonist used in status asthmaticus. We report the first IV terb. overdose in a pediatric patient (pt.). *Case Report:* The pt. is 11 mo, 10.8 kg F in status asthmaticus. Initially, she was in marked respiratory distress. T 36.7° C, HR 170, RR 48, BP 122/64, 87% O_2 sats RA. The remainder of the exam was normal. She received 3 albuterol (alb) 5 mg nebulizer treatments (nebs), epinephrine nebs 2 mg, and 7 hours of continuous alb nebs (105 mg total). Magnesium sulfate IV 75 mg/kg was given. During the 7 hours of alb nebs, the pt. was tremulous and pale. VS: HR 170–209, RR 47–80 and BP 90/41–145/95. Wheezing and decreased breath sounds noted. The pt. was given 4 (400 mcg/kg) mg IV terb. The error was recognized & all β agonists were discontinued. Laboratory results were normal with the exception of atelectasis on CXR. Post terb infusion VS varied from HR of 210–194, BP 118/63–79/42, RR 50–34, O_2 sats 100% on FiO_2 30%. Pt. remained alert. Pt. was transferred to the ICU where her symptoms resolved over 12 hours. *Discussion:* Mechanism of the anti-asthmatic action of β adrenergic agonists is linked to the direct relaxation of airway smooth muscle and consequent bronchodilatation. Peak effects of the parenteral drug can be seen within 30 minutes. In IV, SQ and larger PO administrations, there is a loss of β2 receptor selectivity with greater cardiovascular side-effects. This pt. had a significant amount of β agonist stimulation from 7 hours continuous alb nebs but she tolerated a 40-fold overdose of IV terb. without further effects. β blockers use was considered but the possibility of worsening pt s asthma was paramount. *Conclusion:* We report the first intravenous terb. overdose in a paediatric asthmatic patient with minimum toxicological effects which resolved spontaneously with close observation. As with all medication error cases, the situation should be analyzed for systemic faults and miscommunication should be minimized.

231. Multiorgan System Failure in a 9 Year-old Girl after a Ten-fold Overdose of Amphotericin B: Formulation Folly

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Objective: Amphotericin B overdose may be lethal (1). Multiple formulations of amphotericin B exist and each requires unique dosing. Confusing abbreviations and similar names have led to clinically significant errors. We report an error that lead to an overdose of amphotericin B resulting in multiorgan system failure. *Case Report:* A 9-year-old girl received outpatient intravenous pipperacillin/tazobactam after surgical repair of her perforated appendix. She developed a temperature of 40°C on post-op day 9, and vancomycin was added. Further evaluation was negative, but fevers persisted for three days prompting readmission. Intravenous clindamycin, meropenem, and amphotericin B were started. Shortly after receiving this regimen she developed hypotension, seizures, acute lung injury, and oliguria. Her AST rose to 28,000U/L. It was later realized that she had received 5 mg/kg of aqueous amphotericin B deoxycholate (fungizone; abbreviation AmBd). This was an appropriate dose for Abelcet, a liposomal formulation of the drug (abbreviation ABLC). An appropriate dose of aqueous amphotericin B deoxycholate is 0.5–0.7 mg/kg making this a seven to ten-fold dosing error. Her condition worsened, but ultimately she made a full recovery approximately one month after readmission. *Conclusion:* Amphotericin B overdose may be lethal. Avoiding its occurrence requires confirmation of the formulation used prior to dosing. Familiarity with the various formulations available and their respective dosing regimens has proven to be inadequate for preventing overdose. Similar names and abbreviations for these formulations has only added confusion and increased the risk for overdose. In an effort to reduce the number of adverse events and deaths attributed to the routine use of this drug, we believe a system of checks should be developed and implemented prior to its administration. *Reference:* 1. Mohr JF, Hall AC, Ericsson CD, et al. Fatal amphotericin B overdose due to administration of nonlipid formulation instead of lipid formulation. Pharmacotherapy 2005; 25:426–8.

232. Toxicity after Medication Errors in the Smallest Children – A Rare but Occasionally Dramatic Phenomenon

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Objective: To analyse the problem of domestic medication errors in children younger than one year, pharmaceuticals involved and risks of poisoning. *Method:* All inquiries to the Swedish Poisons Information Centre concerning medication errors in children less than one year during the period July 2000 to June 2006 were analysed. *Results:* During the study period, the poisons centre had a total of 1,515 consultations concerning domestic medication errors in children below the age of one. The number of cases was 1,430. The most commonly involved medications were paracetamol (497 cases), vitamin A/D-supplement (95), a cough mixture containing ethylmorphine (82), oxymetazoline nasal drops (81), and terbutaline syrup (65). The risk was considered as none in 1,199 cases and as slight to moderate in 210 children. In 15 cases the medication error was estimated to impose a high risk or resulted in significant poisoning. Among these serious incidents, four involved opioids and three were multiple paracetamol overdoses. Among the remaining miscellaneous drugs, two case reports are presented in the following. *Case 1:* A 6-month-old boy was given two suppositories, each containing 25 mg of prochlorperazine, mistaken for paracetamol. He was brought to hospital awake but drowsy and in a state of generalized rigidity (opisthotonus). His eyes were miotic and turned upwards and his pulse rate was 180 bpm. Ten minutes after a dose of 0.4 mg biperiden, he was calm and his tachycardia was reduced. His condition improved during the following hours and no further complications ensued. *Case 2:* A 5-month-old girl was given a suppository of 20 mg metoclopramide mistaken for paracetamol. After about 5 hours, she developed some CNS depression and typical extrapyramidal symptoms (stiffness in legs and neck region). On arrival in hospital, she had opisthotonus with pronounced muscle rigidity in her neck and arms, and to a lesser extent in her legs. She also had dystonic tongue movements. Biperiden (0.04 mg/kg) was administered iv which resulted in rapid improvement. Evaluation after half an hour showed some residual rigidity in neck and arms and another dose of biperiden (0.02 mg/kg) was given

iv. This resulted in complete recovery. The patient was discharged the following day without further complications. *Conclusion:* Medication errors at home are common but seldom impose a serious risk of poisoning, even among the smallest children. Exceptions from this rule are for example multiple acetaminophen overdoses and, occasionally, single errors involving potent medications, e.g., opioids.

233. Codeine Overdose – Just a Dosing Error?

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Objectives: Codeine is widely used as an antitussive in children and adults. Severe side effects like deep sedation and respiratory insufficiency are rare while vomiting is more common (up to 29.2%) (1). Renal impairment lengthens its elimination half-life and increases the toxicity of codeine. There is one sustained release formulation (containing 25 mg codeine in 1 g solution) available in Germany for small children and adults. Dosing errors of such formulations for all ages can give rise to an overdose in small children. *Case Reports:* A 3–1/4 years old boy (weight 13.4 kg) was found breathless by his mother at night. She immediately started resuscitation. He had to be ventilated for 3 days because of aspiration pneumonia. Two hours later his twin brother (14 kg) was found dead. Resuscitation failed. Post mortem examination revealed a massive aspiration of gastric content. Toxicological analyses showed high levels of codeine (179 ng/ml, respectively 547 ng/ml) and its metabolites in blood and urine of both toddlers. Because of persistent cough with fever the twins' mother had given 10 drops instead of recommended 2.5 ml (=10 mg codeine). 10 drops contain 12.5 mg codeine according to the pharmaceutical company. We tested the weight of 10 drops experimentally: dropping bottle was held vertical (0°), or in a 30° or 60° angle. Mean of weight of 6 × 10 drops was 847.0 mg (0°); 673.0 mg (30°), 607.4 mg (60°). Minimum weight was 493.6 mg, maximum 940.2 mg. Thus, the highest possible dose applied by the mother was 23.4 mg codeine instead of the recommended 10 mg. *Conclusions:* Surprisingly the drop weight of pharmaceutical products can vary up to ~90% and this can be a cause of drug overdose. Toxicologists and poison centres' personnel should be aware of this problem. Pharmocokinetic modelling shows that only additional factors like reduced renal function (e.g., during fever and transitory dehydration) or an additional elevation of dose can explain the reported codeine levels of ~500 ng/ml in patient 2. *References*: 1. Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population and its implication for analgesic reliability. Br J Anaesthesia 2002; 89:839–45.

234. Iatrogenic Intravenous Administration Errors of Drugs Reported to the PIC Erfurt

Deters M, Prasa D, Hentschel H. *Poisons Information Centre, Erfurt, Germany*.

Objective: We investigated the incidence of iatrogenic intravenous administration errors of drugs reported to the Poisons Information Centre Erfurt to get further information for effective prevention. *Methods:* Calls regarding iatrogenic intravenous medication errors received by the poison centre from 1997 to the end of October 2006 were analysed retrospectively. Data were categorised into error types, age groups, drugs involved, and estimated risk of toxicity. *Results:* 128 cases of intravenous administration errors of drugs were advised by the PIC. Patients affected were 31% children (75% of them babies and toddlers) and 69% adults. Among adults 32% were in the mean age group (18 to 65 years old); 31% were seniors, but in 48% the age remained unknown. Cases of intravenous administration errors increased from 7 in 1997 to 18 in 2005. In 2006 27 inquiries were received until the end of October. Most frequent drug classes (ATC classification) involved were antipsychotics (10%), antihistamines for systemic use (7.8%), antimetabolites, direct acting antivirals as well as other systemic drugs for obstructive airway diseases (5.4% for each class), other analgesics and antipyretics (4.7%), antiseptics and disinfectants and local anaesthetics (both 3.8%), macrolides, lincosamides and streptogramines, antithrombotic agents, antiepileptics, and adrenergics for systemic use (3% for each class). The main types of errors were overdosage (53.1%) and wrong route of application (29.7%). Other medication errors were mixing up the medication of patients (7.2%), preparation errors (6.3%), and paravenous injection (3.9%). The estimated risk was as follows: 14.1% no risk, 71.8% risk of toxicity, and 14.1% unpredictable risk. In 16 cases (12.5%) poisoning was estimated to be severe (amongst them 14 cases of overdosage). Medical treatment was recommended in 82% of patients. The courses were asymptomatic (5.4%) or symptomatic (10.9%) with minor (9 cases), moderate (1 case with intermittent granulocytopenia), and severe features (4 cases with either coma, seizures, respiratory insufficiency, or sudden cardiac arrest) but complete recovery. In one case sudden cardiac arrest was reported followed by hypoxia-induced brain damage despite resuscitation. In another patient the erroneous intravenous application resulted in sudden cardiac arrest and death despite of immediate resuscitation. Unfortunately, follow-up was impossible in most cases (82%). *Conclusion:* One per million of all calls received concerned iatrogenic intravenous administration errors of drugs. At least 4% of these administration errors resulted in severe symptoms. Overdosage and wrong route of application as the most frequent errors may be avoidable by training of the medical staff and clear distinguishable packing of preparations with different potencies or different application forms.

235. Therapeutic Misadventures with Vitamin K in Newborns: Consequences of New Recommendations

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Background: Optimal methods for the prevention of late vitamin K deficiency bleeding in the newborn have been the subject of a considerable debate in recent years and remain to be fully resolved. After concerns about carcinogenicity of intramuscular vitamin K administration, the oral route has been preferred. It has been shown that orally treated breastfed infants have to continue vitamin K supplementation during the first months of life. For a long time, this has been accomplished with the administration of vitamin K 1 mg once a week, based on the sole available, licensed medicinal product containing vitamin K (Konakion® phytomenadione 20 milligrams/ml, 1 drop = 1mg). In 2004, according to the result of a Dutch study, the National Society of Neonatology recommended the use of a new therapeutic regimen of 25 micrograms/day. In the meantime, a product containing phytomenadione 20 micrograms/ml (Vita K®) was licensed on the market as a nutritional supplement agent. *Objective:* To describe the occurrence of therapeutic errors during vitamin K oral supplementation in infants after the license on the market of a new low dosage product. *Methods:* A retrospective analysis of two years (2004–2005) Bergamo and Pavia Poison Centers' records was performed in order to identify pediatric cases of inadvertent oral administration of high doses vitamin K. The previous 2-year period was analyzed for comparison. Patients' demographic and clinical data were reviewed. The causes of error were investigated. *Results:* In the study period, a total of 30 cases (age: 3 days - 6 months) were identified, compared to 2–4 cases/year observed in the two previous years. Patients received 2 to 3600 mg vitamin K; in 41% of cases repeated large doses were administered. No relevant toxic effects were observed. All cases but 3 were related to the use of Konakion® instead of Vita K®. The causes of error were identified in (i) a dispensing error made by the pharmacist, who misunderstood the proprietary name of the prescribed product (Vita K®) as the name of the active ingredient, and in (ii) a generic request for vitamin K made by parents. In both cases, pharmacists delivered the commonly used, licensed medicinal product Konakion®, which was subsequently administered by parents to the infants at the drops regimen prescribed for Vita K® (20–25 drops/day, corresponding with Konakion® to 20–25 milligrams/day vitamin K). *Conclusion:* Our experience suggests that sudden changes in prescription strategies can cause therapeutic errors that involve the liability of health professionals. Their alerting before such changes take place might reduce the risk of error.

236. Thyrotoxicosis: The "Great Mimicker" of Toxicology

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Objective: Although thyrotoxicosis is not an uncommon disease, it may present itself in many different ways. We report a case in which the signs and symptoms seemed so compatible with a drug ingestion that this disease was not initially thought of. A high level of clinical awareness is necessary, especially when presentation simulates a toxidrome. *Case Report:* A 48-year-old female was found with mental status change. There was a question that she may have taken cyclobenzaprine. Her examination revealed her to have an initial heart rate of 160 beats per minute and the patient was found to be combative, She had motor restlessness with a non-focal examination. Her reflexes were brisk. A urine drug screen was positive for tricyclics. The patient was treated with benzodiazepines and transferred to a medical toxicology service with a diagnosis of cyclobenzaprine toxicity. The patient confirmed taking a cyclobenzaprine tablet to help her relax. She denied an overdose. The urine drug screen was thought to be false positive from the cyclobenzaprine. A thyroid function test done as part of work up of delirium revealed a TSH of < 0.008 uIU/ml, Thyroxine 4 22.2 mcg/dl, T3 1.77 ng/dl, and FTI 39. She was thought to have acute thyrotoxicosis and treated with propylthiouracil and propranolol. She did well and was discharged with an endocrinology follow up. *Conclusion:* Thyrotoxicosis has a protean clinical presentation and simulates some of the common toxidromes that it can be named a "Great Tox Mimicker." It is important to consider thyrotoxicosis in the differential diagnosis, and work up of a potential drug overdose patient.

237. High Incidence of Hospital-Acquired *Pseudomonas aeruginosa* Infection in Cardiotoxic-poisoned Patients Treated with Extracoporeal Life Support

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Objective: The incidence of hospital-acquired infection caused by *Pseudomonas aeruginosa* has increased considerably over the past 30 years (50–60% of all nosocomial infections). There are very few published data regarding hospital-acquired infections during extracorporeal life support (ECLS) performed in poisoned patients. The objectives of our study were to determine the incidence of infections in poisoned patients treated with ECLS performed in an intensive care unit (ICU). *Methods:* We conducted a prospective study including all poisoned patients admitted in our intensive care unit during a 6-month period (November 2005–May 2006) and who underwent an ECLS. ECLS was performed in relation to refractory toxic cardiogenic shock or cardiac arrest following suicidal attempt. We collected all microbiological data during ICU hospitalization. Results were expressed as percentage or mean ± SD. *Results:* Seventeen patients (age: 40±13 years; 14F/3M) were included. ECLS duration was 84 ± 84 hours and hospitalization duration 11 ± 9 days. Ten patients survived and were discharged after 16 ± 10 days from ICU. Mechanical ventilation was prolonged during 7 ± 4 days. All the patients received anti-microbial therapy in the first 24 hours while on ECLS, including: amoxicillin/clavulamate (14/17) and cefotaxime+metronidazole (3/17). Bronchoalveolar sputum cultures were considered positive for infections in 11/17 patients: 5/17 with early infection probably related to an aspiration pneumonia and 9/17 with a hospital-acquired infection. *Pseudomonas aeruginosa* infection was documented in 8/11 patients: pneumonia (7/8), bacteriemia (5/8), cannulation site infection (2/8), central catheter infection (2/8) and/or urinary tract infection (1/8). 5/8 (63%) patients presented infections due to *Pseudomonas* after discontinuation of the ECLS. Other microrganisms were isolated in 10/11 patients, including pulmonary infection (9/10), central catheter infection (4/10), bacteriemia (3/10), and/or sinus infection (1/10). *Conclusion:* In our experience, the incidence of hospital-acquired infection is elevated. Systematic administration of empirical antibiotics may explain part of differences with other results in the literature (1). The high proportion of nosocomial pneumonia due to *Pseudomas aeruginosa* may be in part due to the ecology of our department and to the previously administrated first line antibiotics. *Reference:* O'Neill JM, Schutze GE, Heulitt MJ, et al. Nosocomial infections during extracorporeal membrane oxygenation. Intensive Care Med 2001; 27:1247–1253.

238. A Botulism Outbreak Following a Wedding in a Rural Area in North East Iran, 2006

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Background: Botulism is an uncommon disease. In our previous experience cases were rare between 1993 to 2000 (1). Botulism induces symmetrical cranial nerve palsies followed by descending, symmetric flaccid paralysis of voluntary muscles, which may progress to respiratory failure and death (2). In September 2006, following a wedding ceremony, which took place 80 km southeast of Mashhad, Iran, a group of guests decided to camp the night. On the following morning they used a wide variety of home made canned and fresh foods. It was subsequently found that the host had been treated several times in the previous two weeks for an alleged resistantswallowing problem. *Methods:* All symptoms and signs of the case series of patients referred to Toxicology Outpatient Clinic and Toxicology Ward of Imam Reza University Hospital Mashhad were recorded on a daily bases from 17 September 2006 to 3 October 2006 prospectively. Diagnosis was made on the circumstance of exposure around, clinical findings and response to antidote. *Results:* Overall, 23 patients were diagnosed with botulism and 14 cases were hospitalized for at least one day. Mean age (SD) was 39.5 (17.0) years with a minimum of 14 and a maximum of 60 years. On arrival, vital sings were normal. Their demographic variables, symptoms, and signs are summarized in the table. No deaths occurred and outpatient follow up is currently undergoing. All patients except one (due to hypersensitivity), received antidote. One additional developed infectious complications. These two stayed in hospital for a longer period. Public panic brought a large number of the wedding guests to the Outpatient Clinic for unrelated reasons. *Conclusions:* The frequency of symptoms is different in various outbreaks. Confirmatory serological tests are awaited. The results of this study can be used for defining clinical findings and surveillance within the local health system. *References:* 1. Afshari R. Descriptive epidemiology of intoxication in Mashhad, Iran, 56–111, 2001. Health Faculty, Tehran University of Medical Sciences, Ref Type: Thesis/Dissertation. 2. Afshari R, Majdzadeh R, Balali-Mood M. Pattern of acute poisoning in Mashhad Iran 1993–2000. J Toxicol Clin Toxicol 2004; 42:965–975. 3. Sobel J. Botulism. Clin Infect Dis 2005; 41(8):1167–73.

239. Differences in the Nursing Care of Intoxicated Patients According to Type of Poison: Ethanol Versus other Drugs of Abuse

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Introduction and Objective: Nursing staff provide valuable clinical information on the condition of the patients, aiding evaluation of the severity of poisonings. The objective of this study was to compare the need for nursing care (techniques, procedures and administration of treatments) in patients with acute poisonings due to ethanol (ET) or other drugs of abuse (DA). *Methodology:* Data were collected from the medical and the nursing charts for all patients seen by the Emergency Department (ED) due to poisoning by ET or other DA in October 2004 and October 2005. Nursing procedures were defined as: measuring vital signs, gut decontamination, nasogastric tube, vesicle tube, electrocardiogram, placing of arterial and venous lines, blood samples for general and toxicological analyses, physical restraint and antipyretic measures. Treatments were considered as: tracheal intubation and mechanical ventilation, oxygen therapy, plasma expanders, vasoactive drugs, analgesics, serum therapy, antipyretic agents, antibiotics, antidotes, pharmacological restraint and other non antidote drugs (sedatives, etc.). The results were analysed using the chi square test for qualitative variables and the Student's t test for quantitative variables. The level of statistical significance was established as $p < 0.05$. *Results:* A total of 281 patients with acute poisonings attended: 105 (37.4%) due to ET and 61 (21.7%) to other DA. Compared with ET, DA were younger (age < 25 years, p = 0. 004) and were admitted more often at night compared with ET who were admitted more frequently during the evening (p = 0.012). DA were more frequently managed in the medical area and ET in the psychiatric area ($p<0.001$). The number of symptoms on admittance to the ED did not differ. However, digestive (p = 0.029) and neurological symptoms (p = 0.037) and hypotension (p = 0.073) were more frequent in ET, while respiratory symptoms (p = 0.018), Glasgow Coma Score <12 (p = 0.038), hypertension ($p < 0.001$) and cardiovascular manifestations ($p<0.001$) were more frequent in DA. With respect to the number of procedures, there were no differences between the two groups. With respect to the techniques administered, DA had a greater percentage of ECG ($p < 0.001$) and venous lines (p = 0.005), while ET had a greater need for physical restraint (p = 0.014). There were no differences in the number of treatments administered. However, DA needed more antidotes ($p < 0.001$) and non-antidote drugs (p = 0.014). *Conclusions:* ET patients are older and present different clinical manifestations than DA overdoses, but need the same amount of nursing care. There were no significant differences in the number of procedures or treatments, but DA need more antidotes and non-antidote drugs and less pharmacological restraint than ET.

240. Agitation Related to Acute Poisoning in the Emergency Department - A 10-Year Prospective Study

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Objective: Agitation is a frequent cause of admission to the Emergency Department and it is one of the leading symptoms of some of the more usual drugs of abuse, mainly alcohol and stimulant substances. The aim of our study is to verify the characteristics of the toxic incidents presenting with agitation to our Emergency Department in a 10 year period. *Methods:* We have studied in a prospective way all the toxic cases that have presented with an agitated status in any moment of their clinical evolution between 1995 and 2004 in the ED of a General Hospital covering a population of 360,000 inhabitants. Toxic cases represent nearly 2% of all the emergency cases. *Results:* We have obtained the clinical, epidemiological and analytical data for 661 toxic cases with agitation from a total of 9,322 acute poisonings in the period of study. Analytical confirmation has been performed in 521 cases. Mean age is 32 years. Males represent 72.16%. Overdoses of drugs of abuse are the most frequent origin (76.66%) followed by suicides (14.55%). The main agent is ethanol (65.95%), with a mean blood ethanol concentration of 1.66 g/L, followed by cocaine, amphetamines and opiates. The most frequent association is cocaine plus ethanol (45 cases) followed by opiates and cocaine (18 cases). Medicaments were present in 19.96%, most of them benzodiazepines (13.36%). The route of exposure is oral (71.40%), followed by the respiratory airway (4.79%). Association of both routes was present in 9.25%. The clinical pictures associated with agitation were inebriation (212 cases), pupil alterations (140 cases), delirium (51 cases), convulsions (29 cases) and coma (16 cases). Most cases (429 cases) were treated in a symptomatic way, using benzodiazepines and mechanical restraint. Respiratory support was necessary in 45 cases. In 77 cases, gastric decontamination was performed. 300 patients had to be admitted for observation and there was one fatality. *Conclusions:* Agitation is present in 7% of all acute intoxications in our ED. The usual profile of patients with this clinical picture is a young male with an ethanol overdose during the weekend with an accompanying picture of inebriation. Two third of the patients required symptomatic treatment and half of them had to be admitted for evolution control and observation, but the outcome is generally good.

241. Differences in the Nursing Care of Intoxicated Patients According to Type of Poison: Drugs of Abuse Versus Medical Drug Poisoning

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Background and Objective: Nursing staff provide valuable clinical information on the condition of the patients, aiding evaluation of the severity of poisonings. The most common therapeutic interventions are aimed at maintaining general homeostasis, restraining digestive absorption of the poison and administering antidotes. The objective of this study was to compare the need for nursing care (techniques, procedures and administration of treatments) in patients with acute poisonings due to drugs of abuse (DA) or medical drugs (MD). *Patients and Method:* Data were collected from the medical chart and the nursing chart for all patients seen by the Emergency Department (ED) due to poisoning by DA (except alcohol) or MD in October 2004 and October 2005. A patient needing more than 3 nursing procedures or 2 treatments was considered as needing a large amount of care. Nursing procedures were defined as: measuring vital signs, gut decontamination, nasogastric tube, vesicle tube, electrocardiogram, placing of arterial and venous lines, blood samples for general and toxicological analyses, physical restraint, and antipyretic measures. Treatments were considered as: tracheal intubation and mechanical ventilation, oxygen therapy, plasma expanders, vasoactive drugs, analgesics, serum therapy, antipyretic agents, antibiotics, antidotes, pharmacological restraint and other non antidote drugs (sedatives, etc.). The results were analysed using the chi square test for qualitative variables and the Student's t test for quantitative variables. The level of statistical significance was established as $p<0.05$. *Results:* 281 patients with acute poisonings were treated: 61 (21.7%) due to DA and 85 (30.2%) due to MD poisoning. Compared with MD, DA were younger (age < 25 years, p=0.002), predominantly male ($p<0.001$) and were admitted to the ED at night, whereas MD were admitted in the evening (p = 0.001) and needed more psychiatric consults ($p<0.001$). In DA, the Glasgow Coma Score was lower (GCS <12, $p<0.001$) and presented more symptoms on admittance to the ED ($p<0.001$), mainly respiratory (p = 0.007). DA had also a higher heart rate ($p<0.001$) and less hypotension (p = 0.007). There were no differences between the two groups with respect to the number of procedures, but MD had a higher percentage of gut decontamination and DA a higher percentage of electrocardiograms ($p<0.001$). There were no differences in the total number of treatments administered. *Conclusions:* DA and MD have differing epidemiological profiles and clinical presentations but, overall, need the same amount of nursing care. There were no significant differences in the number of procedures and treatments administered, although qualitative differences in care were observed.

242. Characteristics of Poison-Related Fatality and Timing of Cardiac Arrest

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Objective: Knowledge about the timing of initial cardiac arrest for patients with poison-related fatality has broad public health implications and may determine priorities for future research. We aimed to describe the characteristics of patients with poison-related fatalities, and to determine which poisons were associated with early versus delayed cardiac arrest. *Methods:* We studied consecutive cases resulting in fatality referred to a regional poison control center over the seven-year period from 2000 to 2006. Data were collected prospectively and analyzed retrospectively. Comprehensive clinical data including patient demographics, laboratory information, poisoning information, and free text clinical details were reviewed using an electronic database. For a large number of cases, medical examiner data had been entered into the database and this was used to help determine cause of death. Timing of initial cardiac arrest, defined as loss of pulse, was recorded as either pre-hospital (early) or in-hospital (delayed). Simple descriptive statistics were used to analyze the study population. IRB approval was obtained at the study institution. *Results:* 447 deaths were reviewed during the study period, of which 170 were excluded (66 were unlikely poison-related, 59 were unknown if poison-related, 30 veterinary cases, 15 coding errors), yielding 277 poison-related fatalities (55% males, mean age 44.3) for analysis. Out of 96 pre-hospital cardiac arrests (61% males, mean age 44.2), the 3 most common associated poisonings were opioids (47%), sympathomimetics (21%), and carbon monoxide (17%). Out of 181 in-hospital cardiac arrests (52% males, mean age 44.4), the most common associated poisonings were acetaminophen (30%), opioids (15%), and sympathomimetics (14%). There were 143 single-poison fatalities, of which 54 (38%) had pre-hospital cardiac arrest. The most common single-poison fatalities associated with pre-hospital cardiac arrests were opioids (35%) and carbon monoxide (26%). The most common single-poison fatalities associated with in-hospital cardiac arrests were acetaminophen (24%) and caustics (10%). Among children 6 years or younger (50% males, mean age 1.6 years), there were only 6 fatalities (2 acetaminophen, 1 calcium channel blocker, 1 carbon monoxide, 1 anticonvulsant, 1 opioid). *Conclusions:* The majority of reported poison-related fatalities had delayed cardiac arrest after hospital arrival. Opioids and sympathomimetics were the most common poison-related fatalities. Carbon monoxide was most commonly associated with early

cardiac arrest, while acetaminophen was a significant cause of delayed cardiac arrest. Children with poison-related fatality were exceedingly rare and the profile of responsible poisons was similar to that of adults. Acetaminophen and caustics were the most common delayed single-poison fatalities, and these potentially preventable deaths should be the focus of future research.

243. The Treacherous Killer: Mesenterial Necrosis in Poisonings

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Background: Intoxications can cause serious mesenterial vasodepression or vasoconstriction which may lead to critical decrease of blood flow of the small bowel. *Objective:* To investigate the frequency of small bowel necrosis in poisoned patients. *Patients and Methods:* A retrospective study was performed on all the intoxicated patients who were admitted to our department during the last 15 years. Patients after a suicide attempt, alcohol or drug abuse or accidental poisoning developing small bowel necrosis with no sepsis, enteritis, acute mesenterial thrombosis or embolism, vasculitis and occlusion of bowels were enrolled in this study. The diagnosis was based upon the result of dissection or surgical operation and histological examination. Patients with no verified intoxication were excluded. The following parameters and data were recorded: age, gender, history of patient, laboratory findings (total blood count, serum amylase, creatine kinase, acid-base status), toxicological analysis, complaints of patient, treatment of intoxication. *Results*: We enrolled 22 patients (14 females, 8 males, average age 74.11 years, 20 patient more than 70 years) in this study. A total of 8 patients underwent an operation and the total mortality rate was 77.2% (17/22). The majority of patients were admitted to our department after a long exposition time - in 13 cases the exposition time was more than 12 hours, and in 6 cases it was less than 12 hours. Further data can be seen in Table 1. *Conclusions:* A high index of suspicion for mesenterial necrosis caused by intoxications is needed when prolonged vasodepression, vasoconstriction or hypoxaemia are present in the poisoned patient. The most frequent cause of small bowel necrosis is calcium antagonist overdose. Patients with advanced age and generalized atherosclerosis are of high risk for mesenterial necrosis. Long-term vasopressor therapy may also be a cause of it. The presence of certain clinical signs and laboratory findings (bowel distension, lack of bowel sounds, metabolic acidosis, elevated creatine kinase) should clue into the diagnosis of mesenterial necrosis.

Table 1. Neutralization capacity measurements at time intervals (hrs) up to pH = 6

	Initial pH	NC (mmol NaOH/ 100mL of tested solution)				Percentage change of NC			
Composition of removers:		0	2	4	24	0	2	4	24
A) Amidosulfonic acid 100%	1.3	33.1	30.2	29.5	29.1	100	91.2	89	87.9
B) Amidosulfonic acid 5–15%, ortophosphoric acid 5%, tenzides 2%	2.3	12.0	11.0	10.9	10.7	100	91.7	91	89
C) Citric acid 100%	2.8	36.0	34.5	33.5	32.5	100	95.9	93.1	90.4
D) Citric acid>30%, tenzides 2%	2.3	88.0	92.1	83.6	46.0	100	104	95	52.3

244. Acute Insulin Self-Poisonings: Prognostic Factors and Analysis of the Toxicokinetic / Toxicodynamic Relationships (TK/TD)

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Objective: Insulin self poisoning cases are rarely described in the literature. The prognostic factors and the optimal conditions for glucose infusion are not established. There has been no interest in measurement of the optimum plasma insulin concentration. We aimed to investigate the prognostic factors and the toxicokinetic / toxicodynamic (TK/TD)-relationships. *Methods:* Retrospective chart review of patients admitted to an intensive care unit; prospective TK/TD modelling between glucose infusion rate and plasma insulin concentration (MEIA technology, Axsym® system, Abbott; limit of quantification: 1.0 mU/l); multivariate analysis using step-by step logistic regression to explore prognostic factors; determination of correlations (Pearson tests); presentation of the results as median [25%-75%-percentiles]. *Results:* Twenty-five patients (14F/11M; 46 years [36–58], 52% diabetic, and 20% nurses) were studied. On presentation, Glasgow Coma Score was 9 [4–14] and capillary glucose 1.4 mmol/l [1.1–2.3]. Seven patients were intubated and 5 received catecholamine. Plasma insulin concentration was 197 mIU/l [161–1,566] and total glucose infusion 301 g [184–1,056]. Outcome was favorable except 2 non-survivors and 2 patients with significant neurological sequelae. There was no significant correlation between the injected insulin dose and the administered glucose quantity ($R2 = 0.12$; $p = 0.1$) or the plasma insulin concentration ($R2 = 0.07$; $p = 0.9$). There was a weak correlation between the duration of glucose infusion and the injected insulin dose ($R2 = 0.25$; $p = 0.02$). Delay-to-therapy >6h (Odds-ratio (OR), 60.0; 95%-confidence interval (CI), [2.9–1,236.7]) and ventilation >48h (OR, 28.5; 95%-CI, [1.9–420.6]) were independent prognostic factors. Insulin elimination was of first-order (half-life, 4.3 h [3.7–8.2]; N = 4). During the poisoning course, TK/TD-relationships between glucose infusion rates and insulin concentrations well-fitted the Emax-model (Emax, 29.5 g/h [17.5–41.1]; EC50, 46 mIU/l [35–161]; N = 6). *Conclusion:* TK/TD-relationships are useful to quantify the need for glucose during insulin acute self-poisoning.

245. Antivenom and Neostigmine Failure in Death Adder Envenoming

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Objective: To describe three cases of death adder envenoming that responded poorly to antivenom (AV) and neostigmine. *Case Series:* Case 1. A 14-year-old boy felt a sting while running outdoors. He developed headache and vomiting after 15 min. 6 hrs post-bite he developed ptosis, diplopia on upward gaze and limb weakness. Coagulation studies were normal. He was given one vial of polyvalent AV with only partial improvement. With persistent symptoms the next morning, he was given a second vial of AV to which he responded and was discharged the following day. Case 2. A 53-year-old male was bitten by a death adder while intoxicated. 1hr post-bite he developed ptosis, sixth nerve palsy and required intubation for airway protection. After a single vial of AV he had persistent weakness. Following transfer to a tertiary hospital he was given a second vial of AV. 10 hrs post-bite he had no respiratory effort and persistent weakness. He responded to a bolus of neostigmine with eye opening and respiratory effort. A third vial of AV was given and he was extubated 5hrs later. However, ptosis persisted and he took another 24 hours to recover full power. Case 3. A 50-year-old male was bitten multiple times on his forearms by a death adder. 1hr post-bite the patient was comatose and had a respiratory arrest. He was intubated, ventilated and brought to hospital by helicopter. SVDK performed on urine was positive for death adder venom. The snake was later identified as *Acanthophis antarcticus*. After the first vial of AV, given 5 hrs post-bite, the patient was able to move his left arm. Four further vials of AV given over the next 24hrs did not significantly reverse the neurotoxicity. After an initial response to neostigmine boluses, a 24-hour infusion of neostigmine was administered, however the patient had persistent paralysis requiring ongoing ventilatory support. Neither AV nor neostigmine had dramatic effect on the patient's motor function. He was extubated on day 4 and recovered full motor function by day 7. *Conclusions:* These cases suggest that the neurotoxic effects of death adder envenoming are not reversed or only partially reversed by AV or neostigmine. Although death adder neurotoxicity is thought to be due to reversible and competitive post-synaptic neurotoxins, they may not be completely reversible. Like presynaptic neurotoxicity, early intervention with AV may be important in severe death adder neurotoxicity.

246. Wenckebach Block - An ECG Presentation in Verapamil Poisoning

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Objectives: Verapamil poisonings impair calcium-influx and induce profound negative inotropic effects, hypotension and reduced intracardiac conduction, particularly in SA and AV node. First, second and third degree A-V nodal block is the usual ECG presentation of this intoxication and indicates the severity of the poisoning. *Case Report:* A 29-year-old women was admitted to the Clinic with a history that 1 hour before she had ingested 20 tablets alprazolamum 0.5 mg and 12 film-coated tablets verapamil 80 mg in suicidal attempt. She was somnolent, with TA 80/60 mm Hg, HR 68/min and ECG signs of A-V node block of 2nd degree (Wenckebach block - Mobitz I). Laboratory findings revealed no metabolic or electrolyte disturbances. Verapamil and benzodiazepines were qualitatively confirmed in chromatographic analysis of the urine. During the hospital stay HR fall to 50/min, with persisting signs of Wenckebach block on the monitor and TA decreased to 65/40 mm Hg. She was treated with activated charcoal, 10% $CaCl_2$, atropine, hypertonic glucose with insulin, dopamine and flumazenil. After 16h the ECG showed no signs of A-V block. One week later, 24-hour Holter monitoring was obtained in the patient with no signs of A-V conduction abnormalities. *Conclusion:* Presentation of Wenckebach block in verapamil poisoning is a significant ECG parameter in diagnosing this intoxication. The possible progression of Mobitz I to complete A-V block indicates urgent treatment by taking all therapeutic measures to resolve this hemodinamic and intracardiac conduction inbalance.

247. Heavy Beta Agonist Use Unmasks Possible Hypokalemic Periodic Paralysis in a Susceptible Patient

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Objective: The use of beta-adrenergic agonists causes hypokalemia. However, the decrease from baseline typically is less than 1.0 mEq/L and severe hypokalemia is highly unusual. We report significant hypokalemia and associated musculoskeletal weakness following prednisone and heavy use of albuterol. *Case Report:* A 21-year-old man with a history of asthma presented to the ED with a 1 day history of rapidly progressive, generalized muscle weakness. On arrival, he was afebrile with vital signs: BP, 155/74 mm Hg; HR, 98/min; RR, 25/min; and oxygen saturation, 94% on room air. His neurological examination was remarkable for 0/5 motor strength in the upper and lower proximal muscle groups, with distal muscle groups scored at 3–4/5. In addition, his deep tendon reflexes were significantly diminished. Auscultation of the lungs revealed occasional scattered wheezes. The remainder of his physical examination was normal. Laboratory results included Na, 139 mEq/L; K, 2.0 mEq/L; Cl, 107 mEq/L; bicarbonate, 23 mEq/L; BUN, 3.9 mmol/L; creatinine, 88.4 micromol/L; glucose, 11.0 mmol/L; Ca, 8.9 mEq/L; Mg, 1.2 mEq/L; and P, 0.7 mEq/L. CBC was normal except for a WBC of 37,600 cells/mm^3. Thyroid function tests were normal. Electrocardiogram revealed a prolonged QTc of 492 msec and U waves. Over the next 10 hours the patient received a total of 190 mEq of potassium (as chloride (IV and PO) and phosphate (IV) salts), with complete resolution of muscle weakness in the same time period. Serum potassium was 2.2 mEq/L at 10 hours, and increased to 4.5 mEq/L at 19 hours. The patient reported a recent asthma exacerbation with increased use of his albuterol metered dose inhaler, at times as often as 2 puffs every 30 minutes, and 40–60 mg of prednisone daily over the previous 4 days. Family history was remarkable for maternal hypokalemia of unknown etiology and paternal hyperthyroidism. *Conclusion:* Significant hypokalemia and severe muscle weakness may be associated with the use of a beta-adrenergic agonist. Corticosteroids also may increase the risk of hypokalemia. In addition, this patient may have had a predisposition to develop hypokalemia as a result of an inherited disorder. Hypokalemic periodic paralysis, which has autosomal dominant inheritance, is characterized by episodes of hypokalemia and muscle weakness. Triggers include specific medications such as beta-adrenergic agonists, corticosteroids, and insulin. The risk of uncovering a subclinical inherited disorder during supratherapeutic drug use or overdose in a uniquely susceptible population highlights the need to conduct a thorough family history.

248. Prolonged Severe Toxicity Following Combined Amlodipine and Valsartan Ingestion

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Objective: Overdose of a dihydropyridine calcium channel blocker, such as amlodipine, is considered relatively benign due to its vascular selectivity at therapeutic concentrations. The delayed time to peak concentration, onset of action, and prolonged duration of effect of amlodipine are particularly concerning in excess. An angiotensin II receptor blocker (ARB) such as valsartan, with its ability to blunt vasoconstrictive and sympathetic compensatory responses, could be disastrous in conjunction with amlodipine. We describe a case of severe toxicity associated with amlodipine and valsartan. *Case Report:* A 75-year-old woman presented 45 minutes after a witnessed suicidal ingestion of a "handful" of amlodipine (10 mg) and valsartan (80 mg) tablets. Vital signs were: BP 110/58 mm Hg; pulse 120/min; respirations 18/min, temperature 36.8 C; room air pulse oximetry 98%. Physical examination and laboratory analysis were normal; ECG demonstrated sinus tachycardia. She received 1 gm/kg activated charcoal. Two hours after ingestion her blood pressure fell to 80/45 mm Hg. Hypotension was refractory to calcium gluconate, five liters of IV crystalloid, epinephrine, norepinephrine, phenylephrine, and vasopressin infusions. Repeat ECG demonstrated QTc increase from 433 to 542 ms. Echocardiogram revealed a hyperdynamic left ventricle, normal right ventricle, and no valvular disease. Her mental status remained clear. She was intubated for inadequate respiratory compensation for acidosis and to decrease cardiac demand from work of breathing. Cardiac index reached a nadir of 2.12 L/min/m^2 and systemic vascular resistance was 460 dynes/sec/cm^2. Bolus and infusion therapy with calcium chloride, glucagon, and naloxone were administered, the vasopressin infusion was increased, and the patient was started on high-dose insulin euglycemia (HIE) therapy. HIE therapy produced the most benefit. The remainder of her hospital course was complicated by thrombocytopenia, right lower lobe pneumonia, sepsis, deep venous thromboses, and gastrointestinal hemorrhage. She was discharged 37 days after hospitalization. *Conclusion:* Right heart catheterization confirmed amlodipine's loss of vascular selectivity and negative inotropy in overdose (1). Co-ingestion with an ARB produced profound toxicity. Early institution of HIE therapy to reverse these effects is advocated (2). *References:* 1. Adams BD. Browne WT. Amlodipine overdose causes prolonged calcium channel blocker toxicity. Am J Emerg Med 1998; 16:527–8. 2. Harris N. Case records of the Massachusetts General Hospital. Case 24–2006. A 40-year-old woman with hypotension after an overdose of amlodipine. N Engl J Med 2006; 355:602–611.