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1. CLINICAL SYNDROMES OF NEUROTOXICITY 1: THE BRAIN

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The brain is sensitive to the effects of a large range of substances. Central neurological syndromes encountered in poisoned patients include (a) Reduced level of consciousness is caused by sedative drugs/substances (e.g., alcohols, benzodiazepines and other hypnotics, tricyclic antidepressants, barbiturates, opiates, antipsychotics and gamma hydroxybutyrate) or is occasionally due to hypoxia, acidosis, hypoglycaemia, head injury, cerebral haemorrhage, or infarction. In spite of its limitations, the Glasgow Coma Scale (GCS) is commonly used to describe level of consciousness. Assessment should include history (witnesses, examination, airway, breathing, pupil size, muscle tone, and tendon reflexes. Inadequate airway management is a preventable cause of mortality, carrying a risk of aspiration and respiratory arrest. Endotracheal intubation and mechanical ventilation should be considered for those with GCS < 8, loss of protective laryngeal reflexes, hypoxia, hypercarbia, hyperventilation or refractory seizures. Less severely affected patients may be managed using an oropharangeal airway but frequent assessment is mandatory. Hypoglycaemia should be corrected. Intravenous naloxone is indicated if opioid poisoning is suspected. Patients with prolonged coma will need high-dependency care with regular turning, lung physiotherapy, and a urinary catheter to monitor urine output and to protect pressure areas. The diagnosis should be reassessed regularly. (b) Acute confusional states, often associated with clouding of consciousness (delirium) and hallucinations, can be caused by any drug depressing conscious level, especially anticholinergic and illicit drugs. They may also result from hyperthermia, hyponatraemia, infections, or drug/substance withdrawal. These must be identified and treated. If possible, patients should be managed without drugs or restraint, since sedatives worsen conscious level, hypoxia, and airway control. Benzodiazepines or butyrophenones are usually employed when necessary. Benzodiazepines probably have fewer adverse effects. (c) Convulsions may lead to direct complications such as hypoxia, injury, arrhythmias, and aspiration. Common causes include tricyclic antidepressants, antipsychotic drugs, theophylline, sympathomimetics, and mefanamic acid. Indirect causes of convulsions such hypoglycaemia hyponatraemia, hypocalcaemia, hypomagnesaemia, hypophosphataemia, structural brain lesions, and CNS infections should be identified and treated. Anticonvulsant toxicity or withdrawal may also be responsible. It is important to terminate convulsions rapidly, especially when tricyclic antidepressants and other cardiotoxic agents are involved, since the hypoxia and acidosis caused by the convulsion may precipitate cardiac arrest. Intravenous benzodiazepines are suitable, although there is a risk of respiratory depression. Resistant convulsions may require anaesthesia, neuromuscular paralysis, and mechanical ventilation. (d) Central pyrexia. Pyrexia is a feature of poisoning with sympathomimetic and anticholinergic agents, sepsis, or delerium tremens. Neuroleptic malignant syndrome is characterized by hyperthermia, disturbed conscious level and muscle rigidity, associated with autonomic instability, leucocytosis, tremor, metabolic acidosis, electrolyte disturbances, muscle destruction, and renal failure. It does not appear to be dose-related and usually occurs after use of traditional antipsychotic drugs in therapeutic doses.

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Atypical antipsychotics, antidepressants, and other dopamine antagonists have also been implicated. It usually develops gradually and carries a high mortality. The precipitating agent should be stopped and biochemical abnormalities and dehydration corrected. Temperature should be reduced with physical measures, dantrolene, or bromocriptine. Severely affected patients may require ventilation and dialysis. Serotonin syndrome affects recipients of serotonergic drugs, especially in overdose or in combination. It comprises the rapid onset of altered mental status, neuromuscular hyperactivity, and autonomic instability. Flushing, diarrhea, vomiting, seizures, hyperpyrexia, rhabdomyolysis, renal failure, and coagulopathies can occur. Plasma biochemistry, clotting, creatinine phosphokinase, and urinary myoglobin should be measured. Intravenous fluids are required to correct hypotension, reduce the risk of myoglobin-induced renal failure and to replace insensible losses. Hyperpyrexia should be treated by physical cooling measures. Convulsions usually respond to diazepam or lorazepam. Clonazepam has been used for myoclonic jerks. Cyproheptadine, dantrolene methysergide, and propranolol have all been advocated. Some patients require paralysis and mechanical ventilation.

2. CLINICAL SYNDROMES OF NEUROTOXICITY 2: PERIPHERAL NERVOUS SYSTEM

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Objectives: To understand the physiopathology of toxic neuropathies; to outline the clinical picture of toxic neuropathies; to detail the most important xenobiotics that can cause neuropathies. Background: Many chemicals are known to cause neuropathy in laboratory animals. Some of these have been associated with neuropathy in clinical epidemiological studies. Other chemicals have been reported to be associated with peripheral nervous system

Table 1.

Drugs	Industrial chemicals	Natural toxins
Amiodarone	Acrylamide	Black widow
Chloramphenicol	Allyl chloride	Tetanus
Cisplatin	Carbon disulfide	Tetrodotoxin
Colchicine	Ethylene oxide	Tick paralysis
Dapsone	Hexacarbons	Ciguatoxin
Nucleosides	Methyl N-butyl ketone	
Disulfiram	Parathion	
Diphenylhydantoin	Polychlorinated biphenyls	
Ethambutol	Thallium	
Ethanol	Trichloroethylene	
Ethionamide	Triorthocresyl phosphate	
FK 506	Vacor rodenticides	
Hydralazine	Vinyl chloride	
Interferon-A		
Isoniazid		
Gold		
Glutethimide		
Lithium		
Nitrofurantoin		
Nitrous oxide		
Perhexiline maleate		
Podophyllin		
Pyridoxine		
Taxol		
Thalidomide		
Vincristine		

dysfunction and neuropathy on the basis of retrospective and cross-sectional epidemiological studies. Other associations have been made from many case reports and case series. Pathophysiology and clinical picture: Neuropathy may be classified by presentation (i.e., motor or sensory symptoms), electrodiagnostic aspects, and neuroanatomical location within the peripheral nerve (i.e., demyelinating or axonal, neuronopathy, ion channel neuropathy, neuromuscular transmission) or location (i.e., cranial or peripheral). Toxic neuropathy refers to those presentations that are caused by drug ingestion, drug or chemical abuse, or industrial chemical exposure at the workplace or from the environment. Anatomically, toxic neuropathies may be divided into three groups: (1) distal axonopathy causing "dying back" (regressive) axonal degeneration, (2) myelinopathy or schwannopathy with primary segmental demyelination, (3) neuronopathy, i.e., neuropathy affecting the cell body, especially of the dorsal root ganglion. Distal axonopathy is the most common form, whereas a few agents have been associated with the second and third type. Axonopathies presents clinically as a "triad of sensory changes in a glove and stocking distribution, distal weakness, and hyporeflexia." The sensory changes include sensory loss in a stocking-glove distribution. Often, progression is distal to proximal. In severe cases, motor dysfunction such as abnormal gait and foot drop may also occur. The recovery could be prolonged. Denervation atrophy is possible. This common clinical pattern is the consequence of pathology related to length and size of axons, whereby the longest and largest axons are affected first and progression occurs with subsequent damage to shorter and smaller axons (Dying-back degeneration). Metabolic processes essential to the maintenance of axonal integrity are primarily affected. Failure of these processes would initially affect fibers in which demand for maintenance is high (largest axons) and delivery of metabolites most challenging (longest axons). Giant axonal swelling has been viewed historically as the morphological hallmark of some axonopathies. However, accumulating evidence suggests axonal swelling could be considered to be of secondary importance or an epiphenomenon. Swollen axons cannot be considered pathogenically necessary or sufficient since peripheral nerve dysfunction can develop irrespective of expression. Causes: A variety of drugs, industrial chemicals, and natural toxins can cause neuropathy (Table 1). Acrylamide is a widely used monomer that produces peripheral neuropathy with a "Dying-back degeneration" mechanism. The specific molecular site and mechanism of toxicant action leading to specific morphological and behavioral abnormalities requires definition. The use of methylcobalamin to ameliorate acrylamide toxicity is being explored. A new immunosuppressant, FK 506, has replaced cyclosporin to facilitate organ transplantation, but unwanted effects, including peripheral neuropathy, have been documented in some patients. Ethanol causes a peripheral neuropathy showing features of axonopathy and demyelination. It is probably due to nutritional deficiency rather than to a direct effect of ethanol. Triorthocresyl phosphate is the prototype of some OP compounds that interfere only slightly with acetylcolinesterase and produce a delayed distal axonopathy. Neuropathy target esterase (neurotoxic esterase, NTE), a protein thought to be involved in the production of OP compound-induced delayed neurotoxicity, has been postulated to be a component of endogenous neuronal protein phosphorylation systems. References: Albers J, Bromberg MB: Chemically induced toxic neuropathy. In: Rosenberg NL, ed. Occupational and Environmental Neurology. Boston: Butterworth-Heinemann; 1995: 175–234. Berger AR, Schaumberg HH: Disorders of the peripheral nervous system. In: Rosenstock L, Cullen MR, eds. Textbook of Clinical Occupational and Environmental Medicine. Philadelphia: Saunders; 1994: 482–513. Feldman RG: Occupational and Environmental Neurotoxicology. Philadelphia: Lippincott-Raven; 1999. Kimura J: Polyneuropathies. In: Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. 2nd ed. Philadelphia: FA Davis; 1989: 462–81.

3. EXCITATORY AND INHIBITORY MECHANISMS IN ACUTE TOXIC NEUROLOGICAL SYNDROMES

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Introduction: The central nervous system contains nerve cells that are interconnected. They "communicate" by releasing chemical messengers—nerve transmitter substances (neurotransmitters)—in response to electrical activity. Electrical activity depends on the ionic charge (e.g., potassium, K+, and sodium, Na+) inside and outside the cell membrane. Resting cells are "polarized"—negatively charged inside. An electric current flows when the negative charge is neutralized and the cell "depolarises." Those things that increase the likelihood of electrical activity are excitatory; those that reduce the likelihood are inhibitory. Nerve transmitter substances are chemicals. They are released from one cell and affect the next cell in a chain. Some neurotransmitters act on cells to excite them, and some to inhibit them. In the normal brain, excitatory and

inhibitory actions are balanced. Excitatory syndromes arise either because excitatory actions increase, or because inhibitory actions decrease. Inhibitory syndromes arise either because inhibitory actions are increased, or excitatory actions decrease. Neurotransmitters, and what they do: More than 300 neurotransmitter substances may exist, but only a few are important for most purposes. Examples include acetylcholine, noradrenaline (norepinephrine), dopamine, serotonin (5-hydroxytryptamine, 5HT), gamma-aminobutyric acid (GABA), glutamate, glycine, enkephalin. The neurotransmitters interact with nerve and muscle cells at specialized points called receptors. Some receptors can influence directly the way ions such as sodium and potassium move into or out of cells, and so influence the transmission of electrical signals, because they are associated with ion channels—the special "passages" that allow ions through the cell membrane. Other receptors are associated with special proteins, G proteins, that span the cell membrane from inside to outside. If a neurotransmitter binds to its specific G protein receptor on the outside of a cell membrane, then the part of the G protein inside the cell can influence events within the cell. Some neurotransmitters can bind to several different subtypes of receptor, and these different subtypes can have different, and sometimes opposing, effects. For example, noradrenaline released from a nerve ending can bind to alpha1-receptors that are excitatory, and on the next nerve, but also on alpha2-receptors that are inhibitory, and on the nerve from which the noradrenaline has been released. This limits the stimulatory effect of the noradrenaline-releasing nerve. Excitatory toxic syndromes: Serotoninergic agents, including selective serotonin reuptake inhibitors such as fluoxetine, can cause serotonin syndrome. This has three groups of clinical features: alteration of mental status—confusion, coma; neuromuscular hyperactivity—tremor, myoclonus, convulsion; and autonomic instability—tachycardia, hypertension or hypotension, sweating, fever. Amphetamines and ecstasy, cocaine, and theophylline are all examples of indirectly acting agents that work by increasing the release or augmenting the effects of excitatory neurotransmitters including noradrenaline, serotonin, and dopamine. The clinical features of poisoning include: psychiatric—agitation, confusion, anxiety; psychosensory—hallucinations; motor—tremor, ataxia, convulsion; and autonomic—tachycardia, hypertension, arrhythmia, dilated pupils, sweating, hyperpyrexia. Agents that antagonize the inhibitory nerve transmitter substance acetylcholine are called anticholinergics, or if they affect only the parasympathetic nervous system, antimuscarinics. The classic patient is febrile (hot as a hare); unresponsive (mad as a hatter); with dilated pupils and blurred vision (blind as a bat); red skin (red as a beet), and without secretion of sweat or saliva (dry as a bone). Strychnine, formerly used as a pesticide, antagonizes the spinal inhibitory neurotransmitter glycine and causes uncontrolled muscular convulsions, without loss of consciousness. Withdrawal of inhibitors that have been present in large amounts can also lead to excitatory syndromes. Alcohol, benzodiazepines, and barbiturates all cause withdrawal syndromes in which insomnia, restlessness, and seizures are common. Opioid withdrawal is followed by restlessness, dilated pupils, diarrhea, runny nose, and other excitatory symptoms. Inhibitory toxic syndromes: GABA is the principle inhibitory neurotransmitter in the central nervous system. It acts on receptors in the cell membrane that allows chloride (Cl^-) ions to flow through the membrane into the cell, and hyperpolarize (stabilize) the cell so that it is less likely to transmit an electrical impulse. The receptor consists of 2 alpha, 2 beta, and a gamma subunit grouped-round a pore. It is the major site of benzodiazipine action (anticonvulsants, hypnotics, muscle relaxants, sedatives), and is also responsible, at least in part, for the actions of alcohol and barbiturates. There is a hierarchy of inhibitory effects mediated by ethanol and benzodiazepines. These include higher centres—disinhibition; cerebellum—ataxia, nystagmus; sensory pathways—anaesthesia; reticular activating system—unconsciousness; brain stem—respiratory arrest. Flumazenil prevents the actions of benzodiazepines at benzodiazepine binding sites on GABA receptors, and so reverses the effects. Opioids, including morphine, diamorphine (>MAM > morphine), codeine, methadone, and buprenorphine, cause a characteristic inhibitory syndrome by their actions at opioid receptors. The major effects, due to actions at the mu-receptor, are analgesia, respiratory depression, and constriction of the pupils. These effects can be reversed rapidly by the administration of the specific opioid antagonist naloxone, provided the opioid itself is not too tightly bound to the receptor. Summary: A great deal of practical toxicology can be understood in terms of a simple balance between excitatory and inhibitory forces in the central nervous system.

4. MANAGEMENT OF BEHAVIOR DISTURBANCE IN THE INTOXICATED PATIENT

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Management of disturbed patients in the setting of clinical toxicology is often a major clinical challenge. As in all physical disorders it is important to consider a differential diagnosis and to exclude causes that may be reversed before use of central sedatives. Disturbed behavior in children and adults carries different connotations. In children poisoning is likely to be

accidental and behavior disturbance will either be the result of metabolic effects of the toxin or due to direct effects of the toxin on the central nervous system. In adults in addition to these causes, since intoxication is more likely to be intentional than accidental, one also has to consider a primary psychiatric diagnosis as part of the differential. In adults psychiatric disorders include psychoses, delirium, phobic states, and personality disorders. In addition it is important to consider drug withdrawal in the differential, particularly withdrawal from benzodiazepines, ethanol, and opiates. Other causes of behavior disturbance include metabolic changes including in particular hypoglycaemia, hypo and hypernatraemia, and vitamin deficiency states, in particular Wernicke-Korsakoff syndrome. Hypoxia and hypoxic brain damage also need to be considered as possible aetiologies, together with encephalopathies of various sorts, including those due to toxins, and those to other conditions, including viral encephalitis. Toxins that may cause acute behavior disturbance are most commonly those that induce psychoses, that is, drugs that have central monoamine effects, including amphetamine, amphetamine derivatives (MDMA), and cocaine; anticholinergics, including antihistamines with anticholinergic effects such as diphenhydramine; dissociative anaesthetics, such as ketamine; hallucinogenic mushrooms; LSD. In addition agents causing a toxic encephalitic process, hypoxic state or secondary hypoglycaemia (e.g., insulin, sulphonylureas, alcohol, sodium valproate) also need to be considered. Management of the disturbed patient therefore includes a full assessment of mental state and an exclusion of potentially reversible metabolic syndromes. A decision needs to be made as to whether therapeutic intervention is necessary, or whether the patient can be cared for simply by standard nursing care in a quiet environment. This may be sufficient for the less-disturbed patient. If it is deemed necessary to treat a patient who has significant agitation, and is a risk to either themselves or to others, a careful management plan needs to be drawn up. This needs to include the objectives of the proposed treatment, and may involve calling in additional nursing and medical staff to ensure physical control of the patient is achieved. In some situations it may be advantageous to obtain a psychiatric opinion. Therapeutic agents that are used to manage disturbed patients fall into two main classes. Sedatives, of which the commonest used are benzodiazepines, with various durations of action—and antipsychotics. From the perspective of the toxicologist the smallest dose of the most effective agent should be chosen. Patients who are acutely disturbed, in particular those who have used drugs on a regular basis, may be resistant to conventional doses of drugs in these classes. There are problems about obtaining appropriate routes of access, particularly when considering parenteral therapy. For speed of onset, the most appropriate route is intravenously, and agents such as diazepam, lorazepam or midazolam will all work in a similar time frame, since they are lipid soluble and have ready access to the brain. The offset of action of all these drugs relates to two factors, first uptake into lipid, and second elimination by the liver. In the case of diazepam it is the former process which is primarily responsible for the offset of its acute clinical effects following standard therapeutic dose. In the case of lorazepam and midazolam elimination is also an important factor. Benzodiazepines have the advantage that they cause little else in the way of pharmacological effects, other than those on the central nervous system. Their only disadvantage is the lack of intramuscular formulations for some of these agents, and the potential to cause respiratory depression when given rapidly intravenously. In addition in some patients a paradoxical reaction to benzodiazepines may be seen in which the disinhibiting effect of these drugs becomes predominant over their sedative effects. In this situation patients' behavior may deteriorate following administration of a benzodiazepine. For this group of patients, and for those with psychotic behavior dopamine receptor antagonist compounds offer a more targeted central nervous system effect. These drugs are, however, ones that tend to posses other pharmacological effects, in particular alpha receptor antagonist activity, with the resulting risk of hypotension, and effects on ion channels, resulting in the risk of arrhythmias secondary to QT prolongation and perhaps of convulsions. Recent concern about the cardiotoxicity of thioridazine has meant this drug has effectively been withdrawn from use in many countries. The alternatives now include haloperidol or chlorpromazine. These agents are generally not licensed for intravenous use, although haloperidol is effective intravenously if appropriate monitoring can be undertaken. This may be difficult in an acutely disturbed patient. One problem with intramuscular administration is the duration of time between administration and onset of CNS actions. Patients in this group represent one of the most challenging management problems in medicine. An understanding of the underlying basic mechanisms involved in the pathophysiological process aids the clinician in treatment.

5. ORGANOPHOSPHORUS COMPOUNDS AND DELAYED PERIPHERAL NEUROPATHY

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Occurrence: Organophosphate-induced delayed polyneuropathy (OPIDP) is a rare toxic effect in humans, although some epidemics have occurred in the past. Neuropathy is characterized by a symmetric distal sensory-motor

central–peripheral axonopathy that affects the legs and, in the most severe cases, also the arms. Not all organophosphates (OP) are capable of causing OPIDP and in the case of OP insecticides currently in use, polyneuropathy develops exclusively after a severe episode of cholinergic toxicity. However, OPIDP is not a consequence of acute cholinergic toxicity but another toxic effect of OPs and in the case of insecticides it will develop at a much higher dose than that which causes cholinergic overstimulation. Insecticides which caused OPIDP in humans include chlorpyrifos, dichlorvos, isofenphos, methamidophos, mipafox, trichlorphon, and trichlornate (Lotti 2000, 2001). Peripheral nerve dysfunction was reported as the consequence of low-level exposures to OPs in U.S. Gulf War veterans and in British sheep-dipping farmers. Apparently none of these individuals ever experienced a characteristic syndrome of acute poisoning by anticholinesterases. However, epidemiological and clinical evidence do not support the proposal that low-level exposures to OPs cause peripheral neuropathy (Lotti 2002). Mechanism: OPs are triesters of phosphoric acid which react covalently with serine esterases at their catalytic center. A neuronal protein with esterase activity, known as Neuropathy Target Esterase (NTE), is tought to be the molecular target of OPs causing OPIDP (Johnson 1990). OPs act as pseudo-substrates for a variety of serine esterases, including NTE. The rate of hydrolysis of the phosphorylated NTE is extremely slow, thus NTE becomes virtually permanently inhibited. The phosphorylated enzyme can subsequently undergo a second reaction, known as aging, which results in the liberation of one of the bound OP's alkyl groups. This leaves the active-site serine residue covalently attached to a negatively charged mono-organophosphoryl moiety. This two-step mechanism, occurring within hours after poisoning, is tought to initiate OPIDP. Other OPs such as organophosphinates also covalently react with the active-site serine residue, but cannot undergo the aging reaction. As a consequence, these OPs do not cause OPIDP and, when given to experimental animals before a neuropathic OP, they protect from OPIDP. This mechanism of OPIDP initiation suggests that either neuropathic OPs cause loss of a non-esterase function of NTE which is required by axons, or NTE has no essential role, but placing a negative charge at its active site induces a toxic gain of function which initiates OPIDP (Glynn 1999). Recent studies with the recombinant domain of NTE purified from bacterial lysates suggest that membrane lipids are the putative cellular substrates of this enzyme, raising the possibility that NTE may be involved in intraneuronal membrane trafficking (van Tienhoven et al. 2002). Clinical manifestations: Symptoms of OPIDP begin 2–3 weeks after single doses when, as in the case of insecticides, cholinergic symptoms have subsided. The lag time between single or short-term exposure and the clinical onset of OPIDP depends on both the chemical involved and the dose. OPs with slow pharmacokinetics may cause OPIDP after a prolonged period following exposure (up to 4 weeks), whereas higher doses of OPs that are powerful in causing OPIDP may shorten this period to about 10 days. Clinical features of OPIDP are usually fully expressed within a few days of the onset of symptoms and signs, and no progression has been observed in the absence of further exposure. After repeated exposures, such as those to non-anticholinesterase OPs, the onset of symptoms and their full development is more variable and less definible. The usual initial complain is cramping muscle pain in the legs, followed by distal numbness and paresthesia. Progressive leg weakness occurs, together with depression of tendon reflexes. Symptoms and signs may also appear in the arms and forearms following those in the legs, but always after severe exposure. Physical examination reveals symmetrical predominantly motor polyneuropathy, with wasting and flaccid weakness of distal limbs muscles, especially in the legs. Signs include a characteristic high-stepping gait associated with bilateral foot drop. Severe OPIDP may result in quadriplegia with foot and wrist drop as well as pyramidal signs. In time there is a complete functional recovery if spinal cord axons have been spared by smaller doses; otherwise, pyramidal and other signs of central neurological involvement may become more evident. The degree of pyramidal involvement determines the prognosis for functional recovery, and spastic ataxia may represent a permanent outcome of severe OPIDP. Objective evidence of sensory loss is usually slight or absent. The electrophysiological changes accords well with the histopathological findings of a distal axonopathy and paralles clinical signs of peripheral neuropathy (Moretto and Lotti 1998). References: Glynn P. 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6. SOLVENT ENCEPHALOPATHY—A CRITICAL APPRAISAL

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When large doses of organic solvents are inhaled certain central nervous system (CNS) effects are known to occur. An acute narcotizing response similar to that seen with general anesthetic agents has been described. A chronic encephalopathy has been well characterized in individuals who inhale high concentrations of toluene. However the latter effects appear to occur after the inhalation of this solvent at such high doses that the effect is seen in individuals whose exposure is from intentional long-term abuse (1). This effect has not been rigorously documented, however, in individuals with lower-level toluene inhalation, such as that seen following occupational exposure. For toluene abusers there is a robust relationship between the cumulative dose of toluene inhaled and magnetic resonance imaging demonstrable sub-cortical abnormalities (1). In contrast, attempts to characterize neurocognitive deficits in this group by formal neuropsychological testing failed to demonstrate a similar dose response relationship, suggesting that the latter studies may be limited to their ability to define the encephalopathy (1). Concern for the possibility of central nervous system effects following chronic low-level occupational organic solvent exposure was initially generated from noncontrolled observations on a group of house painters published in 1979 and 1981 (2,3). These studies, using nonvalidated testing procedures, gave rise to the concept of "painter's syndrome," a concept which has been described in the literature by a prodigious series of other terms, for example the "psycho-organic syndrome." These studies have served as the impetus for a very large number of publications attempting to evaluate the relationship, if any, between occupational organic solvent exposure and CNS effects. Most of this literature, however, is limited by being anecdotal, noncontrolled, failing to assess confounding factors, lack of exposure assessments, or failure to demonstrate a dose–response relationship. Because of the limitations of studies with the above uncertainties the literature supporting the concept of chronic encephalopathy following occupational solvent exposure started to be criticized in the mid-1980s (4). In 1985 the World Health Organization promulgated a grading scale for characterizing cases of possible solvent encephalopathy (5). However, this categorization relies heavily on nonspecific symptoms, does not consider alternative diagnoses, and does not require any assessment of exposure or dose. Many studies on solvent encephalopathy have utilized the WHO classification. Further skepticism regarding the concept of occupationally induced solvent encephalopathy was spurned in 1988 when the group that published the original studies on painter's syndrome (2,3) re-evaluated their population using a nonexposed matched controlled population. Compared to the control group, the organic solvent exposed subjects had no evidence of impairment in this reanalysis (6). Most controlled studies have failed to document a relationship between occupational exposure to organic solvents and chronic adverse CNS effects (e.g., 7–12). One detailed analysis of 30 cases of presumed toxic encephalopathy, all of whom were claimants in litigation because of this diagnosis, found either lack of demonstrable neurologic abnormalities or alternative explanations in all patients (13). Thus, at present, the existing data is insufficient to assert that there is a causal nexus between occupational organic solvent exposure and chronic encephalopathy. A second important question is whether the adverse effects seen with chronic high-dose toluene inhalation are specific to this solvent or represent an effect that is potentially attributable to all organic solvents. The author hypothesizes, based on the very well characterized encephalopathies that derive from the chronic ingestion of high doses of the solvent ethanol, that this effect may be a general consequence of the exposure to large amounts of organic solvents. However, here too, the existing scientific data is inadequate to support a definitive conclusion regarding this hypothesized class effect. References: 1. Rosenberg N, Grigsby J, Dreisbach J et al. Neuropsychologic impairment and MRI abnormalities associated with chronic solvent abuse. *J Toxicol Clin Toxicol* 2002;**40**:21–34. 2. Arlein-Soborg P, Bruhn P, Gyldensted C et al. Chronic painters' syndrome: chronic toxic encephalopathy in house painters. *Acta Neurol Scand* 1979;**60**:149–156. 3. 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7. CHRONIC CENTRAL NERVOUS SYSTEM EFFECTS OF MDMA AND RELATED DRUGS

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MDMA (3,4-methylenedioxymethamphetamine) has come into prominence in Europe over the last 15 years mainly because of its widespread use and highly publicized but relatively uncommon cases of severe toxicity. The acute effects following MDMA ingestion may include euphoria, wakefulness, appetite suppression, and empathy, together with muscle stiffness and jaw clenching (trismus). These effects may be attributed to MDMA's powerful ability to release serotonin (5-HT), and, to a lesser extent, its dopaminergic action. This is followed by temporary 5-HT depletion together with a reduction in tryptophan hydroxylase (TPH) activity, which may account for the residual effects following MDMA ingestion. These include dysphoria and mild cognitive impairment amounting to a "mid week low" following weekend ingestion of MDMA (Curran & Travill, 1997). Patterns of use may reflect the time taken for recovery after use (Solowij et al, 1992). The duration of the residual effects has not been quantified, though the typical interval of two to four weeks between uses of the drug suggests that they may continue for weeks rather than for a few days. Chronic central nervous system effects emerging after long-term use may be related to serotonergic axonal loss and associated functional deficits in learning and memory. There is compelling evidence to support serotonergic neurotoxicity, which has been described in every animal species studied. More recently, evidence of dopaminergic neurotoxicity has emerged following administration of acute repeated high doses of MDMA to non-human primates (Ricaurte et al, 2002). Neurotoxicity has not been definitively demonstrated in man, though electrophysiological and electroencephalo-graphic evidence support its existence (Croft et al 2001; Dafters et al 1999). Evidence from imaging studies also suggests serotonergic neurotoxocity (Semple et al, 1999), which may be persistent (Reneman et al, 2001). The clinical significance of the neurotoxic potential of MDMA in human users remains to be established. Numerous studies comparing MDMA users with nonusers on cognitive tests have found MDMA users significantly impaired on measures of immediate and delayed recall (Parrott et al, 1998), the effect being more marked in heavy users. However, studies comparing users with nonusers rarely take individual differences into account and many fail to consider that the memory deficits observed may be associated with polydrug use. Prospective human studies that control for extraneous factors are the way forward to uncover the truth about ecstasy. In one such study, MDMA use was associated with progressive cognitive decline over 1 year (Zakzanis & Young, 2001). However, despite their practical importance, such experiments are difficult to conduct due to ethical concerns and methodological problems. The serotonergic neurotoxicity of MDMA may be expected to lead to psychiatric illness. There have been a number of case reports of immediate and long-term adverse psychological effects following MDMA use (Cohen, 1995). The severity and duration of psychological effects may depend on the number of risk exposures and the extent of polydrug use involved (Schifano et al, 1998). Other amphetamine derivatives related to MDMA have also come into prominence. Some of these drugs appear to have a different spectrum of acute effects to MDMA. Their potential for serotonergic neurotoxicity has been less well studied, and long-term effects have not yet been reported. Part of the problem is that MDMA is so widely used, and other related drugs have not achieved such prominence. It is well established that long-term marijuana (cannabis) use has been associated with adverse neurophysiological effects on the frontal lobes (Lundqvist et al, 2001) and functional deficits in memory and behavior. Since many MDMA users also report the use of cannabis, it is difficult to establish the true effects of MDMA on humans

and make an accurate hazard assessment (Gouzoulis-Mayfrank et al, 2002). Future studies will have to control more effectively for cannabis use. It may be expected that any adverse effects resulting from MDMA and related drugs may be accelerated by age related decline. Since there is already early evidence of cognitive effects from MDMA, it is clear that the long-term socio-economic implications of the use of MDMA and related drugs may be considerable. References: Cohen RS. Subjective reports on the effects of the MDMA (ecstasy) experience in humans. *Prog Psychopharmacol Biol Psychiatry* 1995;**19**:137–45. Croft RJ, Klugman A, Baldeweg T, Gruzelier JH. Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. *Am J Psychiatry* 2001;**158**:1687–92. Curran HV & Travill, RA. Mood and cognitive effects of (±3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): weekends high followed by mid-week low. *Addiction* 1997;**92**:821–831. Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. *Psychopharmacology (Berl)* 1999;**145**:82–90. Gouzoulis-Mayfrank E, Becker S, Pelz S, Tuchtenhagen F, Daumann J. Neuroendocrine abnormalities in recreational ecstasy (MDMA) users: is it ecstasy or cannabis? *Biol Psychiatry* 2002;**51**:766–9. Lundqvist T, Jonsson S, Warkentin S. Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicol Teratol* 2001;**23**:437–43. Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. Cognitive performance in recreational users of MDMA of 'ecstasy': evidence for memory deficits. *J Psychopharmacol* 1998;**12**:79–83. Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J. Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Arch Gen Psychiatry* 2001;**58**:901–6. Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD. Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"). *Science* 2002;**297**:2260–3. Schifano F, Di Furia L, Forza G, Minicuci N, Bricolo R. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. *Drug Alcohol Depend* 1998;**52**:85–90. Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone EC. Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* 1999;**175**:63–9. Solowij N, Hall W, Lee N. Recreational MDMA use in Sydney: A profile of "Esctasy" users and their experiences with the drug. *Br J Addict* 1992;**87**:1161–72. Zakzanis KK, Young DA. Memory impairment in abstinent MDMA ("ecstasy") users: a longitudinal investigation. *Neurology* 2001;**56**:966–9.

8. TEMPERATURE DISTURBANCE IN NEUROLEPTIC MALIGNANT AND SEROTONIN SYNDROMES

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Background: The neuroleptic malignant syndrome and the serotonin syndrome are rare but life-threatening complications in therapy and poisonings with psychotropic drugs. Both syndromes are typically characterized by altered mental state, neuromuscular abnormalities, and autonomic dysfunction. Hyperthermia is a common feature in both syndromes standing usually for a very severe disease process, with significant mortality and complication rates. Early recognition of these syndromes is essential for their successful treatment. Neuroleptic malignant syndrome (NMS): The NMS was first described and named by Delay and Deniker in 1968 after the introduction of neuroleptics in 1960. Its incidence is estimated at approximately 0.2% of patients treated with neuroleptics. The aetiology of NMS is related to a dysregulation of the dopaminergic system with a blockade of the dopaminergic transmission in the basal ganglia and in the hypothalamus. The blockade of dopamine receptors in the hypothalamus is thought to lead to impaired heat dissipation and the blockade of dopamine receptors in the corpus striatum is thought to cause muscular rigidity, generating heat. The excess heat production, in association with a decrease in heat dissipation, produces hyperthermia in NMS. Contributing factors to developing NMS include ambient heat, dehydration, infection, concurrent organic brain disease, dementia, high dosing and depot forms of neuroleptics, history of alcoholism and previous episodes of NMS. NMS is associated with all neuroleptics in current use, including phenothiazines, butyrophenones, thioxanthenes, benzamides, and miscellaneous novel antipsychotic agents such as clozapine and risperdone. Abrupt discontinuation of antiparkinsonian agents (e.g., L-dopa) have also been reported to produce NMS. The onset of the syndrome is not related to the duration of exposure to neuroleptics or to toxic overdoses. NMS typically develops over a period of 24–72h. and lasts 5 to 10 days after oral neuroleptics are discontinued. The characteristic clinical symptoms associated with NMS are 1) hyperthermia, 2) muscle rigidity, 3) autonomic instability, and 4) altered consciousness. Temperature varies from mild elevations to marked hyperthermia with 41°C and higher. The muscle rigidity may be accompanied by extrapyramidal symptoms including akinesia, dyskinesia, dysarthria or fluctuating tremor and

develops concomitantly with or shortly before temperature elevations. Autonomic instability may result in a massive peripheral hyperadrenergic state with hypertension, tachycardia, and diaphoresis. The altered consciousness ranges from confusion, psychomotor agitation or alert mutism to stupor or coma. Other clinical signs of lesser frequency such as opisthotonus, seizures, Babinski's signs, and trismus have been reported. Clinical features are accompanied by the laboratory findings of increased creatine phosphokinase (CPK), leukocytosis, elevated pCO_2 and myoglobinuria. Beside this typical constellation, there exist incomplete forms of NMS, in which some of the classic clinical features are at least initially absent. Complication in NMS include acute myoglobinuric renal failure secondary to rhabdomyolysis, aspiration pneumonia, tachypneic hypoventilation due to increased muscle tone and decreased chest-wall compliance, arrhythmias and cardiac arrest in consequence of hyperkalemia, hypercapnia due to an increased carbon dioxide production, thromboembolism, thrombocytopenia and disseminated intravascular coagulation. The mortality rate in NMS is estimated at 11 to 15%. The most important differential diagnoses are central nervous infections, serotonin syndrome, anaesthetic-induced malignant hyperthermia, phenothiazine-related heat stroke, tetanus, stiff-man syndrome, acute dystonic reactions, malignant catatonia, thyrotoxicosis and poisonings with monoamine oxidase inhibitors or lithium. In addition to a careful history and physical examination diagnostic procedures include laboratory tests with the measurement of electrolytes, creatinine, urea nitrogen, liver enzymes (ALT, AST), creatine kinase (CK), C-reactive protein, and thyroid hormones in the serum, complete blood count, coagulation tests, blood gas analysis and toxicological and microbiological screening. The technical diagnostic procedures comprise CT scan or MRI of the brain, electroencephalogram (EEG), electrocardiogram (ECG), chest X-ray and lumbar puncture. The management of NMS focuses primarily on discontinuation of the neuroleptic medication and symptomatic treatment including fluid and electrolyte replacement and physical cooling measures. Pharmacological treatment comprise mainly dantrolene and bromocriptine. Dantrolene exerts its therapeutic effect by means of the blockade of calcium release from the muscle fiber's sarcoplasmic reticulum, decreasing available calcium for ongoing muscle contracture. The drug is a nonspecific, directly acting muscle relaxant and a decrease in body temperature coincides with muscle relaxation. The initial dosage should be $2\,mg\,kg^{-1}$ given intravenously. The dose may be repeated every 10 min, up to a total dose of $10\,mg\,kg^{-1}$. The therapeutic effect of bromocriptine is related to its dopamine agonism, resulting in enhancement of dopaminergic transmission. Bromocriptine doses range from 2.5 to 10 mg three times a day and lead to a decrease in rigidity and temperature within a few hours strengthening the hypothesis of a dopamine-receptor blockade in NMS. Occasionally, bromocriptine has been implicated in the production of the serotonin syndrome. Its use in patients with serotonin syndrome misdiagnosed as having NMS may potentially result in worsening of serotoninergic signs. Other proposed drugs are pancuronium, carbamazepine, the dopamine agonist amantadine, and benzodiazepines. However, the benefit of adding specific treatment approaches to supportive measures is still debated. There are no controlled studies of treatments for NMS. Efficacy of specific therapies is supported only by single case reports and by one study evaluating treatment options of 64 cases derived from a review of the literature. Another therapeutic option in NMS is the electroconvulsive therapy (ECT) with full anesthesia and muscle relaxation which has improved some symptoms of NMS, notable fever, sweating and level of consciousness. However, its role remains controversial and ECT should be reserved for cases of NMS that fail to respond to supportive and pharmacological therapy. Haemodialysis may be indicated in case of renal failure. Rechallenge with neuroleptics with the same potency has a very high risk of recurrent NMS. The safest approach for prevention of recurrence is a regimen where doses of low-potency neuroleptic are increased very slowly. Serotonin syndrome (SS): The SS is an occasionally fatal disorder increasingly reported in the literature due to expanding use of highly serotonergically active agents. The SS is caused by excess stimulation of serotonin-receptors (5-HT-receptors) and most investigators favor the central $5\text{-}HT_{1A}$ receptor as the primary target of this excess stimulation even though other central and peripheral subtypes of 5-HT-receptors may be involved in the aetiology of the SS too. There are different pathways by which excess $5\text{-}HT_{1A}$ receptor stimulation can occur. Excess amounts of serotonin precursors or agonists (L-tryptophan, lithium, LSD, L-dopa and buspirone), enhanced release of serotonin (cocaine, 3,4-methylenedioxymethamphetamine [MDMA or "ecstasy"]), decreased serotonin reuptake (SSRIs and tricyclic antidepressants) and decreased serotonin metabolism (MAOIs) have been shown to cause $5\text{-}HT_{1A}$ receptor stimulation and to trigger serotonin syndrome. Generally, a combination of two or more agents that increase serotonin availability by separate methods must be coadministered for the syndrome to develop, although cases involving a single agent have been reported. The most common drug combinations causing the serotonin syndrome are monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs), MAOIs and tricyclic antidepressants (TCAs), MAOIs or SSRIs in combination with tryptophan, pethidine and dextromethorphan and SSRIs or TCAs in combination with lithium. The SS is characterized by a rapid onset with the classic triad of altered mental status, autonomic dysfunction, and neuromuscular abnormalities. Altered mental status ranges from drowsiness and agitation to confusion and coma. Autonomic dysfunction includes hyperthermia, blood pressure fluctuation, tachycardia, diaphoresis, diarrhea, mydriasis, and shivering. Neuromuscular abnormalities result in

hyperreflexia, incoordination, ataxia, myoclonus, rigidity, tremor, and nystagmus. Laboratory findings may include an increase of total WBC count, creatine phosphokinase and arterial pCO_2. For the diagnosis of SS Sternberg suggested a constellation of at least three of the following symptoms: mental status changes, agitation, myoclonus, hyperreflexia, hyperthermia, shivering, diaphoresis, ataxia, tremor, and diarrhea, in the setting of a recent addition or increase in dosage of a serotonergic agent. In addition, other aetiologies for these clinical features should have been ruled out, and no neuroleptics should have been started or increased in dosage prior to the onset of these symptoms. Mild to moderately severe cases of the serotonin syndrome usually resolve completely within 24 to 72h. Severe cases of SS may be complicated by rhabdomyolysis, myoglobinuric renal failure, hyperkalemia, ventricular arrhythmias, hypercapnia due to an increased carbon dioxide production, respiratory failure, disseminated intravascular coagulation, and seizures. Suggested differential diagnoses of SS encompass other diseases, including NMS, malignant catatonia, acute dystonic reactions, meningoencephalitis, thyrotoxicosis, malignant hyperthermia, tetanus, heat stroke, delirium tremens and poisonings with amphetamines, cocaine, lithium, LSD and MAOIs. In particular the NMS and the SS are very similar and may be easily confused, but careful medical history and physical examination may solidify the distinction. Common to both conditions are hyperthermia, altered consciousness, diaphoresis, autonomic instability, and elevated CPKs. NMS, however, typically presents after prolonged exposure to neuroleptics or withdrawal of dopamine agonists. The onset is usually slow and the physical examination is characterized by "lead-pipe" rigidity and akinesia, but not by myoclonus, hyperreflexia, hyperkinesia, shivering, dilated pupils, or diarrhea. Laboratory tests do not distinguish between the two syndromes. At this time, no prospective studies of the management of the SS exists. Clinical case studies are the primary source of information regarding effective interventions. Analogous to the management of NMS, the treatment of SS focuses primarily on discontinuation of the offending medication and symptomatic treatment including fluid and electrolyte replacement and physical cooling measures. Benzodiazepines such as lorazepam or diazepam are recommended for controlling myoclonus. In severe hyperthermia (temperature $> 40.5°$ C) patients require the institution of muscular paralysis and endotracheal intubation. Specific treatments with serotonin antagonists (e.g., cyproheptadine, chlorpromazine, methysergide, and propranolol) have been proposed; however, no well-designed studies have been performed. At present cyproheptadine in a dosage of 8 mg every 8h seems to be the antiserotonergic treatment of choice. Also a miotic response to the first dose may help to confirm the diagnosis. In particular, if tachycardia and hypertension are predominant a trial with propranolol might be justified. Other interventions of undetermined benefit include benadryl and nitroglycerin.

9. CONVULSIONS IN POISONING

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Background: Drug or toxin-induced convulsions may represent a life-threatening condition. After acute poisoning, the incidence of seizures may vary according to the intrinsic epileptogenicity of the substance, but also to individual factors related to the patient. Convulsions are also possible manifestations of withdrawal syndrome. Definition: Acute symptomatic seizures are related to a provoking illness or circumstance such as therapeutic or illicit drug use. In contrast, epilepsy is defined as recurrent unprovoked seizures. Status epilepticus can be defined clinically by the following findings: continuous or repetitive seizures lasting 20 to 30 minutes, or two or more seizures with no lucid interval between them, as demonstrated by persistent confusion, disorientation, and decreased responsiveness. Status epilepticus may be secondary to medical, toxicologic, or structural symptoms. Some toxic substances seem to be more frequently related to the onset of status epilepticus: theophylline, cocaine, amphetamines, isoniazid, alcohol withdrawal. . . The pathogenesis of epilepsy is complex. An imbalance between glutamate and gamma-aminobutyric acid neurotransmitter systems can lead to hyperexcitability but catecholaminergic neurotransmitter systems and opioid peptides were shown to play a role in epileptogenesis as well. Incidence: The exact incidence of convulsions in poisoning is not precisely known [1]. Tricyclic antidepressants overdose was a very common cause of epilepsy. The introduction of less-toxic substances (selective serotonin reuptake inhibitors) has considerably decreased this risk. Illicit drug use (cocaine) is now a frequent etiology. Indirect factors, like metabolic disorders (hyponatremia, hypocalcemia, hypoglycemia) or hypoxic injuries, have to be taken into account. *Carbon monoxide* poisoning is a good illustration of the role of indirect factors. Direct factors: Drug-induced seizures are typically brief, generalized tonic-clonic convulsions, but as many as 15% may present as status epilepticus. Although the mechanism by which medications or toxic substances induce seizures is not always precisely known, some substances have a well-defined mechanism for causing seizures. This would be important for the management because a specific antidote or a preferred anticonvulsant drug may be required [2]. *Tricyclic antidepressant*

(TCA) overdose was leading to seizures in up to 20% of patients. Seizures occur within a few hours of ingestion and are associated with encephalopathy. Among TCA, it seems that amoxapine and maprotiline were particularly likely to cause seizures in the setting of overdose. There was for TCA a dose-dependent seizure risk. *Bupropion* is an antidepressant and smoking cessation aid medication. Seizures may develop in up to 15% of all intentional exposures [3]. Convulsions are usually of short duration and are controlled by benzodiazepines administration. There is also a clear relationship with the quantity ingested as the medication is safe with daily doses <450 mg. *Antipsychotics* overdosage seems less prone to cause seizures with significant differences among the substances (aliphatic phenothiazines), while *antihistamines* (diphenhydramine) were clearly associated with seizures. *Isoniazid* (INH) is still responsible for a potentially severe neurotoxicity. Most INH-induced seizures occur in the setting of either intentional or accidental overdosage [4]. The mechanism of INH-related seizures seems well documented: INH is competing with pyridoxine for transformation to pyridoxal phosphate by the enzyme pyridoxine kinase. Pyridoxal phosphate is an essential cofactor required for the synthesis of gamma-aminobutyric acid (GABA). The result is an enhanced cortical excitability and seizures. The ingestion of INH doses >80 mg/kg typically results in severe neurotoxicity. Seizures begin within hours of ingestion and often evolve to status epilepticus. The only effective therapy is the intravenous administration of pyridoxine (several grams may be required). *Theophylline* poisoning may also be complicated by convulsions. They may occur either after deliberate overdose or in the setting of chronic overmedication. The mechanism by which theophylline causes seizures is not precisely understood. It might antagonize the inhibitory effects of adenosine by inhibition of phosphodiesterase. *Opiates* overdose is exceptionally complicated by convulsions that are usually related to indirect factors (hypoxia…) [5]. Independently, long-term use of heroin seems to be a risk factor for new-onset seizures, the underlying mechanism being unknown. Exposure to tramadol in overdose may result in a significant incidence of seizures [6]. There is a possibility that the administration of naloxone could worsen the clinical picture. *Cocaine* use by all the routes is reported to cause convulsions with a variable incidence. The role of indirect factors has particularly to be ruled out (head trauma, brain hemorrhage,). Seizures may also occur as a direct toxic effect of psychostimulant use. Cocaine shares some pharmacological properties with local anesthetic substances, like lidocaine, that provoke seizures probably by blockade of inhibitory cortical synapses. While seizures usually begin immediately or within a few hours of cocaine exposure, a delayed onset may be occasionally noted. The role of the metabolite benzoylecgonine may then be discussed. It seems also to a kindling phenomenon may be observed with the chronic use of cocaine. Finally, convulsions may also be observed with environmental toxins. Among *natural toxins*, shellfish poisoning involves tetrodotoxin and saxitoxin that are responsible for a potentation of the excitotoxicity of glutamic and aspartic acid [7]. Domoic acid is another example of an excitotoxic substance that binds to non-methyl-N-D-aspartate kainate receptors. In addition, it seems also that domoic acid may provoke permanent neuronal damages. *Metals* exposure is also a possible cause of convulsions, as illustrated by lead poisoning or aluminum toxicity. Alterations of blood–brain barrier and subsequent neuronal changes are the hypothetical mechanisms. *Organophosphate* chemical agents also cause convulsions. A primary cause could be excess of acetylcholine which follows acetylcholinesterase inhibition, but there is also evidence that organophosphates might stimulate the release of norepinephrine in the brain. Conclusion: Exposure to drugs, illicit substances, or environmental agents may result in convulsions. The severity of neurotoxicity depends upon the intrinsic properties of the substances, but is also influenced by individual factors. The evolution to status epilepticus requires aggressive therapy, but in most instances convulsions are of short duration and respond well to benzodiazepines administration. References: 1. Olson KR, Kearney TE, Dyer JE, Benowitz NL, Blanc PD. Seizures associated with poisoning and drug overdose. *Am J Emerg Med* 1994;**12**:392–395. 2. Garcia PA, Alldredge BK. Medication-associated seizures. In: Seizures: Medical causes and management. Delanty N (Ed), Humana Press, Totowa, 2001, pp 147–165. 3. Belson MG, Kelley TR. 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10. FOMEPIZOLE

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Fomepizole is the generic name for the chemical substance 4-methylpyrazole, which is marketed in the United States under the name Antizol™. It is an alcohol dehydrogenase (ADH) inhibitor which was developed as an alternative to the hepatotoxic ADH inhibitor methylpyrazole. In 1969 Li and Theorell demonstrated that fomepizole is a strong competitive inhibitor of human ADH in vitro. (1) At approximately the same time Blomstrand and Theorell demonstrated that it inhibits the oxidative metabolism of ethanol in humans. (2) Being an ADH inhibitor its potential therapeutic utility in the treatment of ethylene glycol or methanol poisoning was studied and demonstrated in monkeys in several studies published in the 1970s (3,4). McMartin et al demonstrated that fomepizole prevents formate accumulation and is therapeutic for methanol-induced metabolic acidosis in monkeys, even in the absence of hemodialysis (5,6). An important finding from these studies is that a plasma concentration of 10 uM is sufficient to inhibit formate accumulation in the methanol-poisoned monkey. Thus, this was the target plasma concentration of fomepizole that was felt to be sufficient in prospective human trials of this antidote (7,8). Similar data was obtained in various animal models of ethylene glycol toxicity (9,10). In the 1980s a series of human volunteer studies on fomepizole were carried out by Jacobsen, McMartin, and colleagues (11–14). At approximately the same time fomepizole was reported by Baud and Bismuth (15,16) as being effective in the treatment of ethylene glycol poisoning, even in the absence of hemodialysis. Ultimately the META (MEthylpyrazole for Toxic Alcohols) trial, a multicenter prospective clinical study on ethylene glycol and methanol poisoning was conducted in the U.S. showing that fomepizole is safe and effective in preventing the accumulation of toxic metabolites from methanol and ethylene glycol poisoning (7,8). Similar data appeared in retrospective studies from Europe (17,18). Fomepizole is a competitive inhibitor of ADH with an in vitro inhibitory constant for human enzyme of 0.2 uM (1). It has three metabolites, 4-hydroxymethylpyrazole (HMP) and 4-carboxypyrazole, and a glucuronide. Only HMP is active, albeit at only approximately one-third of the potency of the parent compound. The affinity of fomepizole for ADH is 500–1000 times higher than that of ethanol for the enzyme. Although fomepizole also inhibits the alcohol metabolizing cytochrome P450 2E1, it has an inhibitory constant for this enzyme in the millimolar range, indicating that this inhibition is unlikely to be significant at therapeutic doses. However, this enzyme appears to have a very minor role in methanol or ethylene glycol metabolism. Initial studies with human volunteers showed that fomepizole has the ability, after 48h, to induce its own metabolism (13). Thus current dosing recommendations suggest that the dose be increased for the unusual patient who will require more than 48h of therapy (19). Fomepizole is rapidly and almost completely absorbed orally although it is almost always used as an intravenous preparation. Its volume of distribution has been reported to be 0.59–0.74 L/kg (14). It has very low plasma protein binding. Fomepizole is virtually entirely eliminated by hepatic metabolism. This metabolism is saturable with a K_m of 6 uM, a concentration which is almost always markedly exceeded during therapeutic use. Thus it should be considered to be eliminated with zero order kinetics therapeutically. The zero order elimination rate for fomepizole is 4–15 umol/L/h (12,14). Fomepizole is readily dialyzable (49–51) and thus higher doses are recommended during this procedure (19) based on the dosing protocol that has been validated in the META study (7,8). Randomized, placebo controlled, double-blinded studies in human volunteers by Jacobsen, McMartin et al. (11,13,14) indicated that fomepizole is well tolerated at doses used therapeutically, although at significantly higher doses dizziness, nausea, and CNS depression was observed (11–13). However, there have been no major adverse effects associated with its use either in these studies or in the published clinical experience. Although in the volunteer studies there were slight increases in hepatic transaminases this did not appear to be a dose-related phenomena. The major side effects reported in volunteer studies and clinical trials are headache, agitation, irritation at the injection site, transient eosinophilia, and fever. None of these have required the discontinuation of therapy. The currently recommended dosing regimen, based on Practice Guidelines developed by the American Academy of Clinical Toxicology, is a loading dose of 15 mg/k followed by 10 mg/k every 12h for four doses, after which the doses increase to 15 mg/kg to account for its enhanced metabolism (19). As described above this dose is increased during hemodialysis (19). The above dosing protocol has been validated in the META study (26,27), which demonstrated it to be associated with plasma fomepizole concentrations substantially in excess of those required to inhibit ADH. 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11. IS THERE A REMAINING PLACE FOR HEMODIALYSIS IN TOXIC ALCOHOL POISONINGS TREATED WITH FOMEPIZOLE?

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Objectives: Acute ethylene glycol and methanol poisonings are relatively uncommon, but are still frequently involved in suicide or epidemic poisonings, resulting in death and serious sequelae. Toxicity is related to the production of toxic metabolites by liver alcohol dehydrogenase (ADH). Classic treatment of these poisonings includes infusion of sodium bicarbonate, in the case of severe acidosis, administration of ethanol as a competitive substrate of ADH, and hemodialysis to remove the toxic alcohol and its toxic metabolites. Fomepizole, 4-methylpyrazole (4-MP), is a potent inhibitor of ADH and can thus prevent the metabolism of ethylene glycol or methanol into their toxic metabolites. Two recent prospective clinical trials performed in the USA established the efficacy of 4-MP in the treatment of ethylene glycol and methanol intoxication[1,2]. Our objectives were to analyze the remaining indications of hemodialysis, and role of 4-MP in the treatment of toxic alcohol poisonings. Methods: Systematic Medline review of the literature on toxic alcohol poisoning treatments. Results: The place of 4-MP in the treatment of ethylene glycol and methanol poisonings is now well established. The antidotal efficacy of 4-MP in toxic alcohol poisonings is related to its inhibitory effect on the alcohol metabolism by liver ADH. 4-MP has been successfully used in France since 1981, in the treatment of several cases of ethylene glycol and methanol poisoning. No mortality or significant morbidity occurred in patients treated within 24 hours of intoxication, and all these patients recovered from their poisoning. More recently, two prospective clinical trials were performed in the U.S. with promising results[1,2]. In patients with ethylene glycol poisoning, 4-MP administered early in the course of intoxication was shown to prevent renal injury, by inhibiting the formation of toxic

metabolites. In patients with methanol poisoning, 4-MP appeared to be an effective antidote, by blocking ADH metabolism. In methanol and ethylene glycol poisonings, the following regimen was proposed: a loading dose of 15 mg/kg, followed by doses of 10 mg/kg each 12h, as long as plasma concentrations of the toxicants could be detected or remained greater than 20 mg/dl. Some authors recommended furthermore the increase of the doses to 15 mg/kg each 12h, after 48h of treatment, to counteract the induction of 4-MP metabolism. Both oral and intravenous routes were proposed. The bioavailability of the oral preparation is not known, but, when the oral route is possible, it appears to be equally effective to intravenous route. The usual contra-indications of 4-MP administration are the previous known allergy to pyrazole derivates and the pregnancy, due to the lack of data on safety in this case. Toxicological studies carried out in monkeys and rats demonstrated no apparent adverse events attributable to 4MP, particularly in the presumed therapeutic dose range. To date, clinical experience with 4-MP use appeared safe, with only limited adverse effects, including abnormalities of liver function tests within the first two weeks, local irritation after intravenous administration, skin rash and eosinophila. There is no comparative clinical or economical study of 4-MP with ethanol. However, unlike ethanol, therapeutic concentrations are reliably achieved with the proposed dosing regimen and no central nervous system significant liver toxicity or hypoglycemia occurred in 4-MP-treated patients. Therefore, considering all the data on 4-MP clinical efficacy and safety, we can now recommend 4-MP as a first-line antidotal treatment in poisoned patients. In the cases of exposure to a toxic alcohol or in patients with a metabolic acidosis with unexplained anion gap and non-elevated serum lactate concentration, we propose a loading dose of 4-MP, till measurement of the toxic alcohol concentrations are obtained, which enable a definitive diagnosis. In patients with normal renal function throughout the course of the poisoning, the renal clearance of ethylene glycol and methanol is respectively 19 ml/min and 1 ml/min. In relation to ADH blockade, 4-MP administration results in the prolongation of the elimination half-life of ethylene glycol and methanol, to 12 and 50h respectively. Thus the antidotal regimen (dose and duration) should be sufficient to avoid further metabolism of toxic alcohol since it remains in the body for a longer time. In the patients without renal failure, renal handling of ethylene glycol appears sufficient to clear the body, without a prolonged course of 4-MP administration. In methanol poisoning, due to its long elimination half-life, it is clear that antidote administration should be prolonged. Therefore, the respective place of hemodialysis and 4-MP antidote therapy is still discussed. In the U.S. clinical trials, patients were systematically dialyzed when plasma ethylene glycol or methanol concentrations were greater than 50 mg/dl. In ethylene glycol poisonings, we showed that patients treated with fomepizole prior to the onset of significant acidosis often do not require hemodialysis[3]. We also suggested that fomepizole might obviate the need for hemodialysis in selected patients poisoned with methanol, without neurological, ocular impairment or severe acidosis on admission[4]. Nevertheless, when dialysis is indicated, 1 mg/kg/h continuous infusion of 4-MP should be provided, to compensate its elimination in the dialysate. Finally, one should also consider the potential usefulness of 4-MP and the respective place of hemodialysis in the treatment of other toxic alcohol. Several case reports discussed the benefit of 4-MP in the treatment of disulfiram–ethanol reaction and various toxic alcohol or glycol poisonings, including isopropanol, diethylene glycol, triethylene glycol and 1,4-butanediol. Conclusion: 4-MP appears to be an effective and safe antidote for the treatment of ethylene glycol and methanol intoxication. Its use should now be recommended as a first-line treatment in poisoned patients. Moreover, we believe that 4-MP might obviate the need for hemodialysis in selected patients poisoned with ethylene glycol or methanol. References: 1. Brent J et al. Fomepizole for the treatment of ethylene glycol poisoning. *N Engl J Med* 1999;**340**:832–8. 2. Brent J et al. Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001;**344**:424–9. 3. Borron SW et al. Fomepizole in the treatment of uncomplicated ethylene glycol poisoning. *Lancet* 1999;**354**:831. 4. Mégarbane B et al. Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 2001;**27**:1370–8.

12. METHANOL POISONING: METHANOL KINETICS IN FOUR PATIENTS DURING FOMEPIZOLE TREATMENT WITHOUT DIALYSIS

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Objective: Methanol is metabolized by alcohol dehydrogenase to formaldehyde, which is further degraded to formic acid. Formic acid is responsible for the toxicity in methanol poisoning. Fomepizole (4-methylpyrazole) is a potent competitive inhibitor of alcohol dehydrogenase and is indicated as an antidote to treat methanol poisonings. We report

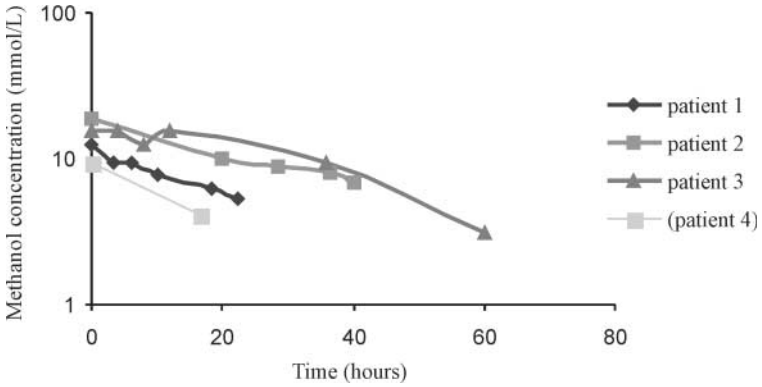

Figure 1. Methanol concentration (mmol/L) during formepizole treatment.

serum methanol kinetics in four patients treated with bicarbonate and fomepizole only. Methods: The four patients were part of an epidemic of methanol poisonings in 2002. They were selected to toxicokinetic studies because of low serum methanol levels, moderate metabolic acidosis, and no visual disturbances. As such, hemodialysis was not indicated and they were treated with bicarbonate and fomepizole only. Serum methanol concentrations were analyzed by gas chromatography. Results: Upon admission the mean pH was 7.23 (range 7.12–7.33), base deficit 17 mmol/L (range 10–21 mmol/L), S-methanol 14.1 mmol/L (45 mg/dL) (range 9.4–18.8). The kinetics of methanol during fomepizole treatment was described by first order elimination one-compartment model in three patients (Fig. 1). In one patient there were too few analyzes to do reliable toxicokinetic calculations (Fig. 1). The mean correlation coefficient (R^2) describing the first-order elimination model was 0.94 (range 0.90–0.97). The plasma half-life ($t_{1/2}$) of methanol was 25h (range 20h–29h). The mean correlation coefficient (R^2) describing a zero-order kinetic model was 0.92 (range 0.91–0.92), making limitation to the results. During the treatment period, acid–base status was frequently measured and found normal, indicating no accumulation of formic acid. Conclusion: Our data indicate that patients with no visual disturbance, moderate metabolic acidosis and S-methanol levels up to 19 mmol/L (60 mg/L) may safety be treated with bicarbonate and fomepizole only, without dialysis. The mean plasma half-life of methanol was 25h during treatment. References: Jacobsen D, McMartin KE. Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986;**1**:309–334. Jacobsen D, McMartin KE. Antidotes for Methanol and Ethylene Glycol Poisoning. *J Toxicol Clin Tox* 1997;**35**:127–143. Bekka R, Borron SW, Astier A et al. Treatment of Methanol and Isopropanol Poisoning with Intravenous Fomepizole. *J Toxicol Clin Tox* 2001;**39**:59–67.

13. RETHINKING TOXIC METHANOL LEVELS

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Objective: Treatment thresholds for methanol poisoning are based on case reports and published opinion. Most guidelines recommend treatment for a methanol level ≥ 20 mg/dl in a non-acidotic patient. Supportive data have not been offered nor has the time of the exposure been addressed. No distinctions have been made between a level drawn 1h versus 1 day from ingestion. We analyzed all reported cases of methanol poisoning to determine the applicability of the 20 mg/dl threshold in a non-acidotic patient. Methods: Using predefined search criteria; a rigorous systematic review of the world literature was performed using MEDLINE and EMBASE. In addition, each article's references were hand-searched for pre-1966 articles, as were fatality abstracts from all U.S. poison centers. Human cases were included if they reported a known time of a single methanol exposure, acid–base data, blood methanol, and blood ethanol (if not acidotic). Results: Dating to 1879, 372 articles in 18 languages were abstracted using a standard format. A total of 329 articles (2433 patients) involved methanol poisoning. Seventy articles (173 patients) met inclusion criteria. Only 22 of these patients presented for care within 6h of ingestion with an early methanol level. All but one was treated and a clear acidosis developed only with a methanol level ≥ 126 mg/dl. The untreated case involved an infant with an elevated early methanol level (46 mg/dl) that was given folate alone and never became acidotic. Intra and inter-rater reliability were

0.95. Conclusions: Nearly all reports of methanol poisoning involve acidotic patients far removed from ingestion. The small amount of data regarding patients arriving early show that 126 mg/dl is the lowest early blood methanol level ever clearly associated with acidosis. Contrary to conventional teaching, there are reports of acidosis after only a few hours of ingestion. The data are inadequate to apply 20 or even 50 mg/dl as a treatment threshold in a non-acidotic patient arriving early for care. Potentially, many such patients may be managed without antidotal therapy or dialysis.

14. EPIDEMIC POISONING WITH METHANOL IN ESTONIA—EXPERIENCE OF PÄRNU COUNTY HOSPITAL

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In September 2001, 147 patients were admitted to Pärnu County Hospital in Estonia with suspicion of acute methanol poisoning due to consumption of illegal alcohol. Retrospective analysis showed that 111 of them were intoxicated with methanol. Such a high number of admissions within a limited time-period was a challenge for the small 5-bed ICU and 135-bed county hospital and for the entire emergency system of Estonia. On the first day of the accident 17 victims were hospitalized. During the second day, 39, third, 46, fourth, 18, fifth, 13, and sixth, 14 patients were admitted. From these 111 patients admitted, 83 were quickly transferred to tertiary care centers in Tallinn or Tartu for further intensive care and haemodialysis. As the laboratory data for blood methanol levels were available only after a delay of 24h, the initial medical management of the patients was mainly directed by the severity of metabolic acidosis and neurological impairment at admission. In retrospective analysis we identified the following groups of the patients: I (coma group)—Patients were already in coma at admission. This group included 38 methanol consumers, 28 men and 10 women; average age 50 (22 to 77) years. Nineteen patients survived, 3 remained with persistent neurological disability and 15 patients died. II (conscious—coma group) Included patients who were in conscious at admission, but felt in coma after 10–30 minutes. There were 18 men and 12 women in 30 victims in this group. Average age was 46 (22 to 65) years. Twenty-five patients survived, 2 patients had persistent neurological disability and 3 patients died. III (conscious-symptoms positive group) Patients were conscious at admission and remained conscious. However, symptoms of methanol intoxication (visual disturbances, metabolic acidosis) were well evident in these patients. Among the 26 patients in this group methanol 19 were men and 7 women, with the average age of 51 (19 to 77) years. All of the patients in this group survived. IV (conscious-symptoms negative group) Patients were conscious at and after admission and they did not develop clinical signs of methanol intoxication. However, laboratory analysis revealed presence of methanol in

Table 1. Blood acid–base status at admission ([1]) and after initial fluid resuscitation ([2]), and blood methanol levels (mmol/l). Data are mean ± SD (min. . .max). HD—haemodialysis.

Group	pH[1]	BE [1]	pH [2]	BE [2]	Time between blood gas analysis (h)	Methanol concentration at admission to county hospital	Methanol concentration immediately after HD
I	6.9 ± 0.21 n = 37	−26.1 ± 4.2 n = 37	7.19 ± 0.19 n = 32	−15.4 ± 7.7 n = 32	4.3 ± 4.3 n = 24	2.72 ± 1.47 (0.57. . .6.23) n = 28	1.05 ± 1.18 (0.00. . .4.96) n = 26
II	7.1 ± 0.23 n = 28	−22.1 ± 7.1 n = 28	7.28 ± 0.14 n = 24	−13.4 ± 7.1 n = 24	3.8 ± 4.2 n = 23	2.09 ± 1.40 (0.30. . .5.60) n = 17	0.59 ± 0.44 (0.00. . .1.65) n = 25
III	7.17 ± 0.15 n = 25	−18.7 ± 9.0 n = 25	7.36 ± 0.1 n = 23	−10.5 ± 7.0 n = 23	8.0 ± 12.2 n = 19	1.87 ± 1.49 (0.27. . .4.20) n = 15	0.40 ± 0.32 (0.00. . .1.00) n = 14
IV	7.45 ± 0.15 n = 17	0.9 ± 4.5 n = 17	—	—	—	0.60 ± 0.71 (0.04. . .2.50) n = 17	—

their blood. This group consisted of 15 men and 2 women, with average age of 47 (26 to 66) years. Survival was 100%. V Contained 36 consumers of illegal alcohol, who were admitted to hospital due to the suspicion of methanol intoxication. They were followed for 24h at Pärnu Hospital, but as no laboratory and clinical signs of methanol intoxication developed they were discharged from hospital. The initial therapy included artificial ventilation, fluid resuscitation, vasopressors if needed, infusion of sodium bicarbonate and 10% ethyl alcohol as an antidote. Laboratory data are shown in Table 1. In conclusion, the clinical picture of methanol poisoning may vary in extent. Our experience suggests the importance of early correction of metabolic acidosis with sodium bicarbonate, infusion of 10% ethanol and early haemodialysis in the management of acute methanol poisoning. The emergency system of Estonia, and Pärnu County Hospital in particular, smoothly and effectively managed the crisis situation of this epidemic poisoning.

15. FLUMAZENIL: ANTIDOTE OR TOXIN?

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Objective: Flumazenil competitively antagonizes the binding and allosteric effects of benzodiazepines (BZDP) and other ligands. When BZDP are administered for sedation during short procedures, flumazenil safely and effectively reverses the benzodiazepine-induced sedation. However, the benefit and safety of flumazenil administration to reverse conscious sedation has been extrapolated to flumazenil administration in the overdose patient without serious analysis of the consequences. Currently, physicians consider flumazenil administration when a somnolent overdose patient ingests either BZDP alone or when BZDP may be one of multiple drugs ingested. Although it may appear self-evident that reversal of BZDP-induced sedation and hypoventilation is desirable in a patient with either a BZDP overdose or a mixed-drug overdose, the issue is not so clear. Methods: The Risk: Benefit ratio of flumazenil administration is evaluated. Benefit is determined by assessing case series to determine if flumazenil administration changes morbidity, mortality, and length of hospital stay, number of procedures or other outcome measures. Risks of flumazenil administration include precipitation of seizures, death, cardiac arrhythmia, aspiration, and ARDS. Risk assessment is performed by reviewing animal data, case reports of adverse events, and data regarding the ability to identify patients with contraindications to flumazenil administration prior to the drug's administration. Change in outcome following flumazenil administration is compared to the risk of adverse events. Conclusion: The healthy child who presents with BZDP-induced coma (or significant somnolence) and hypoventilation may benefit from flumazenil administration. However, due to the well-known variables in overdose patients, it is difficult to draw conclusions about the safety and efficacy of flumazenil in other scenarios. The literature offers weak evidence that flumazenil administration improves outcome. Because it is difficult to identify patients that are at risk (i.e., chronic benzodiazepine use, tricylic antidepressant coingestion, history of seizures, drug of abuse coingestion) for adverse events, the drug may potentially cause harm (1). If anticipated side effects of a drug are necessary to achieve patient benefit and are proportionately less harmful than the condition for which the patient sought care, imposition of risk is justified. Does flumazenil fulfill this criterion? Reference: Mathieu-Nolf M, Babe M, Coquelle-Couplet V et al. Flumazenil use in an Emergency Dept: A survey. *J Toxicol Clin Tox* 2001;**1**:15–20.

16. PYRIDOXINE IN CLINICAL TOXICOLOGY: A REVIEW

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Introduction: Pyridoxine (vitamin B6) is a cofactor in many enzymatic pathways involved in amino acid metabolism: the main biologically active form is pyridoxal 5-phosphate (P5P), a phosphorylated aldehyde. It occurs naturally in many foods, especially meats and vegetables. Normal adult needs (1 to 2 mg/day) are usually covered by nutritional sources, but are increased during pregnancy. Clinical uses of pyridoxine in non-acute conditions: Pyridoxine has been used successfully to control nausea and vomiting in early pregnancy. The need for supplemental pyridoxine during isoniazid (INH) therapy is debated. INH reacts with P5P to form a hydrazone, a strong inhibitor of P5P kinase, leading to profound tissue depletion of this important cofactor. Pyridoxine (10 to 25 mg daily) may prevent the development of peripheral sensory-(motor) neuropathy, especially in malnourished or pregnant patients and in those with HIV infection,

alcoholism, or diabetes who are likely to suffer pyridoxine deficiency before initialization of antituberculous therapy. Some authors also recommend pyridoxine administration to decrease the incidence of adverse neurological effects of cycloserine (50 mg for every 250 mg of cycloserine). Pyridoxine has also been used to reverse the dyskinesias and choreoathetosis due to levodopa. Uses of pyridoxine in acute intoxications: Pyridoxine has been used in several indications in acute intoxications, including isoniazid overdose, gyromitra mushroom or false morrel (monomethylhydrazine, MMH) poisoning and hydrazine exposure. It is also recommended as a cofactor to improve conversion of glyoxylic acid into glycine in ethylene glycol poisoning and as an adjunct of the treatment with d-penicillamine (10 to 25 mg daily), since this chelating agent has been shown to inhibit pyridoxine-dependent enzymes. Some sources recommend the use of pyridoxine in cyanide poisoning or in the management of zipeprol and theophylline-induced seizures, but no significant data support these indications. Pyridoxine has also been shown to be of no value in hastening ethanol metabolism or improving vigilance in acute alcohol intoxication. Only widely recognized indications will be reviewed in depth. Pyridoxine in acute INH intoxication: In INH overdose (characterized by seizure, acidosis, and coma), pyridoxine is the key of treatment, in association with supportive measures and sometimes with elimination procedures, especially dialysis. Convulsions are thought to be caused by P5P depletion, leading to depression of GABAergic tone in the brain. Pyridoxine should be administered in a dose at least equal to the maximum amount of INH ingested to control or to prevent seizures in all alleged or definite cases of INH overdose, even if seizures have not occurred. It is mixed as a 5 or 10% solution with water or 5% dextrose, and administered intravenously over a 30 minutes period. The dose may be repeated at 30 minutes intervals as needed in a comatose or convulsing patient. If the ingested dose of INH is unknown, 5.0 g of pyridoxine (70 mg/kg in a child) should be administered initially, followed in 30 minutes with an additional 5.0 g until seizures cease or consciousness is regained. By controlling INH-induced convulsion, pyridoxine will also help to limit the development of consequent lactic acidosis and duration of coma. Pyridoxine in MMH syndrome: In MMH syndrome, pyridoxine is thought to reduce hepatic, renal and CNS toxicity. The commonly recommended dose is 25 mg/kg IV over 3 hours, but higher amounts may be needed. Pyridoxine in ethylene glycol poisoning: In ethylene glycol poisoning, pyridoxine (as well as thiamine) is a cofactor in the metabolism of ethylene glycol to glycine. Therefore, supplementation may be useful in shunting the metabolism of glyoxylate and glycolic acid to this non toxic metabolite instead of oxalate. The common recommendation consists of the administration of 50 mg pyridoxine IV, twice daily or every 6 hours, until the acidosis has resolved. Although such a supplement is inexpensive, safe and theoretically of benefit, especially in those patients who may be deficient in this vitamin (e.g., alcoholics), there is no scientific data to confirm its effectiveness in this indication. Pyridoxine is usually available commercially in vials of 1 g/10 ml or ampoules of 250 mg in 5 ml, to be stored in the dark. It should never be mixed with sodium bicarbonate. Although very high dosages have been well tolerated by INH overdose patients without adverse effects, tachypnoea, postural reflex abnormalities, paralysis, and convulsions may follow excessive pyridoxine dosage. Excessive chronic administration (0.5 to 2 g daily) over months or years may occasionally result in the development of a sensory neuropathy that usually resolves within 6 months of pyridoxine withdrawal.

17. ANTIDOTES FOR GAMMA-HYDROXYBUTYRATE POISONING

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Background: Gamma-hydroxybutyrate (GHB), a poorly understood endogenous metabolite of gamma-aminobutyric acid (GABA) in the mammalian brain, remains popular as a dietary health supplement and illicit drug of abuse. Inadvertent poisoning and overdoses with GHB and its chemical precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), have resulted in coma, respiratory depression, apnea, and death[1]. The medical management of the GHB toxidrome has been unsuccessfully attempted with the coma reversal agents, naloxone, and flumazenil. Recently, physostigmine has been reported to reverse GHB toxicity in several patients. Preclinical murine trials with 4-methylpyrazole (4-MP), CGP 35348, and SCH 50911 have identified alcohol dehydrogenase inhibitors and $GABA_B$ receptor antagonists as promising reversal agents for GHB-related toxicity. Objective: To review the scientific literature for the use of naloxone, flumazenil, physostigmine, 4-MP, CGP 35348, and SCH 50911 as potential reversal agents for GHB-related toxicity. Discussion: Several lines of study indirectly support GHB modulation or potentiation of CNS

opiod mechanisms. In microdialysis experiments, the local administration of GHB into the caudate-putamen of awake rats caused displacement of [^{3}H]-naloxone in the dialysates[2]. GBL, the GHB precursor, has been shown to induce EEG abnormalities, produce catalepsy, and increase striatal dopamine. Naloxone attenuated or blocked all of these effects[3]. In hippocampal slices, GHB induced an increase in cGMP and inositol phosphate turnover, which was blocked by naloxone and other opiate antagonists[4,5]. In hamsters, GHB was demonstrated to have a protective effect in regional intestinal ischemia, which was partially blocked with naloxone[6]. However, naloxone failed to attenuate or reverse GHB-induced coma in murine studies[7] or numerous human case reports of overdoses[1,8]. There is additional evidence that GHB may act as a neuromodulator at the $GABA_A$/benzodiazepine receptor complex. In the elevated plus maze, the number of entries and the time spent in the open arms of the maze were increased in rats given GHB. However, this GHB anxiolytic effect was antagonized by the benzodiazepine receptor antagonist, flumazenil, suggesting an interaction of GHB with the $GABA_A$ receptor complex which mediates the anti-anxiety effect of benzodiazepines. In human volunteers, oral GHB administration induced a significant elevation in growth hormone (GH) plasma concentrations. However, flumazenil pretreatment antagonized GHB action on GH secretion[10]. Despite the apparent neuromodulatory role of GHB at the $GABA_A$/benzodiazepine receptor complex, the successful clinical use of flumazenil in reversing GHB toxicity has not been reported. Recently, two small, uncontrolled, and unblinded case series reported the apparent successful use of physostigmine in reversing 5/6 GHB overdoses in the emergency department within a range of 2–15 minutes of administration[11,12]. However, there are no animal studies demonstrating GHB modulation of cholinergic neurotransmission or physostigmine reversal of GHB toxicity. Recently, our group targeted respectively, the alcohol dehydrogenase enzyme and the $GABA_B$ receptor, as potential sites of pharmacologic blockade for toxicity from 1,4-BD specifically and GHB, GBL, and 1,4-BD collectively. In preclinical murine trials, we demonstrated that 4-MP administration significantly decreased GHB blood concentrations and prevented neurotoxic manifestations[13,14]. Clinically, rapid awakening was observed following 4-MP administration to a patient with a confirmed 1,4-BD overdose[15]. Since the pharmacologic effects of GHB are thought to be mediated by GABAergic mechanisms (via direct $GABA_B$ receptor activation or indirectly through GHB metabolic conversion to GABA via GHB dehydrogenase), we employed the selective, post-synaptic $GABA_B$ receptor antagonists CGP 35348 and SCH 50911 in preclinical murine trials. Using a standard battery of tests for neurotoxicity (righting reflex, roatrod test, grip strength measurement, and open field locomotion), both agents significantly reduced GHB-related toxicity for these outcome measures, with SCH 50911 exhibiting a greater potency than CGP 35348[14,16]. To date, the use of these $GABA_B$ receptor antagonists in human GHB overdoses has not been reported. Conclusion: While in vitro and in vivo animal studies suggest that GHB may modulate opiod and $GABA_A$/benzodiazepine receptors, the use of naloxone and flumazenil has failed to reverse the clinical effects of human GHB intoxication. The apparent successful use of physostigmine in very small, uncontrolled cases series of GHB intoxication should be interpreted cautiously and warrants further controlled clinical trials; until such studies are done, the risks of physostigmine administration prohibits its administration to GHB-intoxicated patients. In preclinical murine trials, 4-MP effectively decreased 1,4-BD biotransformation to GHB and prevented neurotoxic manifestations in CD-1 mice, hence warranting further controlled clinical studies. In preclinical murine trials, the $GABA_B$ receptor antagonists, CGP 35348 and SCH 50911, decreased neurotoxic manifestations of GHB-related overdose, thus warranting further controlled clinical trials. Until further controlled clinical trials are done with physostigmine, 4-MP, CGP 35348, and SCH 50911, the management of GHB-related intoxication should remain aggressive supportive care.

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18. THE EPIDEMIOLOGY OF OCCUPATIONALLY RELATED POISONING IN THE UNITED STATES

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Objective: The purpose of this keynote address is to discuss the epidemiology of occupationally related poisonings in the U.S. and to address some of the limitations of collection and compilation of this data. Discussion: Each day, approximately 9,000 U.S. workers sustain disabling injuries on the job, 16 workers die from an injury sustained at work, and 137 workers die from work-related diseases. The resulting economic is extraordinary. Recent studies reported $171 billion annually in direct and indirect costs of occupational injuries and illnesses ($145 billion for injuries and $26 billion for diseases). An important subset of the total numbers of work related illness and injury in the US involves occupationally related poisoning. Occupationally related poisoning is strictly defined by US Occupational Safety and Health Agency (OSHA) as the work-related "systemic effects of toxic materials." However, a more comprehensive assessment of the epidemiology of occupationally related poisonings must, of necessity, also consider occupationally skin diseases, dust diseases of the lung, and respiratory conditions that may be due to potentially harmful chemicals. The determination and compilation of accurate data regarding the epidemiology of occupationally related poisoning in the United States has been, and continues to be, problematic. Multiple different governmental agencies may collect data relevant to the epidemiology of occupationally related poisoning and reporting standards vary. Among the federal governmental agencies that strive to collect this data are OSHA, the National Institute for Occupational Safety and Health (NIOSH), and the Department of Labor's Bureau of Labor Statistics. In addition, various state agencies as well as multiple private organizations also collect data regarding the epidemiology of occupationally related poisoning. Currently, there is no single recognized clearinghouse agency to compile, analyze, or disseminate this important information. Nonetheless, several important data reservoirs exist from which data regarding epidemiology of occupationally related poisoning may be extracted. In 1970, The Occupational Safety and Health Act directed the Secretary of Labor to compile accurate statistics on occupational injuries and illnesses and to make periodic reports on such occurrences. The responsibility for collecting statistics regarding occupational illness and injuries was delegated to the Bureau of Labor Statistics (BLS). It is this agency that has compiled what may be the most reliable epidemiologic information regarding occupationally related poisoning in the U.S. BLS data reflects the following information regarding occupational poisoning in the U.S.

Year	Fatalities—all industries due to harmful substances or environments	Non-fatal illness cases (000's) poisonings
1995	609	7500
1996	533	4800
1997	554	5100
1998	576	4000
1999	533	4400

The most common cause for occupationally related poisoning for all years appears to be exposure to carbon monoxide with the second most common cause being exposure to hydrogen sulfide. Conclusion: Reporting, as well as other forms of bias, may restrict the accuracy of BLS data. In addition, the fact that many workers (including workplaces employing

less than 50 workers, military, and others) do not fall under the jurisdiction of the OSHA act and thus may not be reflected in BLS data sets also may limit the usefulness of these data sets.

19. PNEUMOPROTEINAEMIA: A NEW CONCEPT FOR THE EVALUATION OF RESPIRATORY EFFECTS OF AMBIENT AIR POLLUTION

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Introduction: The lung is the major route of entry and in most instances the main target of air pollutants. There is growing evidence that ambient air pollutants can produce various adverse health effects. However, assessment of the respiratory effects of air pollutants has so far relied largely on such endpoints as lung function impairment or respiratory symptoms which although sensitive do not permit the evaluation of the extent of lung epithelium damage. The integrity of the lung epithelium can indeed be assessed only by the analysis of the epithelial lining fluid sampled by bronchoalveolar lavage (BALF), a procedure too invasive to be applied on environmentally exposed populations. Recently, a new approach for assessing lung effects of air pollutants has been suggested, based on the finding that proteins secreted by the lung epithelium (pneumoproteins) occur physiologically in the serum (pneumoproteinaemia) where they may serve as peripheral reporters of toxic events taking place at different levels of the respiratory tree (Bernard et al, 1997, 1998; Hermans and Bernard, 1998, 1999). This approach mainly stems from observations made with the 16 kD Clara cell protein (CC16), a small protein secreted by the non-ciliated Clara cells at the surface of airways. Studies carried out in smokers and occupationally exposed populations indicate that the assay of CC16 in serum can be used to assess the integrity of the bronchoalveolar blood barrier which is frequently compromised in various lung diseases or chemical stresses. By contrast, when this barrier is intact or only slightly impaired, CC16 appears to reflect the number and/or the integrity of the Clara cells. Besides CC16, surfactant-associated proteins A and B (SP-A and SP-B) secreted by bronchiolar and alveolar cells have also been shown to occur in serum and to serve as useful peripheral lung markers. We summarize here studies we have recently carried out to assess the sensitivity of this new approach for detecting acute or chronic effects of ozone and other air polluants on the respiratory epithelium. Studies on rodents with short-term exposure to ozone: Ozone (O_3), the main oxidant of photochemical smog, can produce a variety of pulmonary effects. One of the earliest manifestations of the initial injury caused by O_3 is an increased permeability of the epithelial barrier, facilitating the passage of inhaled agents into blood and the leakage of serum proteins into airways which is clasiccaly assessed by albumin in (BALF). Our observations on rodents demonstrate that the disruption of lung epithelium barrier by O_3 can be assessed less invasively from the other side of the barrier by the measurement in serum (or plasma) of lung-specific proteins such as CC16. In a first series of experiments, CC16 was determined in the serum of Sprague–Dawley rats after a single 3h-exposure to 0.3, 0.6 or 1 ppm O_3. The concentrations of CC16 in the lung or trachea homogenates, the lung CC16 mRNA levels and classical markers of lung injury in bronchoalveolar lavage fluid (BALF) were also determined. O_3 produced a transient increase of CC16 concentration in serum that reached values on average 13 times above normal 2h after exposure to 1 ppm O_3. The intravascular leakage of CC16 was dose-dependent and correlated with the extent of lung injury as assessed by the levels of total protein, LDH and inflammatory cells in BALF (Arsalane et al, 1999). These observations were confirmed in a second series of experiments comparing the response of different strains of rats (Lewis, Wistar and Fisher) and mice (CBA, AKR, C57B, C3H, SJL). These animals were exposed to O_3 levels ranging from 0.08 to 1.8 ppm for during 3 to 48h. In both species, acute exposure to O_3 produced a transient elevation of CC16 in serum that was parallel to the elevation of albumin in BALF, as a reflection of the increased bidirectional leakage of proteins across the bronchoalveolar/blood barrier. In mice this leakage of CC16 from the lung was dose-dependent and detectable at exposure as low as 0.08 ppm (this value is closed to the new air quality guideline of WHO, 0.06 ppm avergage over 8h). These results demonstrate that the assay of CC16 in serum represents a new non-invasive test to detect the increased lung epithelial permeability induced by O_3. Study on human subjects exposed to air pollutants: A quasi-experimental study was carried out on cyclists exposed to episodes of photochemical smog, in Parma, Italy. Twenty-four nonsmoker cyclists, 15 women and 9 men, aged 28.5 ± 3.4 years performed two runs of 2h, between 2 and 4 p.m. on roads characterized by different levels of air pollution. Mean O_3 concentrations during the runs, obtained from the nearest stations of a local monitoring network varied between 0.033 and 0.103 ppm (mean 0.076 ppm). After the run, the serum concentration of CC16 (μg/L) was significantly increased in both men (12.3 ± 0.9 *vs.* 11.2 ± 0.8, $p = 0.011$, $n = 18$) and women (11.9 ± 1.3 *vs.* 11.1 ± 0.6, $n = 30$, $p = 0.012$). Stepwise regression

analysis of all data shows that the increase in serum CC16 during the run (i.e., the difference between post and pre-run concentrations) was independent of sex and of cystatin C (a marker of glomerular filtration) variations in serum ($r2 = 0.01$, $p = 0.41$) but correlated with the O_3 concentrations ($r2 = 0.18$, $p = 0.0024$). To examine dose–effect relationships, we have divided the subjects into quartiles of increasing O_3 levels. Both pre- and postrun concentrations showed an exposure-related trend, the rise over the first quartile being significant from the fourth and third quartile onward, for the pre- and postrun, respectively. Although the long-term significance of this altered epithelial permeability caused by O_3 in ambient air is unknown, these observations indicate that air pollutants can produce effects on the pulmonary epithelium that are unerestimated or undetected with the usual tests (Broeckaert et al 1999, 2000). To evaluate the sensitivity of new lung markers to the chronic effects of air pollution, we carried out a cross-sectional study on policemen exposed to urban air pollutants in Brussels. The study was involved a group of 66 policemen working in Brussels and a control group of 62 foresters working in the Belgian Ardennes [mean age ± SD: 41 ± 9 *vs* 44 ± 10, respectively]. All subjects were examined during the autumn or winter in order to avoid the acute effects of O_3 on the lung epithelium. The proportions of smokers were similar in both groups [23/66 *vs* 27/62]. The urinary excretion of muconic acid (μg/g creatinine), a marker of benzene exposure, was significantly increased in smokers compared to nonsmokers and also significantly higher in policemen than in foresters, in both smokers [0.17 ± 0.08 *vs* 0.13 ± 0.06, $p = 0.027$] and nonsmokers [0.11 ± 0.09 *vs* 0.07 ± 0.04, $p = 0.021$]. Lung function tests were significantly impaired by tobacco smoking but no influence of air pollution was found. The serum levels of SP-A (μg/L) were increased by tobacco smoking but they were similar between policemen and foresters [68.1 ± 45.2 *vs* 72.1 ± 42.2]. By contrast, serum CC16 (μg/L) was significantly reduced by tobacco smoking and of interest, this effect was significantly more pronounced in policemen than in foresters [8.97 ± 3.96 *vs* 10.93 ± 3.85, $p = 0.041$], suggesting a possible interaction between air pollutants and tobacco smoke on the respiratory epithelium. Although the number of subjects examined is too small to draw definitive conclusions, this study shows that lung epithelium markers measurable in serum can be used to refine the assessment of the chronic effects of air pollutants. In a further study, we evaluated whether the assay of CC16 and SP-A in serum might detect long-term toxicity of urban air pollutants on the pulmonary epithelium in a large homogenous group of male subjects belonging to the French Gazel Cohort. All participants were healthy volunteers living in or in the vicinity of six French cities of different size located across the French territory. The study population involved 305 male healthy volunteers aged on average 52 years recruited from Paris ($n = 135$), Marseille ($n = 51$), Bordeaux ($n = 44$), Toulouse ($n = 38$), Nice (21), and Manosque ($n = 16$). They were nonsmokers ($n = 122$), past-smokers ($= 129$) or current smokers ($n = 24$). Participants either lived in urban ($n = 256$) or rural suburbs ($n = 47$). The mean annual NO_2 level was higher (μg/m^3, 55 versus 34) whereas the mean annual O_3 level was lower (μg/m^3, 31 versus 50) in Paris compared to other cities. Comparative statistical analysis did not show significant differences for the serum levels of lung-specific proteins, lung function tests and respiratory symptoms between the different groups. By multiple regression analysis, we found that changes of pulmonary indicators were determined only by the smoking status. These data suggest that chronic exposure of the general population to ambient levels of ozone and nitrogen dioxide is not associated with chronic effects on the respiratory tract as assessed individually by the measurement of CC16 and SP-A, lung function tests, and respiratory symptoms. This lack of difference might be due to the fact that the gradient of air pollution between the different groups was not sufficiently important or by the influence of other environmental or lifestyle factors (indoor pollution, physical exercise) which could have masked small associations with ambient air pollution (Hermans, manuscript in preparation). We also investigated among current smokers whether the simultaneous assay of CC16 and SP-A in serum might provide a useful index of lung epithelial damage induced by tobacco smoke. Concentrations of SP-A and CC16 were determined in serum from 169 healthy subjects, including 80 nonsmokers (aged 18 to 70 years) and 89 active smokers (aged 19 to 67 years, smoking history of 12.2 pack-years [0.15–80]). The concentration of SP-A (geometric mean and range, in μg/L) was significantly increased in serum of healthy smokers compared to nonsmokers (66.2 [13.6–250.8] vs. 44.9 [6.5–217.9], $p < 0.0001$), reflecting its increased leakage from the lung epithelial surface into the blood. By contrast, the CC16 level was significantly decreased (11.5 [2.7–39.0] vs. 13.4 [3.0–42.2], $p < 0.02$), mirroring in serum the well-known toxicity of tobacco smoking on Clara cells number and/or integrity. The CC16/SP-A ratio showed the most dramatic difference, being significantly lower in smokers compared to nonsmokers (0.17 [2.94–0.02] vs. 0.30 [2.50–0.07], $p < 0.0001$). This study suggests that the assay of SP-A in serum is complementary to that of CC16 since it allows to differentiate Clara cell toxicity (decrease in CC16) from increased epithelial barrier permeability (increase in SP-A). Moreover, if one assumes that SP-A reliably reflects the permeability to proteins of the lung epithelial barrier, this ratio should allow to better evaluate the extent of Clara cells damage caused by tobacco smoking by adjusting for changes in CC16 diffusibility. Even without this assumption, the ratio may be a useful index, integrating both cellular toxicity and epithelial barrier alterations

(Robin, in press). Conclusion: Studies summarized here confirm that the assay in serum of lung secretory proteins such as CC16 or SP-A represents a new non-invasive approach to detect lung epithelium damage caused by acute or chronic exposure to air pollutants. The sensitivity of this new approach clearly emerges from our observations on rodents and humans exposed to O_3, showing an increase of the lung epithelial barrier at O_3 levels commonly encountered in the environment. Although the exact mechanisms governing the transepithelial passage of lung proteins are still poorly understood, we think that the higher sensitivity of serum CC16 to a disruption of the lung epithelial barrier in comparison with BAL albumin mainly stems from the differences in the concentration gradients that drive the diffusion of these proteins across the bronchoalveolar/ blood barrier (Broeckaert et al, 2000). These observations led us to propose the concept of pneumoproteinemia as a new non-invasive approach to evaluate the permeability of the lung epithelial barrier which is the initial site of injury caused by most air pollutants. The determination of lung specific proteins—pneumoproteins—in serum would have the same utility as the proteinuria in kidney diseases involving the glomeruli, the passage of proteins across the lung epithelium being governed by similar structural and functional features as the filtration of plasma proteins by the glomerular filter (Hermans and Bernard, 1998, 1999). Acknowledgements: Studies summarized in the review have been conducted with the support of the European Union (ENV4-CT96-0171 and QLK4-99-01308), the Belgian Government (OSTCA, MD/006), the PRIMEQUAL Project of the French Ministry of the Environment (97-021) and the National Fund for Scientific Research. References: Arsalane K, Broeckaert F, Knoops B, Clippe A, Buchet JP, Bernard A. Increased serum and urinary concentrations of lung clara cell protein in rats acutely exposed to ozone. *Toxicol Appl Pharmacol* 1999;**159**:169–174. Bernard A, Hermans C. Biomonitoring of early effects on the kidney or the lung. *Sc Total Environ* 1997;**199**:205–211. Bernard A, Broeckaert F, Hermans C, Knoops B. The Clara cell protein, CC16, is a biomarker of pulmonary toxicity. In: *Biomarkers*. Proceedings of the Meeting on "Biomarkers and the Human genome" held at Charleston, USA, April, 1998. Broeckaert F, Arsalane K, Hermans C, Bergamashi E, Brustolini A, Mutti A, Bernard A. Serum Clara cell protein: a sensitive biomarker of lung epithelial damage caused by xambient ozone. *Lancet* 1999;**353**:900–901. Broeckaert F, Arsalane K, Hermans C, Bergamashi E, Brustolini A, Mutti A, Bernard. A Serum Clara cell protein: a sensitive biomarker of lung epithelial damage caused by ambient ozone. *Environ Health Perspectives* 2000;**108**:533–7. Hermans C, Bernard A. Pneumoproteinemia, a new perspective in the assessment of lung disorders. *Eur Resp J* 1998;**11**: 801–803. Hermans C, Bernard A. State of the Art. Secretory proteins of pulmonary epithelial cells: characteristics and potential applications as peripheral lung markers. *Am J Resp Crit Care Med* 1999;**159**:646–678.

20. PEST CONTROLLERS—A HIGH RISK GROUP FOR MULTIPLE CHEMICAL SENSITIVITY (MCS)?

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Objective: Cullen (1987) has set up the hypothesis that chemical exposure at work can bring on multiple chemical sensitivity (MCS). Based on this theory it can be assumed that professional groups with frequent chemical exposure are at a high risk for developing MCS. We investigated the health complaints, physical and psychiatric morbidity, neuropsychological performance, toxic burden, and chemical sensitivity of 45 professional pest controllers. Methods: We contacted pest control companies in Munich and Southern Bavaria by mail and telephone. Fourty-five persons were examined in a standardized diagnostic routine consisting of a physical and laboratory examination, a structured psychiatric interview (SCID), a neuropsychological test battery including the California Verbal Learning Test (CVLT), several psychometric scales, and a chemical sensitivity questionnaire (QEESI). Urine samples were screened for metabolites of pyrethroids. Results: 78% of the pest controllers never had any work-related health problems 22% reported rare, mild and transient complaints. Persistent or serious work related health problems were not reported. 62% had pre-existing medical diseases such as allergies and cardiovascular diseases. In 62% of the test persons no psychiatric disorder could be diagnosed 38% had two or more, the most frequent diagnoses were substance abuse, mood and anxiety disorders. They had low somatization scores. Increased liver enzymes and blood count deviations were rather common. The urine analysis of pyrethroid metabolites revealed the following: Br2CA was detected in 11%, F-PBA in 7%. 3-PBA exceeded the normal range in 9%, Cl2CA (cis and trans) in 20%. The pest controllers as a group showed normal results in the neuropsychological testing. A number of participants, however, had significant reductions in tests of verbal memory and recall as well as visual memory. The pest controllers did not regard themselves as chemically sensitive. They scored very low on the different subscales of the chemical sensitivity inventory (QEESI). Conclusion: Despite a definable

occupational exposure to toxic chemicals, our group of pest controllers did hardly report any health complaints or chemical sensitivity. Psychiatric disorders are rare and the profile of diagnoses differs from the psychiatric profile of patients in environmental medicine. The results do not support the hypothesis that work-related insecticide exposure promotes chemical sensitivity. References: Cullen MR. The worker with multiple chemical sensitivities: An overview. In: Workers with Multiple Chemical Sensitivities (Ed. M.R. Cullen). *Occupational Medicine: State of the Art Reviews* 1987;**2**:655–661.

21. OCCUPATIONAL HIGH PRESSURE INJECTION INJURIES OF THE HAND: A TOXICOLOGIC AND SURGICAL EMERGENCY

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Background: High-pressure injection injuries may result from the accidental discharge of foreign material through the skin by several types of equipment. The contaminant penetrates through a tiny skin wound and spreads widely through fascial planes and along tendon sheaths. Damage results from the impact, ischemia due to vascular compression, chemical inflammation and burns, and secondary infection. A limited number of reports underline that this problem is frequently mismanaged. Case series: Four men aged 28 to 67 years (Patients 1 to 4) suffered high-pressure injection injuries of the hand. Injected substances were epoxy paint (1 case), mineral oil (2 cases), and paint diluent (1 case). All patients but one (Patient 4) presented to the Emergency Department (ED) within one hour after the accident. At presentation, all patients exhibited a tiny wound in the fingertip of the first or second digit of the nondominant hand; signs of ischemia were observed in two cases. In Patient 1, clinical risks were initially underestimated, and he was quickly discharged form the ED; he presented again 12h later with severe pain and mild finger swelling. Poison Center advice was requested to assess systemic toxic effects of the contaminant: in all cases, it was evident that ED physicians ignored the potential severity of local chemical effects and surgical risks. In some cases, finger X-Ray showed radio-opaque material and bone lesions due to high-pressure impact of the contaminant. Ultrasonography demonstrated dyshomogenous infiltrates in the fingertip and tissue swelling. Surgical intervention was indicated in all cases. Chemical burns with necrosis involving tendons and vascular structures were documented. Proximal extension of the lesions was not observed in Patient 2, who was wearing protective gloves. Outcome was different for the patients considered: patient 1 underwent rehabilitation for 3 months and had a compete motor *restitutio ad integrum*, with sensation deficits; patient 2, two years after the accident, still presents mild dysesthesias and motor impairment; patient 3 completely recovered; patient 4 underwent finger amputation two weeks after the accident. Discussion: The introduction a foreign material under high pressure induces severe effects. The innocuous appearance of the wound may hide the severity of the injury. Toxicologists may be concerned for toxic damage both local and systemic, but have also to be familial with surgical aspects of this emergency, because orthopedic and plastic surgeons can underestimate proximal diffusion of the chemical and therefore may limit wound surgical exploration to a too narrow area.

22. OCCUPATIONAL EXPOSURES DURING PREGNANCY

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Objective: Evaluation of the potential adverse effects of maternal occupational exposure on the unborn child is difficult to evaluate. Much less is known about the effects of paternal exposure. In principle, it is difficult to distinguish between industrial and environmental chemicals. Chemical exposure, especially at work, has become a matter of public concern because the concentration of chemicals is usually higher than in the environment, and such exposures are often perceived as dangerous, or associated with adverse health effects. Although there is widespread public perception that the majority of fetal malformations are caused by drugs or chemical exposures in pregnancy, this is not true. Drugs and chemicals together are thought to account for only about 4–6% of malformations. To date, most birth defects have no known cause. This situation is problematic for several reasons: there is legislation in most developed countries which prevents sex discrimination in employment and protects the rights of women to work during pregnancy; there is a lack of data about

exposure to most chemicals used in the workplace and fetal development; and the degree of responsibility of employer and employee is poorly defined. Thus, there is need for adequate information on the possible risks of exposure in the workplace. Methods: There are a limited number of epidemiological studies and reports of case series concerning occupational exposures during pregnancy and fetal development. Individual case reports are of limited value. The results of such studies are difficult to interpret because of the large number of confounders. One of the major problems associated with collecting occupational exposure data is that in most cases the degree of maternal/paternal exposure (several routes of exposure) is difficult to ascertain with certainty. Exposure to a single compound is rare, and the concentration reaching the fetus is virtually unknown. Little is known about the kinetic properties of the majority of these chemicals or genetic variations in metabolism. Reference data such as NOAELs (no observable adverse effect levels) are mostly derived from animal experiments that are difficult to extrapolate to the human situation and thus have limited clinical significance. Therefore, risk assessment is usually based on the current knowledge about the chemicals, the possible adverse effects related to the maternal (paternal) illness, toxicity associated with the exposure and the timing of the exposures in relation to the stage of gestation when adverse events can occur. Results: There are in excess of 100,000 substances in the European Inventory of Existing Commercial Substances (EINECS); this figure excludes naturally occurring substances and mixtures. There are about 60,000 chemicals currently in use, and new entities are being introduced at the rate of over a thousand each year. So far, only about two thousand of these chemicals have been evaluated for their fetotoxic potential in animals. Approximately half of these are reported to be teratogenic in these animal studies. However, fewer than 50 substances have been shown to be teratogenic or cause spontaneous abortions in humans. Although much has been written on the problems of detecting increases in malformation rates and Malformation Registries exist in many countries with the aim of detecting such increases, success has been limited. One of the most common exposures, especially in the photographic and printing industries, is to mixed hydrocarbon solvents and much of the epidemiology is based on unspecified solvent mixtures. There is no conclusive evidence to suggest an increased incidence of malformations. However, chronic exposure, especially if associated with maternal toxicity, has been reported to cause an increased risk of miscarriages and intrauterine growth retardation (IUGR). Similar data are available for exposure to dry cleaning fluids. There are equivocal data for substances such as acetone, carbon disulphide, carbon tetrachloride, ethylene glycols, formaldehyde methyl ethyl ketone, and chloroprene. Data on reproductive toxicity are lacking for the majority of chemicals. Under EC legislation in the 7th Amendment to the Dangerous Chemicals Directive there is a requirement for reproductive toxicity tests to be carried out on new chemicals when these are sold in amounts exceeding certain tonnages. However, this covers only a small fraction of the total numbers of chemicals to which women may be exposed in the workplace, the majority of these chemicals are not new but are covered by the existing chemicals regulations. There is a requirement in the EC Directive for the production of materials safety data sheets; these should indicate what information exists on the reproductive toxicity of the chemical, so occasionally provide a useful reference source. Exposures to lead and organic mercury have been well documented and there is clear evidence of reproductive toxicity and adverse pregnancy outcome following maternal exposures to high concentrations. The reproductive problems surrounding exposure to low-level ionizing radiation in both women and men working in the nuclear industry remain unresolved and require further investigation. A similar situation exists for men and women working with anaesthetic gases. Conclusion: Working patterns have changed over the last 20 years and are continuing to do so with a prediction that there will be more women than men in the workforce by 2020. This may lead to workers being exposed to a variety of chemicals over varying periods of time rather than the same chemical over a lifetime. Little is known about the range of individual susceptibilities to occupational and environmental hazards. These may be genetic, or may be associated with gender and/or certain periods of growth and development, e.g., fetus, neonate, infant, child adolescent, or the elderly as well as any pre-existing diseases or loss of function resulting from unusual lifestyles. It is clear from the lack of knowledge of the reproductive toxicity of the majority of chemicals, gases, and metals in both males and females that further research is required. A more thorough characterization of the women who gave birth to infants with malformations is needed. The human reproductive data on individual chemicals is sparse. Many studies have shown a small increase in the incidence of malformations and spontaneous abortions but the number of exposures to individual chemicals is low and in some instances is not known. The presence of an agent in the environment is not synonymous with exposure, since absorption into the body must occur for an adverse effect to be produced. Moreover, care must be taken to distinguish between exposure and poisoning. Some of these exposures cause little, or no maternal-fetal toxicity. Detailed documentation of the type of exposure and an objective measurement of the concentration of the chemical in the mother would improve the quality of any risk assessments. Until a clear causal association is shown for occupational exposures to chemicals, minimizing the exposure of all pregnant (and potentially pregnant) women seems prudent advice. However, financial and other considerations sometimes make this impossible.

To implicate all chemicals as potential developmental toxicants or teratogens would be wrong and would be a great disservice to society. The data currently collected on occupational exposures during pregnancy require further clarification. This is an important area of work that would benefit from continued data collection and more prospective cohort studies. It is important to provide evidence-based advice concerning exposure to chemicals and other substances in the workplace in order to reduce unwarranted anxieties and to enable individuals to make informed choices regarding their exposure to chemicals in the workplace. References: McElhatton P, Garbis H, Schaefer C. Industrial and environmental chemicals. In: Schaefer Ch, Ed. Drugs During Pregnancy and Lactation. Amsterdam: Elsevier, 2001:225–245. IEH report on variability and susceptibility in human response to occupational exposure to chemicals in the UK. Report R13, 2002. ISBN 1 899110 36 4.

23. ACUTE CARBON MONOXIDE POISONING AT THE WORKPLACE: A FIVE-YEAR PROSPECTIVE OBSERVATIONAL STUDY

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Occupational exposure is one of the principal circumstances of accidental carbon monoxide (CO) exposures. However, few data are available on the epidemiology of acute occupational CO poisoning. Objective: To describe characteristics of patients poisoned by CO in the workplace. Methods: Prospective descriptive study of acute CO poisonings related to work from 1995 through 1999 based on case and death reports collected routinely in the different hospitals of the region. Characteristics of the poisoning incidents were recorded at initial patient presentation, at hospital discharge, and during follow-up phone interviews. Results: 184 individuals were poisoned at the workplace in 128 separate episodes. Three died at the site of incident. There were 153 men (83%) and 31 women (17%) of which 2 were pregnant at the time of poisoning. Age ranged from 17 to 73 years (36 ± 11 years). Carboxyhemoglobin levels ranged from 0.2% to 90.4% (17.06 ± 14.69%) at hospital admission. Coma or loss of consciousness occurred in 57 cases (31%). Other symptoms occurring in more than 20% of patients were headache (n = 117; 64%), nausea (n = 80; 43%), vomiting (n = 37; 20%). Hyperreflexia and/or up-going plantar response was noted in 48 patients (26%). Less frequent symptoms included vertigo (n = 28), malaise (n = 22), seizures (n = 5), hypertonia (n = 4), dyspnea (n = 11), paresthesia (n = 6), chest pain (n = 5), abdominal pain (n = 4), tinnitus (n = 3), sinus tachycardia (n = 3). All patients recovered and were discharged from hospital after normobaric (n = 112, 62%) or hyperbaric (n = 69, 38%) oxygen treatment. Seasonal distribution shows a slight predominance for colder periods with 55% (102/184) in autumn and winter. Males were more frequently involved while working in building and public work (31/153), fire fighting (25/153), agriculture and wood industry (21/153), as prison workers (19/153), and in smelters (14/153). In females most incidents occurred in stores and offices (15/31) or in food services (5/31). The main sources of CO were heating system faults, fire, non-automobile gas-powered engines (e.g., saws), automobile engines, and smelters. Conclusion: CO is a serious hazard in the workplace. Preventive measures including CO and fume detectors. Employees should be encouraged to be vigilant and report problems with equipment.

24. CARBON MONOXIDE—NEUROTOXICITY PREDICTING FACTORS

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Objective: The brain is one of the most sensitive organs affected by carbon monoxide poisoning. It is still unclear which factors and clinical symptoms are prognostic of neurotoxic effects. The aim of the study was to evaluate clinical and biochemical factors observed on admission and their value in prognosis of central nervous system sequelae in acute carbon monoxide poisoned patients. Methods: In a retrospective study two groups of patients poisoned with carbon monoxide were compared, with and without pathology in neuropsychological tests in the initial examination. Patients had no history of the previous brain lesions. A neuropsychological assessment (attention and processing speed, learning and memory, problem solving and judgment) was performed by means of subtests of Wechsler Intelligence Scales, Benton Visual Retention Test, Raven's Progressive Matrices, Digits Tests, Verbal Fluency Test and Lucki's set. The following parameters were compared age, carboxyhaemoglobin (COHb) level, lactate concentration, time of exposure,

duration of unconsciousness. The neuropsychiatric sequelae evaluation was based on subjective complaints, neurological and psychiatric examination, detailed neuropsychological evaluation. In some cases Magnetic Resonance Imaging (MRI) and proton magnetic resonance spectroscopy (H^1-MRS) were performed. Results: Total number of analyzed cases was 103, mean age was 25.9 years (range 14–47). In all patients between the fourth and seventh day the neuropsychological tests were performed. According to obtained results patients were divided into two groups. Group 1: 36 patients, mean age 26.8 years, who demonstrated in initial neuropsychological examination different pathology, mainly memory disorders, and group 2: 67 patients, mean age 25.4 years, who had no changes in neuropsychological test. Mean time of exposure was longer in group 1 (102.3 min. vs. 70.1 min), mean COHb concentration was higher in group 1(26.3% vs. 23.7%), but these differences were not statistically significant. Lactate concentration was higher in group 1 (3.56 mmol/L vs. 2.44 mmol/L), the difference was statistically significant. Also the duration of unconsciousness was longer in group 1 (164 min. vs. 12 min.), this difference was also statistically significant. In 18 patients from group 1 MRI was performed and revealed changes in the amygdaloid nuclei, caudate nuclei, globus pallidus and haemorrhagic lesion of internal capsule. The next examinations revealed the regression of described changes and the progressive dilation of subarachnoid space. In 9 patients H^1MRS was performed and showed also functional pathology in CNS (decreased NAA/Cr and Cho/Cr ratio). Conclusion: Neuropsychological tests are useful in the evaluation of CO neurotoxicity. Lactate concentration and duration of unconsciousness seem to be best for predicting neurotoxicity of CO, but the further studies are necessary.

25. NITRILE POISONINGS—CYANIDE FORMATION, CLINICAL COURSE AND TREATMENT

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Case series: Aliphatic nitriles like propionitrile and olefinic nitriles like acrylonitrile can result in significant metabolic formation of cyanide after inhalation or dermal uptake. Except for acetonitrile—cyanide will always be formed after exposure to aliphatic nitriles. As cyanide formation from acrylonitrile is subject to polymorphisms and there is individual variation in detoxification capacity toxicity is less predictable. In addition the pathway and duration of exposure will influence the amount of cyanide formed. One case of propionitrile and 10 cases of acrylonitrile poisoning are presented. In propionitrile poisoning the clinical picture was characterized by nausea and anterograde amnesia. The cyanide level was 3.15 mg/l initially. Therapy with sodium thiosulfate alone proved to be efficient and sufficient, as the liberation of cyanide is a slow process, which allows for a slower acting antidote: Slight poisoning: (patient somnolent or HCN level <3 mg/l blood): sodium thiosulfate 10% 20 ml i.v. or 25% 10 mL i.v.—may be repeated. Severe poisoning: (patient unconscious or HCN level >3 mg/l blood): 4-dimethylaminophenol (4-DMAP) 5 ml $=$ 250 mg (3–4 mg/kg b.w.), if available, or other fast acting HCN antidotes, followed by sodium thiosulfate 10% 20 ml i.v. or 25% 10 ml i.v.—repeatedly. Acrylonitrile is an animal carcinogen, and it has intrinsic toxic effects on the central nervous system. Therefore some years ago a specific antidotal regimen was developed in Germany using N-acetylcysteine (NAC) in a similar regimen to paracetamol poisoning. Cyanide levels up to 4.3 mg/l have been observed in acrylonitrile poisonings. We have learned that the application of NAC alone does reduce the cyanide level in blood. However, the additional application of sodium thiosulfate is recommended. The therapeutic regimen has been shown to be relatively (NAC) or perfectly (sodium thiosulfate) tolerable: Slight poisoning: (patient conscious, few central nervous symptoms): NAC 150 mg/kg b.w. during 15 minutes undiluted or in 250 ml glucose 5% i.v. Severe poisoning: (patient unconscious, or severe central nervous symptoms): NAC 300 mg/kg b.w.: 150 mg/kg b.w. as above, 50 mg/kg b.w. in 500 ml glucose 5% during 4 hours i.v. 100 mg/kg b.w. in 500 ml glucose 5% during 5–40h. Plus: cyanide antidote regimen as above. Our results show a difference in the course of acrylonitrile poisoning depending on the route of exposure. In prolonged inhalation plus slight dermal contacts there can be a significant cyanide production with moderate acrylonitrile levels, while in acute splashes with immediate decontamination no cyanide could be detected, though acrylonitrile levels were high.

26. THE MANAGEMENT OF AN UNDERGROUND FIRE AT BRYNLLIW COLLIERY WASTE TIP

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Objective: In 1996 an underground fire started at the former Brynlliw colliery in Grovesend (population 900) near Swansea. It continued to burn until remedial work was started in November 1999. The site was in close proximity to the M4 motorway and residential areas including a primary school and nursing home. The fire produced large clouds of smoke and fumes and, on occasions, this necessitated the closure of the motorway. There was also concern about the detrimental effect of the noxious gases on the health of the local residents. When work was started to extinguish the fire, which involved parts of the site being excavated, the Chemical Incident Management Support Unit (CIMSU) was involved in an advisory role. Methods: A range of monitoring equipment was utilized to carry out a continuous risk assessment program of the noxious gases and particulate matter which was liberated as a result of the work being carried out at the site. Mobile analyzing equipment was employed at the site of the fire to monitor the levels of NO_x, CO, SO_2, H_2S, O_3 and atmospheric particulates (PM10). Data was retrieved by telemetry using a package that polled data at half-hour intervals through GSM radio modems connected to the data logger at each monitoring location. The same system was established on a laptop computer for use by the duty on-call Local Authority Pollution Control Officer out of hours. Data was polled from the laptop computer using a Nokia mobile phone to connect to the GSM radio modems at the monitoring locations. A link-up was established with the Cardiff Weather Centre to obtain a continuous flow of meteorological information. The Pollution Control Division was then able to provide information to remediation contractors in 3-h segment blocks to advise if it was safe to work. Results: The environmental monitoring instigated at the site allowed the work to be carried out whilst simultaneously monitoring the movement of gaseous and particulate emissions in various weather conditions. This allowed preventative action to be taken before pollutant levels approached the first action level in the Authorities' Emergency Evacuation Plan. Local residents experienced minimal inconvenience and did not need to be evacuated. The fire is now extinguished and a landscaping scheme is now being carried out on the site. Conclusion: Environmental monitoring was essential in order that the whole procedure could be managed with minimum inconvenience to the local residents whilst ensuring that their health would not be put at risk.

27. PHYSOSTIGMINE: THE PENDULUM SWINGS

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Objective: The Efik people of Old Calabar practiced trial by ordeal with the bean of *Physostigma venenosum*, also known as the Calabar bean. In the 1870s, Fraser demonstrated that the active eserine [physostigmine] the active ingredient in Calbar bean antagonized the effects of atropine on pupil reactivity. In 1864 Kleinwachter was first credited with the use of physostigmine to reverse atropine poisoning in 2 men. Subsequently physostigmine was introduced into clinical medicine to lower intraocular pressure in patients with glaucoma (1877), to reverse nondepolarizing neuromuscular blockade (1900), and to treat myasthenia gravis (1934). Physostigmine is now known to be a reversible acetylcholinesterase inhibitor that is currently used both as a nonspecific analeptic agent and as a specific antidote for antimuscarinic poisoning. The purpose of this presentation is to review the literature to support these practices and develop a rational role for physostigmine in modern clinical toxicology. The role of physostigmine as maintenance therapy for Alzheimer's disease or other disorders will not be discussed. Methods: A Medline search was performed using the words physostigmine, poisoning, overdose, and toxicity. Pertinent articles were obtained and references from these articles were hand-searched until no additional articles were found. Data were synthesized and ranked according to standard criteria for levels of evidence. Results: Multiple anecdotal case reports from the 1960s or 1970s suggest that physostigmine enhances arousal of patients with antimuscarinic poisoning. Several large case series support the use of physostigmine for reversal of scopolamine-induced delirium in postoperative patients. This practice is further supported by a controlled trial in normal volunteers. Nonspecific effects of physostigmine were investigated in consecutive poisoned patients (Nilsson) where it was found to have limited efficacy in reversing benzodiazepine-induced central nervous system depression as well as central nervous system depression produced by other unspecified drugs. Further support for physostigmine's ability to enhance arousal in patients with benzodiazepine-induced sedation can be derived from EEG and PET scan data in normal human volunteers. Similar studies support enhanced arousal following either ketamine-induced or propofol-induced anesthesia. Interestingly, a small randomized trial in overdose patients comparing naloxone to physostigmine for heroin-induced central nervous system and respiratory depression concluded that whereas both drugs were equally efficacious in producing arousal, physostigmine was preferred by the authors because it failed to produce any signs of withdrawal. With regard to effects of physostigmine as an analeptic, no controlled trials evaluated desirable endpoints other than arousal, and there are limited data on adverse outcomes. With regard to direct antagonistic

effects, only a single retrospective study (Burns) compared physostigmine to supportive therapy in patients with antimuscarinic poisoning. Among the 52 consecutive patients investigated, those who received physostigmine had significantly less agitation and fewer complications. More importantly, the physostigmine treated group had a statistically shorter time to recovery and a trend toward shorter hospitalization. Conclusions: At one time, based largely on anecdotal experience, physostigmine was a standard adjunct for the treatment of patients with tricyclic antidepressant poisoning and was widely touted by experts despite animal evidence that it lowered the LD50. This practice was abandoned when a few cases of asystole resulted in very complicated patients. Consequently, the routine use of physostigmine, even for pure antimuscarinic toxicity was largely avoided by many practitioners both for a lack of proven effect on morbidity and mortality and for fear of adverse effects.(Rodgers) Recent evidence, however has tried to refocus the use of physostigmine toward both safe and effective therapy. Although in some circumstances, arousal may appear beneficial, more important outcomes such as complications, survival, and stability for hospital discharge need to be evaluated. Similarly, if arousal is desired, the risks and benefits of other antidotes, such as flumazenil and naloxone should be compared to physostigmine. Finally, for isolated antimuscarinic toxicity, multiple levels of evidence support the use of physostigmine if no contraindications exist. References: Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann Emerg Med* 2000;**35**:374–81. Nilsson E. Physostigmine treatment in various drug-induced intoxications. *Ann Clin Res* 1982;**14**:165–72. Rodgers GC Jr, Von Kanel RL. Conservative treatment of jimsonweed ingestion. *Vet Hum Toxicol* 1993;**35**:32–3. Rupreht J, Dworacek B, Oosthoek H et al. Physostigmine versus naloxone in heroin-overdose. *J Toxicol Clin Toxicol* 1983–84;**21**:387–97.

28. TACRINE IN THE TREATMENT OF ANTICHOLINERGIC DELIRIUM

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Background: Treatment options for anticholinergic delirium include sedation or the use of the cholinesterase inhibitor physostigmine. Physostigmine's duration of action is relatively short. Other cholinesterase inhibitors such as tacrine are reported to have efficacy in anticholinergic delirium and have kinetics which suggest that a longer duration of response may occur. Case series: We report 26 patients who received tacrine for anticholinergic delirium. In 11 patients, data was collected prospectively as part of a pilot study, data for the other 15 patients was retrieved from our clinical toxicology database. Charts and study records were examined for evidence of adverse events, presence and duration of efficacy and for evidence of optimal dose. Patients were included if they had taken a known anticholinergic drug and had clinical evidence of an anticholinergic delirium. Results: Drugs ingested by patients and the number of responders are shown in the following table:

Drug	Number	Responders
Benztropine	12	12
Benzhexol	4	4
Hyoscine	1	1
Promethazine	4	3
Pheniramine	1	1
Unknown	2	2
Olanzepine	1	0
Amitryptilline	1	0

No significant adverse effects were noted, the administration of tacrine was associated in a reduction in pulse rate (Mean 17.9%, Median 16.3%, Range 7.1%–34.3%), an increase in bowel sounds but no other effects. Both the degree of response and the duration of effect appeared to be dose-dependent. Review of each individual's response to their first exposure to a given dose showed that the 26 patients had 45 administrations of tacrine at different doses. Failure of clinical response was observed in 70% of patients who received 15 mg (n = 17), 28% of 30 mg dose (n = 21), 50% of

45 mg (n = 4) and 0 % of 60 mg (n = 3). For responders the mean duration of response for doses of 15, 30, 45, 60 mgs was 1.48, 4.21, 3.19, and 5.6 hours respectively. Conclusion: Tacrine appears to have efficacy in anticholinergic poisoning. There is therefore sufficient basis to conduct a randomized clinical trial to compare efficacy with other agents.

29. CRITICAL REVIEW OF NALOXONE AS AN OPIOID ANTIDOTE

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Objective: To review the scientific literature on the clinical use of naloxone to treat opioid intoxication. Methods: Medline was searched using the keyword "naloxone" and relevant articles were retrieved and reviewed. Additional resources identified during the initial review were subsequently examined. Results: Naloxone is an nonselective opioid antagonist created by the addition of a hydrocarbon side chain to oxymorphone. Naloxone has no intrinsic activity at conventional doses. However, antagonism of the effects of endogenous opioids peptide may be noted during pain, stress or exercise, and perhaps during placebo administration and acupuncture, when such effects are clinically significant. The most prominent adverse clinical effects of opioid agonists, such as respiratory depression and sedation, are mediated by agonism at the μ_2 opioid receptor. These effects are completely antagonized in a dose dependent manner by naloxone. Buprenorphine may be unique among the μ-opioid agonists since its high affinity for this receptor makes it resistant to antagonism by naloxone. Since naloxone antagonizes most potently at the μ receptor subtype, reversal of the effects of κ (kappa) agonists may require higher doses of naloxone than are normally administered. Clinical effects not mediated through opioid receptors are not reversed. These include morphine-related histamine release, propoxyphene-induced cardiotoxicity, or seizures associated with either meperidine or tramadol. Although its etiology is undefined, fentanyl-induced muscle rigidity is reversed. Interestingly, very low doses of naloxone (0.25 μg/kg) may actually enhance opioid-induced analgesia, presumably by selective inhibition at low doses of excitatory (i.e., antianalgesic) opioid receptors. Naloxone has no consequential toxicity even at the extremely high doses utilized (unsuccessfully) to attenuate spinal cord injury following trauma. Indications for the emergent administration of naloxone include respiratory depression, with a respiratory rate or tidal volume that is incapable of maintaining oxygenation, or the need to confirm the clinical diagnosis of opioid intoxication. It is occasionally beneficial in patients with non-opioid poisonings such as with clonidine, valproic acid, or ethanol. The principal adverse effect associated with naloxone is the precipitation of the opioid withdrawal syndrome, which consists of vomiting, diarrhea, mild autonomic instability, and psychomotor agitation and drug craving. While distressing, iatrogenic opioid withdrawal is not generally life-threatening except perhaps during either rapid/ultrarapid opioid detoxification or emergency management of an opioid overdose patient. The most consequential complication of precipitated withdrawal is pulmonary edema which may be either noncardiogenic or cardiogenic. Noncardiogenic pulmonary edema (i.e., acute lung injury) occurs following either profound hypoxia (e.g., apnea) or after inspiratory barotrauma. Cardiogenic pulmonary edema likely represents acute myocardial dysfunction following massive autonomic catecholamine discharge during rapid precipitated withdrawal. In animal models, catecholamine release appears to correlate with the degree of pCO_2 elevation. Additionally, pulmonary aspiration may occur in patients with withdrawal-associated emesis, particularly in those with concomitant use of nonopioid central nervous system depressants that are not reversed by naloxone. Both autonomic stimulation and emesis can be minimized by the use of both temporizing ventilatory support and of low-dose naloxone (0.05 mg initially) that is titrated slowly to the clinical endpoint of normalized ventilation. Conclusion: Naloxone is a highly effective and safe antidote when utilized in a conservative fashion for patients with appropriate indications.

30. THE USE OF NALOXONE FOR RESUSCITATION OF NON-OPIOID TOXICITY

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Objective: Naloxone is one of the prototypical antidotes used in toxicology practice for the reversal of opioid toxicity. Several other drugs can present with clinical signs and symptoms identical to the opioid toxidrome. The objective of this presentation is to discuss the clinical and scientific evidence that support or refute the role of naloxone in non-opioid toxicity— specifically ethanol, valproic acid, and the imidazolines. Methods: Review of all published literature on the use of naloxone for reversal of clinical toxicity due to ethanol, valproic acid, and the imidazolines. Review of basic

scientific evidence to explain the pathophysiology of the clinical effects of naloxone in these circumstances. Results: Naloxone has been used successfully for the reversal of coma in pure ethanol intoxication, the first case being reported in 1978. Postulated mechanisms of action for these effects include naloxone's reversal of the central effects of endogenous opioids released by acute ethanol intoxication, especially in "enkephalin sensitive" patients; reversal of CNS effects of isoquinolones, and inhibition of calcium depletion caused by ethanol. Animal studies demonstrate that naloxone causes an accelerated metabolism of ethanol through reversal of redox disturbances, specifically the $NADH/NAD^+$ ratio. Since 1979 the literature reports 5 of 8 cases where naloxone was successful in reversing valproic acid (VPA)-induced coma. Scientific evidence demonstrates that naloxone acts as an antagonist to beta-endorphin release by VPA, reverses the VPA blockade of GABA uptake by neurons, and acts as a direct competitive antagonist at GABA receptors. Naloxone has been used for imidazoline toxicity with equivocal results. Specifically, with clonidine toxicity, numerous case reports and series both support and refute its effectiveness in reversing coma, bradycardia, hypotension, and miosis. Isolated case reports show naloxone's effectiveness against toxicity of other alpha-2 adrenergic agonists. Proposed mechanisms of action include an "opioidergic" component, i.e., naloxone's reversal of CNS effects of elevated endogenous opioids caused by clonidine. In addition, there is interaction between alpha-2, imidazoline, and opioid receptors as evidenced by similar signal transduction mechanisms, similar geographic location of receptors in the medulla, and pharmacologic studies of newer drugs with more selectivity for the imidazoline receptor. Differential clinical responses after naloxone may be explained by age, genetic predisposition, resting sympathetic tone, and the concentration of circulating endorphins and norepinephrine. Conclusions: Naloxone is not a specific antidote for opioid toxicity. It can be beneficial to reverse coma, respiratory depression, and cardiovascular depression in some non-opioid poisonings. Clinical and scientific evidence are present to demonstrate and explain naloxone's effect on ethanol, valproic acid, and imidazoline toxicity.

31. THE PHYSOSTIGMINE TEST—AN APPROACH TO ANTICHOLINERGIC POISONINGS

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Objective: In recent years the clinical use of physostigmine has been considered controversial due to fear of adverse effects such as seizures and arrhythmias. The purpose of our study was to examine the efficiency and safety of physostigmine administration in cases of poisoning with central anticholinergic agents. Methods: In our study physostigmine was administered in a dose of 0.03 mg/kg bodyweight to emergency patients who were admitted to our department with an unclear history and showing at least one central (coma, agitation, hallucination, disorientation) and two peripheral (tachycardia, mydriasis, red and dry skin, reduced bowel sounds) anticholinergic signs. In advance of the test contraindications of the proper use of physostigmine, such as asthma, ketoacidosis or coronary heart disease were excluded by means of auscultation of the lungs, measuring the blood glucose levels and interpretation of an ECG. The latter was repeated 15–20 minutes after administration of the drug, and at the same time the physical condition of the patient was reassessed to identify clinical changes. The test was rated as positive if there was an obvious increase in consciousness and personal orientation, disappearance of hallucinations, normalization of cardiac rhythm disorders or pupil size. After a positive outcome of the test a therapeutic repetition of treatment with physostigmine was undertaken if a relapse occurred in the toxic state. We subsequently tried to find out the toxin ingested and responsible for the anticholinergic signs using toxicological-analysis of blood and/or urine specimens. Results: The test was done in 50 cases of which 39 were rated positive (78%). In these positive cases, the agents involved were diphenhydramine ingested alone (10/10); diphenhydramine + coingestion 8/9 (89%); alkaloids from atropa and datura species alone 8/9 (89%) or +coingestion (2/2); tricyclic agents (TCA) alone (3/3); TCA + coingestion (1/1); phenothiazines (3/3); doxylamine (1/1); benzodiazepines + coingestion (3/4). Negative results were documented in acute psychosis and poisonings with amphetamine, ethanol or amanita mushrooms for which improvements in consciousness were below a certain threshold. Adverse effects were rarely seen, respectively, once ventricular extrasystoles and seizure. Conclusion: We recommend the use of physostigmine in the treatment of central anticholinergic syndromes due to ingestion of poisons such as antihistamines (diphenhydramine) or the parts of atropa and datura species. It was effective in reversing all peripheral and central anticholinergic effects, and we consider it safe if the patient's cardiac status is carefully monitored.

32. TAKE HOME NALOXONE: FEASIBILITY, SAFETY, AND EFFICACY

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Fatal and nonfatal opiate overdose (OD) occur at a high or increasing higher rate in many parts of the world. Unintentional fatal opiate OD in opiate abusers is usually due to heroin but sometimes also methadone and buprenorphine. Sedative hypnotic coingestants especially ethanol or benzodiazepines, reduced tolerance from voluntary or forced abstinence (jail) and increased purity contribute to increase opiate-related mortality. Opiate abusers who witness an OD may not summon EMS because they don't trust them and fear police who often respond with them. Police may arrest and charge opiate abusers for outstanding warrants, possession, or murder if they supplied or injected the illicit substances[1]. EMS staff may transport users to the hospital involuntarily and/or give larger than necessary doses of naloxone to ensure a rapid reversal and less risk of renarcotization. Opiate abusers often attempt ineffective street remedies before summoning help. Take home naloxone was first suggested by Strang in 1992 to minimize the harm from opiate misuse[2]. To be feasible, take home naloxone programs must be acceptable to opiate abusers and prescribing physicians, affordable, easily teachable and applicable at opiate OD scenes. Most opiate abusers would favor taking home naloxone, would keep it in their home and use it if it were available[3]. The legal risk for U.S. physicians who prescribe naloxone for laypersons was judged to be low for those who act in good faith, in the course of professional practice and for a legitimate medical purpose[1]. Take home naloxone programs are feasible. Dispensing naloxone should be preceded by education that includes the purpose of naloxone use, potential adverse effects, recognizing serious opiate OD, indications for and technique of use, summoning EMS, reporting outcome and getting more naloxone. The education program should be designed for naloxone use on a fellow opiate abuser or by friends or family on the recipient. Mouth-to-mouth or cardiopulmonary resuscitation instructions are optional. Recipients should be taught to suspect a serious OD if heroin or other opiate has been used within the past 3h and the user is blue, unresponsive to vigorous stimulation, or cannot maintain arousal without constant or frequent stimulation. Naloxone is indicated for opiate OD who is unresponsive to vigorous stimulation. EMS should be summoned whenever naloxone is given, when arousal cannot be maintained without constant or frequent stimulation or when "nodding off" is occurring and a responsible observer cannot remain present. The optimal route for layperson naloxone would be easy to learn and perform, with minimal risk of injury to the victim and rescuer, facilitates rapid onset of arousal but not abrupt withdrawal and needs little to no special equipment. The IM, SQ and intranasal (IN) routes appear to have the most attractive risk benefit and cost considerations. The IN route requires a special aerosol-generating device. The duration of action of IV naloxone was found to be substantially less than combined IV/IM naloxone (90 vs >360 min, respectively) in reversing morphine-induced respiratory depression[4]. In a comparison of SQ vs IV naloxone, the overall time to arousal was nearly identical (9.6 vs 9.3 min, respectively) with the slightly longer onset of action for SQ balanced by the slightly longer time required start the IV[5]. The IM and SQ routes could be considered as 'injected' routes and taught as a deep injection. For the 'injected' route (SQ or IM), 0.8 to 1.0 mg and for the IN route 2 mg are the recommended initial doses. The risks and benefits of take home naloxone programs must be carefully considered. Arousal of heroin OD victims from layperson naloxone use could result in a larger proportion of victims leaving the scene prior to EMS arrival or against medical advice (AMA) afterwards. Because naloxone appears to have a shorter duration of effect than heroin, serious renarcotization may occur. The SQ, IM, or IN routes lead to slower absorption and a reduced risk of renarcotization. Abrupt reversal of CNS depression without prior correction of hypoxia and hypercarbia may result in greater catecholamine levels and risks of adverse sequela. Naloxone can precipitate acute withdrawal resulting in combative or agitated behavior. The slower onset and less severe withdrawal from IM, SQ and IN routes lower the risk of adverse reactions to naloxone. While there is concern that lowering the risk of death will remove an important deterrent, many believe that opiate abuse is not deterred by risk of bodily harm or death. Many experts believe that naloxone misuse by opiate abusers is very unlikely to occur and early evidence from feasibility trials substantiate this belief[6]. The sooner that the respiratory failure is corrected the less likely it will cause pulmonary edema, hypoxic encephalopathy or death. There are scant published data available to judge its efficacy or safety. In Berlin, naloxone, supplies, and instructions were dispensed to 124 opiate abusers. They reported that 22 users gave naloxone on 27 occasions; IM on 14 (48%), IV on 13 (45%) and SQ on 2 (7%). Naloxone use appeared to be appropriate in 26 (90%), of dubious benefit in 2 (7%) and inappropriate (cocaine OD) on 1 (4%) occasion[7]. In Jersey, a minijet prefilled with naloxone along and training were given to 101opiate abusers resulting in 5 successful resuscitations[7]. In Chicago, naloxone has been distributed to over 550 opiate abusers with 52 successful uses reported[8]. In Can Tunis, Spain, naloxone is being provided along with brief

training and 60 successful cases have been reported[9]. There are many challenges in designing a trial to determine the effectiveness of take home naloxone programs. Since naloxone use in these circumstances is a life-saving therapy, it would be unethical to randomize therapy between naloxone and a placebo treatment. These challenges must be overcome and higher-quality data provided before the effectiveness and safety of take home naloxone programs can be assessed. References: 1. Burris S, Norland J, Edlin BR. Legal aspects of providing naloxone to heroin users in the United States. *Int J Drug Policy* 2001;**12**:237–248. 2. Strang J, Farrell M. Harm minimisation for drug misusers. *BMJ* 1992;**304**:1127–8. 3. Strang J, Powis B, Best D et al. Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability. *Addiction* 1999;**94**:199–204. 4. Longnecker DE, Grazis PA, Eggers GWN. Naloxone for antagonism of morphine-induced respiratory depression. *Anesth Analg* 1973;**52**:447–453. 5. Wanger K, Brough L, Macmillan I et al. Intravenous vs. subcutaneous naloxone for out-of-hospital management of presumed opioid overdose. *Acad Emerg Med* 1998;**5**:293–299. 6. Darke S, Hall W. The distribution of naloxone to heroin users. *Addiction* 1997;**92**:1195–9. 7. Dettmer K, Saunders B, Strang J. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *BMJ* 2001;**322**:895–6. 8. Bigg D. Data on take home naloxone are unclear but not condemnatory. (Editorial) *BMJ* 2002;**324**:678. 9. Trujols J. Take home naloxone: Life-saving intervention, medico-legal concern and heroin user's competence. (Editorial) BMJ.COM Rapid Responses 13 May 2001.

33. OCCUPTIONAL MERCURY VAPOUR POISONING IN WORKERS OF A FLUORESCENT BULB FACTORY

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Objective: Elemental mercury (Hg) vapor poisoning is a serious occupational disease, which may cause renal insufficiency and mortality. In this study, urinary Hg concentrations in workers of a fluorescent bulb factory (FBF) exposed to Hg vapor were determined and compared with their clinical findings and the air Hg concentrations of the work place. Effects of D-penicillamine and Dimercapto succinic acid (DMSA) were also investigated. Methods: A questionnaire was designed to record the clinical and Para clinical findings for each worker exposed to Hg vapour in the FBF (test group) and those in another factory (Compact) with much less Hg pollution (Control group). The 24 h urinary Hg concentrations of both groups were estimated by an Atomic Absorption (Perkin Elmer Model 3030) using Mercuric Hydride System, before and after treatment. The Hg vapor concentrations at different areas of the work place were estimated by Hg vapour detector tube (Gastec No 40, Japan) using a personal sampler pump, on three occasions (winter, spring, and summer 2001). The workers who had urinary Hg concentrations of 50–300 μg/L were treated by D-Penicillamine and those who had >300 μg/L were administered DMSA at standard dose regimen. Statistical tests (Student-t, X^2 and Spearman) were used for analyses. Results: A total of 123 male workers aged 21–30 (mean 28.4) years, 102 in the test group, and 21 in the controls were investigated. All control patients were asymptomatic and their urinary Hg concentrations were below 20 μg/L. The workers exposed to Hg vapour had urinary Hg concentrations between 32 and 485 (mean 102.3) μg/L which correlated well ($P < 0.05$) with the clinical findings such as agitation, tremor and loss of memory. Three patients had proteinuria and one had asymptomatic haematuria. Vapour Hg concentrations of the exhaust area, general area around the exhaust tube and further areas of the fluorescent factory were 0.80 ± 0.15, 0.15 ± 0.12, and 0.20 ± 0.11 mg/m^3, whereas the vapor Hg concentrations of the different areas of the Compact factory were all <0.01 mg/m^3, which is below the occupational exposed limit of 0.025 mg/m^3. There was a significant positive correlation ($p < 0.01$) between the vapor Hg concentrations of the work places and the urinary Hg concentrations of the workers. There was significant improvement after treatment and the mean reduced urinary Hg concentrations were 304.6 and 46.3 μg/L with DMSA and D-Penicillamine, respectively. DMSA revealed less side effects than D-penicillamine ($p < 0.05$). Conclusion: Determination of air Hg concentrations of the work place is required at certain intervals and safety measures must be applied accordingly. Estimation of 24h urinary Hg concentration is a good index for the early diagnosis and treatment of occupational Hg poisoning. DMSA has fewer side effects and is more effective than D-Penicillamine in treatment of Hg poisoning. References: 1. Environmental Health Criteria 118, Inorganic mercury; International Program of Chemical Safety, World Health Organization 1976, 12–56. 2. Clarkson, TW. The toxicology of mercury. Crit Rev Clin Lab Sc 1997;**34**:369–403.

34. CONSEQUENCES OF SEVERE CHRONIC TOLUENE INTOXICATION IN PRINTERS

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Objective: To describe symptoms of acute and chronic intoxications caused by unusually high chronic exposure to toluene and to study possible permanent consequences of extreme chronic occupational exposure 10 years after the exposure stopped. Case series: Eight men were examined from the previous group of 58 rotogravure printers from a printing plant where, until 1989, the mean toluene concentration was about 2000 mg m^{-3}, i.e., 250 ppm. After 1989, the air concentration decreased below the Czech TWA (time-weighted average) of 200 mg m^{-3}. High excretion of hippuric acid in urine confirmed the exposure (mean 5.84 g l^{-1}, i.e., 32.58 mmol l^{-1}). In 1992 toluene exposure ceased completely. In the whole group no pathological changes in haematopoesis, liver and kidneys, which could be attributable to toluene, were found. On the other hand, the most frequent subjective complaints included feeling of inebriation and pseudo-hallucinations (58%), mostly auditory (with perception of loud music of different styles) and rarely visual, tiredness (26%), sleepiness (24%) and headache (19%). Examination of visual evoked potentials was abnormal in 24% of printers, in electroencephalography in 27% of persons. In 8 subjects, chronic occupational intoxication with toluene was acknowledged as an occupational disease. Now, 10 years after the exposures ceased, 8 printers were re-examined; their mean age is about 55 years, mean exposure to toluene was 16 years. In three of them an occupational disease had been acknowledged. In most of the previous printers, subjective complaints still persist—25% of them describe tiredness, 50% sleeping disturbances, and 38% headache. About 38% of the subjects have abnormalities in the electroencephalography, 25% in the evoked potentials. The mean color confusion index of the Lanthony test is 1.36 (the ideal value is 1.00). Peripheral neuropathy, which could be attributed to organic solvents occupational exposure, was not found. Biochemical findings did not prove liver and kidneys damage. Mean excretion of hipppuric acid in urine is 0.75 g l^{-1}, i.e 4.16 mmol l^{-1}, the level normally found in the nonexposed population, and there is no suspicion on toluene abuse at present. Conclusion: Ten years after the end of extreme exposure to toluene at the workplace, central neural system impairment was still found in most of the printers of the pilot study. Correlation and comparison with the previous findings will be executed in a larger group of printers. Acknowledgement: Supported by MSM J13/98 111100002 and 111100005.

35. METAL INTOXICATIONS AT WORK: THE ROLE OF THE POISON CONTROL CENTER

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Introduction: Metal occupational exposures are connected with industrial and agrochemical products on many occasions. Fungicides with a metal in their composition are the principal cause of intoxication from agrochemical metallic products whereas industrial metallic poisonings can be due to inhalation of fumes from welding, smelting or galvanising operations that can produce metal fume fever. The goal of this study is to examine the role that a Poison Control Center (PCC) plays in this kind of intoxication. Methods: From January 1991 to May 2002 all occupational exposures to metals collected in our Service were analysed. The following data were included: gender, age, aetiology, type of metal and product, exposure route, clinical manifestations and severity. Results: A total of 200 consults involving metal exposures at work were made during the study period. Eighty-five percent were male; all cases were adults (mean age group 30–45 years old). Acute intoxication corresponded to 97% of cases and 3% (lead and mercury) were chronic cases referred for analytical interpretation purposes. The implicated metal was copper in 42% of cases, arsenic in 16%, lead in 10.5%, aluminium in 6%, chromium in 5.5%, mercury in 5.5%, zinc in 4.5%, magnesium in 4%, tin in 2.5%, cadmium in 1.5%, nickel in 1%, cobalt in 0.5%, and bismuth in 0.5%. 95% of exposures were to inorganic salts. Industrial products accounted for 54% of cases and agrochemical compounds 41% (73% of these were inorganic copper salts). The most frequent exposure route was inhalation (50.5%) followed by ingestion (18.5%), skin contact (14%), ocular contact (5.5%), and subcutaneous exposure (1.5%). The clinical manifestations were: gastrointestinal (24%) and 50% of them were associated with respiratory or neurological manifestations. Dermatological (14.5%), respiratory (14%) neurological (13.5%), fever (10.5%), and other (4.5%) accounted for the remainder. Twenty-three percent of cases

had no symptoms, 23% had mild signs and symptoms, and 50% of patients developed moderate to severe clinical manifestations. Seventy-three percent of the calls came from health care units. Conclusions: A significant number of patients had moderate to severe intoxication. Copper salts were the products more usually implicated in poisoning. Inhalation was the main exposure route. Our Service received enquiries about assessment and medical treatment of acute metal intoxication after occupational exposures with both industrial and agrochemical products. Referrals were also interpretation of urine and blood analysis for a few cases of chronic metal intoxication. The PCC is in a position to establish the relationship between workplace and risk of metal intoxication.

36. THE ENDANGERING CARERS—A DIFFERENT PERSPECTIVE ON CHILDHOOD POISONINGS AND STRATEGIES OF PREVENTION

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95 % of childhood ingestions happen in the house and its surroundings and have a serious course in less than 1%. In analyzing the circumstances of these life-threatening poisonings specific risk factors can be defined, which depend on first the behavior of carers, second specific environmental factors, and third inherent toxicity of a substance or product. Whereas in the early 1990s the retrospective analysis of life-threatening and fatal pediatric poisonings had been successfully focused on the concept of "hazard factors" (1) reflecting both inherent toxicity of a substance as well as product availability, packaging and closure type, it became obvious by the success of the derived passive preventive measures that the "human factor", namely the role of carers had been neglected. The incidence of childhood poisonings of all degrees treated at an ED has been reduced to 3.6/1000 of the age group compared to an overall incidence of childhood ingestions in the range of 37/1000 respectively (data from Greater Berlin area 1997). A closer look into the mode of life-threatening childhood poisonings by a prospective follow-up of 150 cases in 1997 throughout Germany revealed e.g., an incidence of 93 cases caused by pharmaceuticals, of which 13 that is 14% were iatrogenic in origin. Even rare causes like poisoning due to Munchhausen syndrome by proxy become relevant in this context as could be shown by a British prospective study that suggested a low overall incidence of this phenomenon in the range of 0.004/1000 of the age group investigated (2). Typical examples from our study on life-threatening poisonings and retrospective cases of the past decade help to further elucidate the concept of the "human factor" as an important cause of mainly severe childhood poisonings and will be summarized with the view on additional preventive activities in the different fields. Endangering carers: Endangering parents: "pill-eating habit" e.g., methadone, industrial cleaners in household, history of suicides in the family; Endangering father: actively as murder attempt (insulin), passively by hobby-products (methanol); Endangering mother: actively through Munchhausen by proxy syndrome (lead, coumarins, laxatives, sodium chloride), passively by mothers medication (TCAD, SSRI); Endangering siblings: actively by feeding the younger ones, passively through medications of chronically ill sibs (carbamazepine, digoxin, methotrexate, theophylline); Endangering grandparents: as visitors or baby-sitters (clonidine, cardiac medications, antidiabetics); Endangering babysitters: inadequate first aid measures; Endangering physicians: iatrogenic overdose; unnecessary prehospital treatment (instillation of activated charcoal into the lungs). References: 1. Litovitz T, Manoguerra A Comparison of Pediatric Poisoning Hazard: An Analysis of 3.8 Million Exposure Incidents, *Pediatrics* 1992;**89**:999–1006. 2. Mc Clure RJ; Davis PM, Meadow SR et al. Epidemiology of Munchhausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation. *Arch Dis Child* 1996;**75**:530–534.

37. IS PLASMA LACTATE USEFUL IN THE EVALUATION OF PURE CARBON MONOXIDE POISONING?

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Objectives: Acute carbon monoxide (CO) intoxication may result from various sources, including complex mixtures of gases that may cause lactic acidosis. To better understand CO toxicity, we prospectively studied the relationships between plasma lactate and neurological impairment in pure CO poisonings. Methods: Patients admitted with a history of exposure to CO, resulting from dysfunction of cookers or heaters, were studied. Patients were excluded if exposed to

residential fires, automobile exhausts or braziers. Vital signs were recorded. Plasma lactate concentrations were measured by an enzymatic method and blood CO concentrations by infrared analysis. Patients were classified into four neurological impairment groups: "asymptomatic," "mild" (headache, dizziness, weakness, nausea, and/or vomiting), "moderate" (confusion, difficulty in concentration, delirium, and/or agitation), or "severe" (coma or transient loss of consciousness). Comparisons were performed using Chi-squared test or Kruskall Wallis ANOVA followed by Dunn's test and correlations by Spearman test. Results: Over a 5-year-period, 146 pure CO-poisoned patients (age: 31 years [20–51] (median [10%–90% percentiles]), 83F/63M, 41% smokers) were studied. Sources of intoxication were water heaters (72%), gas heaters (24%) and gas stoves (4%). Fifty-four patients (37%) were severely, 12 (8%) moderately and 65 (45%) mildly intoxicated, while 15 (1%) were asymptomatic. No deaths occurred. Seventy-three patients (50%) received oxygen before admission. The delay between the end of exposure and blood sampling was 60 minutes [30–120], not significantly different in the four groups. Severely and moderately poisoned patients received oxygen more frequently than the others ($p < 0.0001$). In the four groups, there were no significant differences in systolic blood pressure (SBP), heart rate (HR), or respiratory rate (RR). Plasma lactate concentrations were significantly higher in severe patients with severe neurological impairment ($p < 0.0001$). There was a significant correlation between plasma lactate and blood CO concentrations ($r = 0.3$, $p = 0.0003$).

Neurological impairment	Severe (n = 54)	Moderate (n = 12)	Minor (n = 65)	Asymptomatic (n = 15)	*p*
Age (years)	26 [16–47]	35 [20–73]	33 [25–50]	38 [26–54]	0.001
O_2 %	70%	67%	35%	20%	<0.0001
Duration (min)	60 [30–117]	85 [38–120]	60 [20–112]	60 [30–80]	0.3
SBP (mmHg)	120 [105–141]	128 [104–149]	120 [105–150]	130 [100–150]	0.8
HR (/min)	86 [70–101]	80 [68–110]	81 [71–88]	80 [74–86]	0.07
RR (/min)	18 [15–25]	20 [14–22]	18 [15–24]	16 [15–22]	0.7
Lactate (mmol/l)	2.8 [1.7–6.06]	2.4 [0.7–4.0]	1.7 [0.8–3.0]	2.0 [1.0–2.8]	<0.0001
CO (mmol/l)	2.12 [1.20–5.87]	1.76 [0.57–3.08]	1.09 [0.08–2.32]	0.38 [0.16–1.36]	<0.0001

Conclusion: Plasma lactate is useful in the evaluation of pure CO poisoning but increases are moderate. Dramatic increases should suggest exposure to associated gases and/or cardiac dysfunction.

38. THE IMPACT OF PACK SIZE LEGISLATION ON PARACETAMOL (ACETAMINOPHEN) POISONING IN THE WEST MIDLANDS (UNITED KINGDOM)

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Objective: In 1998 the UK government introduced legislation limiting the number of paracetamol tablets that could be sold to the general public in a single pack to 32 500 mg tablets (with a maximum of 100 tablets or capsules that can be sold to a person at any one time). We studied the impact of the legislation in the six months following its introduction and four years later. Method: We studied all patients presenting to a large teaching NHS Trust (with over 500,000 admissions each year) with an episode of deliberate self-harm in the periods March–August prior to (1998), just after (1999) and four years after (2002) the change in the law. We also examined the number of admissions with paracetamol toxicity to a tertiary liver unit within the trust and the number of suicide and open verdicts for drug-related deaths referred to the coroner, over similar time periods. Statistics: Results were assessed assuming a Poisson model and a z-statistic was calculated. A p value of less than 0.05 was taken as significant. Results underwent post hoc analysis using Bonferroni multiple regression analysis. Results: The number of patients presenting to hospital with acute paracetamol overdose fell significantly ($p < 0.05$). Similarly the number of patients admitted to the liver unit fell by a third ($p < 0.05$). However, neither the number of paracetamol-related deaths on the liver unit nor the number reported to the coroner changed significantly. Four years later the number of patients admitted to hospital after paracetamol was still significantly lower than before the law changed ($p < 0.05$) although slightly higher than in 1999. Importantly the number of admissions

having taken large doses of paracetamol had also fallen significantly ($p < 0.05$) and remained lower. Admissions to the Liver Unit for large overdoses were similarly reduced. From the coroner's records there was no overall change in the total number of paracetamol related deaths, though the number of other drug-related deaths had increased. Conclusions: The 1998 law limiting the number of 500 mg paracetamol that could be sold in a single pack to the public significantly reduced the number of patients with paracetamol overdose presenting to hospital. This effect appears to persist.

	Date	1998	1999	2002
Hospital	Paracetamol related admission	164	108	119
	Paracetamol overdoses with >32 tablets	41	28	25
	Total overdoses	401	341	332
Liver unit	Paracetamol related admissions	30	20	25
	Paracetamol overdoses with >32 tablets	21	12	15
	Paracetamol related deaths	2	4	3
Coroner	Paracetamol related deaths	7	9	9
	Total deaths	60	61	89

Acknowledgments: Mr A. Cotter and staff at the Birmingham Coroner's Office and B Gunson.

39. PHARMACOKINETIC EFFECTS OF COINGESTED DIPHENHYDRAMINE OR OXYCODONE ON SIMULATED ACETAMINOPHEN OVERDOSE

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Objective: Evidence-based guidelines recommend using activated charcoal only in the first hour after acute acetaminophen (APAP) overdose. Isolated case reports describe delayed APAP absorption with overdose of combined-formulations of APAP and antimuscarinic or opoid agents. Despite the high incidence of such overdoses, no prospective, controlled data exist to support or refute a delay in APAP absorption in these settings. Our objective is to determine the effects of diphenhydramine (DPH) or oxycodone (OXY) on the kinetics of simulated APAP overdose. Methods: IRB-approved, prospective crossover study in healthy human volunteers ($n = 10$). Subjects ingested 5 g APAP (day A), 5 g APAP + 250 mg DPH (day B), or 5 g APAP + 0.5 mg/kg OXY (day C). Study days occurred in random order. We obtained serial serum [APAP] hourly (0–8h) and at 24h. The primary outcome was area under the curve for [APAP] from hours 0–8 (AUC). Secondary outcomes were peak [APAP] and time to peak [APAP]. Data were analyzed using same-subject repeated measures ANOVA (with Scheffe correction for multiple comparisons, SAS version 8.2) and paired 2-tailed T tests. Results: Diphenhydramine coingestion did not affect AUC, peak [APAP], or time to peak [APAP]. Coingestion of oxycodone, however, caused a substantial decrease in AUC (27%) and peak [APAP] (40%),

	Mean AUC (mg/L hrs)	Mean peak [APAP] (μg/mL)	Mean time to peak [APAP] (hrs)
A: APAP	318.3 ± 82.0	71.8 ± 11.9	1.7 ± 0.8
B: APAP + DPH	297.7 ± 70.4	67.6 ± 10.4	1.1 ± 0.3
C: APAP + OXY	232.1 ± 74.5	42.9 ± 13.5	2.4 ± 1.4
p (A vs. B): ANOVA	0.6	0.6	0.7
T-test	0.01	0.2	0.02
p (A vs. C): ANOVA	<0.001	<0.001	0.4
T-test	0.005	<0.001	0.3

with no change in time to peak [APAP]. This curve was lower and flatter than either the APAP only curve or the APAP + DPH curve. The appearance of this curve was reminiscent of a sustained-release drug formulation, with similar [APAP] from hours 1–4 and a gradual decline thereafter. Conclusion: Diphenhydramine does not appreciably alter APAP absorption in simulated overdose. Oxycodone, a common coingestant with APAP, has important pharmacokinetic effects on APAP absorption and bioavailability. This may have clinical implications regarding nomogram interpretation and suggests further investigation of the utility of activated charcoal greater than one hour after mixed APAP and oxycodone ingestion.

40. NEUROPROTECTIVE EFFECT OF GAMMA-HYDROXYBUTYRATE (GHB) AND ITS PRECURSORS, GAMMA-BUTYROLACTONE (GBL) AND 1,4-BUTANEDIOL (1,4-BD)

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Objective: Despite its popularity as a drug of abuse, GHB (sodium oxybate, Xyrem®) was recently approved by the US Food and Drug Administration (FDA) as a pharmacotherapy for narcolepsy-related cataplexy. GHB also possesses the biochemical properties of an ideal neuroprotective agent; it decreases cerebral glucose utilization/cellular metabolism, lowers O_2 demand and consumption, acts as a free radical scavenger, and decreases release of the putative excitatory amino acid glutamate. This study evaluated the potential neuroprotective benefit of GHB, GBL, and 1,4-BD in the rodent model of focal cerebral ischemia by permanent middle cerebral artery occlusion (MCAO). Methods: 48 male Sprague–Dawley rats (300–350 g) were anesthetized with 1.2% isoflurane; under a stereoscopic microscope, a small incision was made in the left internal carotid artery and 4/0 monofilament passed 2 cm proximally until it lodged in the anterior cerebral artery, thereby occluding the origin of the MCA. The filament was sutured into place and the incision closed. Six rats were sham controls and the remaining 36 rats were divided into groups treated with GHB, GBL, or 1,4-BD at 30 min. before and 180 min. and 360 min. after infarction (dose 300 mg/kg i.p.; N = 12 each group). Twenty-four hours after treatments, the brains were removed, cut into 1 mm coronal slices, and stained with 2% TTC, a water soluble and colorless solution that is taken up by viable neuronal cells and reduced to an insoluble red pigment, thus allowing for delineation of viable from infarcted tissue The coronal sections of each rat were photographed with a 4.0 megapixel digital camera and analyzed using SigmaScan Pro® 5.0 image analysis software. The infarct areas were averaged for each group, represented as the mean area (cu.mm) ± SEM as well as the mean percent area ± SEM of ischemic injury, and compared to those of sham animals. ANOVA with post-hoc Neuman-Keuls Test was done with SigmaStat® ($P < 0.05$). Results: The mean volume of infarction for sham control animals was 323 ± 29.5 cu.mm compared to 149.7 ± 45.2, 103.5 ± 35.1, and 229.4 ± 40.5 cu.mm for rats receiving treatment with 1,4-BD, GBL, and GHB, respectively. The mean percent volume of total brain infarction for sham control animals was 30.1 ± 2.0% compared to 13.1 ± 4.0, 8.2 ± 3.0, and 19.1 ± 3.4% for rats receiving treatment with 1,4-BD, GBL, and GHB, respectively. Conclusion: GHB, GBL, and 1,4-BD offer neuroprotection in the rodent MCAO model of cerebral ischemia. This research was supported by Orphan Medical, Inc. (Minnetonka, MN, USA) and NIH National Research Service Award (NRSA) #1T32HD40128-01.

41. FATAL PARAQUAT POISONING BY INGESTION: DETERMINATION OF SERUM MARKERS OF ACUTE LUNG INJURY AND IMMUNOHISTOLOGICAL STUDIES OF LUNG TISSUE

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Background: Paraquat is demonstrated to accumulate in the lung where the formation of superoxide radicals contributes to pulmonary fibrosis. There is an increasing interest for biological markers of acute lung injury that could be analyzed in the serum or other biological fluids. In a case of paraquat poisoning, we performed serial determinations in the serum of the following biological markers: Clara cell secretory protein (CC16), Surfactant Protein A (SP-A), Surfactant Protein B

(SP-B), cystatine C, and β-2 microglobulin. Case report: A 20-year-old man ingested more than 100 mL paraquat and was admitted 90 min later. Gag reflex was absent and the patient was intubated in order to prevent aspiration pneumonia. Renal function was initially normal. Plasma paraquat level on admission was 46 μg/ml (15.4 μg/mL after 3h, and 6.7 μg/ml after 7h), indicating an extremely poor prognosis. Treatment by hemodialysis-hemoperfusion, cyclophosphamide, and methylprednisolone was however tried. In the serum, a progressive increase of CC16, cystatine C, and β-2 microglobulin was observed together with the worsening of renal function. Serum SP-A and SP-B levels also gradually increased with a peak value of 222.6 and 1740 ng/ml 70h following admission. Gas exchanges worsened 80h after admission with progression to adult respiratory distress syndrome. The patient died 92 h after admission from respiratory failure and an autopsy was performed. Immunohistological studies using markers for CC16, SP-A, and SP-B were applied to postmortem lung tissue specimens. In comparison with a control patient, a marked decrease of specific binding was observed for the three markers in the paraquat specimen. Discussion: CC16 is essentially localized to Clara cells in terminal bronchioles, but expression of CC16 has also been demonstrated in the urogenital tract. The exact role of CC16 is not precisely known.[1] After exposure to pneumotoxicants, serum CC16 has been shown to increase in rats. As CC16 is eliminated by glomerular filtration, serum increase may be observed in renal failure. SP-A is the major surfactant-associated protein. Circulating levels of SP-B are significantly higher than those of SP-A. Few studies have investigated in humans the changes in serum SP-A and SP-B levels after toxic exposure. The elimination of SP-A and SB-P is independent from renal function. Conclusion: Markers of bronchiolar and alveolar cells injury can be found in the serum after paraquat exposure. Reference: [1]Hermans C, Bernard A. Lung epithelium-specific proteins: characteristics and potential applications as markers. *Am J Respir Crit Care Med* 1999;**159**:646–78.

42. RESEARCH IN CLINICAL TOXICOLOGY—THE SAGA OF GASTROINTESTINAL DECONTAMINATION

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The quality of clinical toxicology research has long been and continues to be a frequent subject of discussion. The Evidence Based Medicine movement has brought additional focus to this discussion. Over the past decade or so, gastrointestinal decontamination of the overdose patient has undergone tremendous change. The foundation for this metamorphosis was clinical toxicology research conducted largely during the 1980s. The goal of this Louis Roche address is to utilize the saga of gastrointestinal decontamination research as a model to discuss research in clinical toxicology. The scientific design and relevance of key gastrointestinal decontamination models and studies will be discussed. Review of this past and recent research will set the stage for the discussion of "the definitive gastrointestinal decontamination study." Many of the challenges that must be addressed in order to design this "definitive study" pertain to the scientific design of research studies within the general discipline of clinical toxicology. Consideration and appreciation of these factors will contribute to the setting of rational and attainable clinical toxicology research goals.

43. OVERVIEW OF ANTIDOTES FOR SNAKEBITES

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Major advances in immunotherapy against snake venom have taken place in recent years. Initial approaches, dating back to the late 19th century, involved the use of whole IgG antibodies from crude serum that was harvested from horses' hyperimmunized with different venoms. Purification techniques to reduce the fraction of nonneutralizing proteins were incorporated into the manufacturing process but the final product remained quite impure. Despite these limitations, the use of equine antivenin containing whole IgG antibodies (e.g., antivenin (Cratalidae) Polyvalent (ACP)), became standard therapy for the treatment of snake venom poisoning in most centers. In the case of crotaline envenomation, the antivenin indications included clinical evidence of progressive local or systemic venom poisoning. Although mortality dramatically decreased over the years from as much as 5–25% in the 19th century to probably less than 0.1% today, better supportive care and changing prehospital approaches may account for much of this improvement. Most of the proof of efficacy has relied on animal data, retrospective

studies and case reports, and (at least with ACP) has never been subject to prospective randomized clinical trials. Evaluating efficacy from these reports is confounded by the different types of venom-induced injuries (reversible [e.g., coagulopathy] vs. irreversible [e.g., tissue necrosis]), as well as the differences in venom load. Moreover, the high incidence of immediate hypersensitivity reactions (i.e., anaphylaxis, bronchospasm, urticaria,) and delayed hypersensitivity reactions (i.e., serum sickness) has always raised concerns about the risk-benefit ratio of whole IgG approaches. Calls to produce a more purified antivenin with lower antigenicity and fewer adverse effects led to the employment of enzymatic techniques to produce antivenins with a predominance of $F(ab')_2$ or F(ab) fragments. A mouse study comparing equine derived IgG and $F(ab')_2$ polyvalent (Crotaline) antivenins showed comparable efficacy and a decreased anti-immunoglobulin response in the $F(ab')_2$ treatment group. Clinical studies on the use of equine $F(ab')_2$ to treat *Vipera berus* envenomations showed decreases in edema, anemia, and hospital stay. Hypersensitivity problems, however, remained as evidenced by a 10% rate of urticaria and serum sickness in those receiving the *Vipera berus* $F(ab')_2$. It wasn't until the 1990s, 20 years after the initial introduction of ovine Fab for digoxin toxicity, that ovine derived papain cleaved Fab fragments targeted at a variety of snake venoms were introduced. Fab is now available against venom from *Vipera berus*, *Crotaline* species, *Echis ocellatus*, and the Russell's viper. Compared to $F(ab')_2$, the smaller Fab has a more rapid tissue penetration and larger Vd. In a series of mouse studies comparing equine $F(ab')_2$ with a variety of monospecific ovine Fab, certain monospecific ovine Fab proved more protective while other Fab proved less protective compared to $F(ab')_2$. An early clinical study of Fab in *Vipera berus* envenomation showed ovine Fab has similar efficacy to the equine $F(ab')_2$ without producing hypersensitivity reactions. Mice lethality studies investigating crotaline Fab (Crotaline Polyvalent Immune Fab (CroFab)) showed that the ovine Fab was about five times as potent as the equine whole IgG (ACP) product. A direct comparison of Fab and whole IgG for Crotaline envenomation has not been performed but early studies showed that the Fab halted progressive crotaline venom poisoning. Another advantage of Fab is that the Fab antivenin has a shorter reconstitution time compared to ACP. Unlike the initial report that Fab for *Vipera berus* envenomation was not associated with hypersensitivity reactions, crotaline Fab has been associated with immediate and delayed hypersensitivity reactions although the incidence of such reactions appears to be much less when compared to the ACP product (immed 14% vs ~23–56%; delayed 16% vs ~75%). One unexpected finding in the early crotaline Fab clinical trials was the relatively frequent recurrence (worsening after clinical improvement) of local symptoms and coagulopathy. This finding suggests that Fab tissue penetration and venom neutralization is incomplete and that the unbound antivenin clearance may be faster than the clearance of some venom components. In addition, Fab complexed to large-molecular weight venom components may not undergo renal clearance resulting in dissociation of the venom–Fab complex. Given crotaline Fab's short half-life compared to whole IgG, the continuation of crotaline Fab dosing for 3 additional maintenance doses after achieving control had been recommended to prevent recurrence. Unfortunately, recurrence and, at times, delayed onset of hematological abnormalities 2–3 days after completion of the maintenance doses, has still been reported. The rational for treatment with antivenin for single component coagulopathy has been questioned since clinically significant bleeding is quite uncommon in the vast majority of crotaline snake envenomations. In the absence of bleeding (and local progression) it has been suggested that additional antivenin need not be given unless patients have a platelet count of $<50{,}000/mm^3$, fibrinogen < 75 mg/dL and INR > 3.0. Early reports show that crotaline Fab is also safe and effective in pediatric patients. Given that a recent study on crotaline Fab reported that the mean number vials received was 16 vials (range 10–28), the economics of Fab treatment also needs to be considered since the hospital charge may be as much as $2000 US per vial. Selected references: Clark RF, McKinney PE, Chase PB et al. Immediate and delayed allergic reactions to Crotalidae polyvalent immune Fab (ovine) antivenom. *Ann Emerg Med* 2002;**39**:671–6. Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. *Ann Emerg Med* 2001;**37**:181–8. Dart RC, Seifert SA, Boyer LV et al. A randomized multicenter trial of crotalinae polyvalent immune Fab (ovine) antivenom for the treatment for crotaline snakebite in the United States. *Arch Int Med* 2001;**161**:2030–6. Miller MA, Dyer JE, Olson KR. Two cases of rattlesnake envenomation with delayed coagulopathy. *Ann Emerg Med* 2002;**39**:348. Offerman SR, Bush SP, Moynihan JA et al. 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44. AVAILABILITY OF ANTIVENOMS—A EUROPEAN PERSPECTIVE

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Objective: Accidents with venomous animals may lead to a life-threatening medical emergency, so that treatment with antivenom is necessary. If the animal is correctly identified, two questions arise and are to be answered: Which antivenoms are indicated and where are these antivenoms available? Methods: In 1989 the poison center Munich developed a database on antivenoms. The model of this database consists of five entities: Producer (address), antivenom (name, product information), indication (name of species), storekeeper (address) and antivenom, which is kept by a storekeeper (volume of vial, expiration date, amount of vials, last update). As source of data we use information published by producers of antivenoms and information delivered to us by storekeepers. The latter data are kept confidential unless agreement of publishing is present. To make the database available to other users a HTML-application was developed and published in the Internet. A local use of the application is enabled by downloading a ZIP-archive. Results: There are 26 producers, 79 antivenoms, 199 indications (name of species) and 89 storekeepers with about 290 available antivenoms are currently stored in the database. The HTML-application combines these five entities in three different ways (document types) corresponding to three specific usage contexts. The first document type, used in case of an accident, lists for a single species all indicated antivenoms and their storekeepers. To find the antivenoms, which are next to the site of the accident, the storekeepers are ordered by country and by postal code. The second document type, used by storekeepers, lists all currently registered antivenoms of a single storekeeper. Besides informing the storekeeper, this document should be used to send an update message to the poison center Munich. The third document type gives a complete description of an antivenom consisting of the producer's address, the product information (image) and the list of species, which are defined as an indication. This document can be used, if specific information about an antivenom is needed. All three document types are linked to each other and an index lists all species, storekeepers, and antivenoms currently available. Conclusion: Treatment with antivenom in case of an accident with venomous animal may be difficult, since the antivenom is not available in the treatment center and the storekeepers are not known. A database connecting the name of the species with all indicated antivenoms and listing all storekeepers who have those antivenoms available has been shown to improve the beginning of appropriate therapy in the poison center Munich. So that other European poison centers can benefit of these data they are now published in the Internet at http://www.toxinfo.org/antivenoms. As well as direct access to the current version a free download is available for local use. We invite poison centers to participate in this cooperative project by register antivenoms kept by themselves and by mediating storekeepers known by them to the project.

45. DIGOXIN ANTIBODIES. WHEN? HOW MUCH?

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Introduction: The first use of digoxin-specific Fab fragments in the clinical setting of severe digoxin poisoning was reported in 1976 by Smith et al (1). Since then the efficacy and the safety of digoxin-specific Fab antibodies (DA) in digitalis intoxication have been demonstrated in numerous case reports and clinical trials. In a multicenter study of 150 cases, 80% of patients responded completely to treatment with DA and 10% improved substantially (2). In an observational surveillance study including 717 adults, 50% of patients had a complete response to treatment, 24% a partial response, and 12% no response (3). The currently recommended dosage of DA is an equimolar dose, but, because of the high cost of DA, treatment has been mostly limited to patients with severe poisoning. However, the minimal optimal dose required to obtain a satisfactory cardiac response is still not determined. Dosing of DA can be based on two different objectives, a kinetic neutralization or a dynamic effect. Kinetic neutralization: The optimal dosage is an equimolar dose of DA to achieve neutralization of the body-load of digoxin or digitoxin which can be calculated according to the amount ingested or to the serum concentration. The binding capacity is 1 mg digoxin for 80 mg antibody with Digidot® and 0.6 mg digoxin for 40 mg antibody with Digibind®. However, calculation of equimolar dose is subject to several pitfalls. The exact amount ingested in acute poisoning is often not known exactly. The interpretation of serum digitalis concentrations has to take in

account many parameters: steady-state kinetics; accuracy of the analysis, especially for high concentrations; variations of volume of distribution (in neonates and elderly); differences in the relation between serum concentration and toxicity according to the type of poisoning—acute, acute upon chronic, or chronic. Moreover, many other factors may affect the sensitivity to digitalis such as age, underlying cardiac diseases, electrolyte disturbances, especially potasium, associated cardiotropic drugs. Kinetic studies have also shown that when the antibody is infused during a short period of time about half of Fab fragments dose is cleared before enough digoxin has re-diffused from the tissues for binding (4). Therefore, it has been proposed that a loading dose of 160 mg over 25 min, followed by an additional dose of 160 mg in 7h, be used (4). In the prospective multicenter study of 150 patients treated with equimolar dose of DA, the median dose administered was 200 mg: 80% of the patients had a complete reversal, 10% a partial reversal and 10% no response. Partial or no response to treatment was related to inadequate Fab dose in only 2 out of 29 patients (2). In the observational surveillance study including 717 adults, the median dose of DA administered was 120 mg and the most frequent dose was 80 mg. Fifty% of the patients had a complete reversal, 24% a partial reversal, and 12% no response. 50% of the patients had received a dose higher than the estimatesd adequate dose (calculated on an equimolar basis). No clear relation between the initial response to treatment and the percent of the estimated adequate dose administered was observed. In the patients with a response less than complete (mostly chronic poisonings) residual abnormalities were still believed to be due to digitalis intoxication in only 18% of the cases. Moreover, only 2.8% of all the patients developed recrudescent toxicity, although 42.8% had received a dose below the estimated adequate dose (3). Dynamic neutralization: The objective is to adapt the dose of DA in order to obtain a reversal of digitalis toxicity, especially of life-threatening features. This objective may be achieved without the neutralization of the total body-load of digoxin. This principle can only be applied if clinical monitoring can estimate rapidly the effect of DA administration. In a prospective study the time response from termination of DA infusion was mean 19 min for the intial response and mean 88 min for the complete response. The time response was not dependent on concurrent cardiac disease nor on the age or the type of intoxication (2). This pragmatic strategy is also justified by the fact that the monitoring of digitalis poisoning after administration of DA can only be based on clinical signs (and kalemia in acute poisonings), because anti-digoxin Fab fragments interfere with RIA for digitalis and thus serum tests are unreliable for 5–7 days post-administration. Indications of DA: Usually, DA are indicated in digitalis poisoning with criteria of severe prognosis including atrio-ventricular block, ventricular dysrhythmias, underlying cardiac diseases, age higher than 60 years and hyperkalemia in acute poisonings. However, most digitalis poisoning are actually chronic poisonings occuring in patients with cardiac disease treated also with other cardiac drugs such as antiarrhythmics or ACE inhibitors. In these patients, the occurence of cardiac dysrhythmias (bradycardia, atrio-ventricular block) and hypotension may be related to digitalis poisoning but also to the evolution of the cardiac disease or to the additive cardiotoxic effect of other drugs. Serum digoxin concentrations are mostly not greatly increased, and it is often difficult to distinguish the symptoms related to a digoxin cardiotoxic effect and those due to other factors, unless digoxin cardiotoxicity has been reversed by DA. DA treatment protocol: The following management of digitalis poisoning can be proposed. Administration of an initial dose of 160 mg DA over 20–30 min. In the case of no response within 1h, a further dose of 160 mg may be administered, but other factors such as toxicity by other cardiotropic drugs or an underlying cardiac disease should also be considered. In acute poisonings with life-threatening complications (ventricular tachycardia or fibrillation, high-grade atrio-ventricular block, hyperkalemia) administration of an initial half-molar dose may be considered. Conclusion: Digoxin-specific Fab antibodies have proven to be safe and markedly effective. Because of their high cost, the indications have been reserved to severe poisonings. Based on clinical reports and kinetic and dynamic data, the administration of an equimolar dose seems not to be justified. Most poisonings respond to an initial dose of 160 mg. In the case of partial or no response, other factors responsible for cardiac symptoms should be considered especially in patients with chronic poisoning. References: (1) Smith TW, Haber E, Yeatman L et al. Reversal of advanced digoxin intoxication with Fab fragments of digoxin-specific antibodies. *N Engl J Med* 1976;**294**:797–800. (2) Antman EM, Wenger TL, Butler VP et al. 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46. MANAGEMENT OF YELLOW OLEANDER POISONING

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Background: Self-poisoning with yellow oleander (*Thevetia peruviana*) seeds is a major clinical problem in South Asia. Management has classically involved gastric emptying, atropine to treat bradycardia, and transfer to tertiary centers for temporary cardiac pacing, with a 5–10% death rate. We have assessed the effectiveness of therapies for yellow oleander poisoning. Methods: We carried out an RCT to test the efficacy of anti-digoxin Fab fragments in reversing cardiac dysrhythmias and hyperkalaemia, and then studied the effect of introducing and then withdrawing its use in Sri Lanka. An observational study of gastric lavage in six Sri Lankan hospitals assessed the risks associated with lavage. An RCT (recruitment target of 7000 patients; 3000 with oleander poisoning) is now under way to test the effectiveness of single and multiple dose activated charcoal in both all forms of acute poisoning and in oleander poisoning. Results: Cardiac dysrhythmias had completely resolved by 2h in 2/32 control patients and 15/34 patients treated with anti-digoxin Fab. Eight hours post-treatment, 5/32 control patients and 24/33 treated patients had reverted to sinus rhythm > 44 bpm. Introduction of the antitoxin into clinical practice resulted in a 4.4% ARR of death (8.6% to 4.2%) in one tertiary hospital with facilities for cardiac pacing. Withdrawal of the antitoxin increased the death rate from 3.1% to 9.3% in secondary hospitals of the North Central Province. Gastric lavage as performed in Sri Lanka is associated with a 70% aspiration rate and a significant number of deaths. Conclusions: Anti-digoxin Fab are highly effective in treating oleander-induced dysrhythmias and electrolyte disturbances. However, their great cost means that they are unaffordable—major efforts must be made to make it at a cheaper price. Gastric lavage is unsafe and should not be performed in a resource-poor location. Activated charcoal may be safer. Its effectiveness is currently unknown; however, over 400 patients have now been recruited to a RCT. The results of this trial and the availability of an affordable antitoxin should create the basis for a rational evidence-based approach to the management of yellow oleander poisoning.

47. ASSESSMENT OF CONSCIOUS LEVEL IN THE POISONED PATIENT USING THE GLASGOW COMA SCALE AND THE AVPU SCORE

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Objective: Patients with reduced conscious level may have impaired protective airway reflexes and are at risk of aspiration. The Glasgow Coma Score is commonly used to determine conscious level, with GCS ≤ 8 suggesting the need for airway protection. Although the Glasgow Coma Score was initially developed for assessment of head-injured patients, it is now widely used in clinical practice. An alternative form of rapid neurological assessment using AVPU is currently taught on advanced life support courses. Our aim was to determine the association between GCS and AVPU and whether AVPU could be used as a rapid predictor of patients at potential risk of airway compromise. Methods: A prospective assessment of conscious level was undertaken on all patients admitted to the Toxicology unit of the Royal Infirmary of Edinburgh over a six-month period. Nursing staff were asked to grade level of consciousness on admission using GCS and AVPU. AVPU was defined as A = no stimulus required to elicit patient response, V = any response to a verbal stimulus or gentle shake, P = any response to a painful stimulus, U = no response to any stimulus. Results: 1055 patients were studied. Incomplete data was recorded on 9 patients. The median GCS was 15 on the remaining 1046 patients. The number of patients in each AVPU category was A = 851, V = 114, P = 68, U = 13. Mean GCS for each AVPU score was A = 14.92 (95% CI 14.90 − 14.95), V = 12.69 (95% CI 12.40–12.99), P = 8.25 (95% CI 7.83 − 8.67), U = 3.23 (95% CI 2.72–3.73). Conscious level was felt to be difficult to assess using GCS in 43 patients and in 27 patients using AVPU ($p = 0.068$). Conclusion: AVPU scores A,V, P and U appear to correlate with Glasgow Coma Scores of 15, 13, 8 and 3 respectively. There was a non-significant trend toward ease of assessment using AVPU. Patients who are not fully alert or responsive to a verbal stimulus are likely to have a GCS ≤ 8. AVPU therefore offers an easy, rapid method of assessing poisoned patients at potential risk of airway compromise.

48. RESPONDING TO TERRORISM: THE US NATIONAL PHARMACEUTICAL STOCKPILE PROGRAM

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Objective: To describe the US National Pharmaceutical Stockpile Program and its role in responding to a terrorism event. Report: The US National Pharmaceutical Stockpile (NPS) is a national repository of pharmaceuticals, vaccines, medical supplies, and medical equipment that can be delivered anywhere in the United States or its territories in response to a terrorism event or other large-scale public health disaster. The program was federally mandated and created in 1999 and is managed by the Department of Health and Human Services, Centers for Disease Control and Prevention. Pharmaceuticals and medical supplies are chosen for the formulary based on factors such as effectiveness for a particular threat agent, FDA approval, cost, rotation capability, market availability within the US, multiplicity of use, dosage forms, storage considerations, and the need for ancillary supplies. Currently, the NPS contains items useful for category A biological threat agents (organisms causing anthrax, plague, tularemia, smallpox, botulism, and viral hemorrhagic fevers) as well as chemical nerve agents. The formulary undergoes continual validation based on current research and new intelligence information. The NPS program is able to respond to an incident with one of three options: 1) 12h Push Package; 2) Vendor Managed Inventory (VMI); and 3) technical assistance. A 12h Push Package is comprised of over 90 different items, weighs 50 tons, and is pre-configured in over 100 specialized cargo containers. It can arrive at an affected area within 12h of the federal decision to deploy the assets. This method is used when little information is known about the threat. Once the threat agent is specifically identified, or as a follow-up to a 12h Push Package, shipments can be made directly from NPS-owned VMI. This allows for a more tailored response. For any large-scale deployment, the NPS also sends a Technical Advisory Response Unit (TARU) to assist the affected area with receipt, storage, distribution, dispensing, and reordering of NPS assets. Many other federal, state, and local government agencies also have a role in planning for terrorism events, each with a specific responsibility; however, all groups must plan to work together in a crisis. The NPS program relies heavily on partnerships with federal, state, and local agencies, and within the private sector to accomplish its mission. At the federal level, the NPS program works closely with other entities within the Department of Health and Human Services such as the Food and Drug Administration, and the Office of Emergency Response, as well as with Department of Veterans Affairs National Acquisition Center, Department of Defense, Department of Justice, and Department of Energy. A federal medical materiel coordination group was established among all entities procuring pharmaceuticals and medical supplies for stockpiling in order to share inventory information and ensure that shortages are not created. At the local and state level, partnerships exist between the NPS program and state emergency management agencies and public health departments. In the private sector, the NPS program relies on pharmaceutical manufacturers, vendors, wholesale distributors, transportation companies, vaccine repositories, and repackaging/packaging firms to assist in the NPS mission. Preparing for a terrorist event or other large-scale disaster is a tremendous task, and federal grants have been awarded to each state to develop a plan to receive NPS assets. Extensive guidance and training have been available to each state and territory regarding areas such as planning; receiving, storing, and staging assets; distributing, and dispensing. The NPS program also assists states and cities with exercises to test their plans, and participates in numerous tabletop and large-scale nationwide exercises to ensure readiness. NPS assets were deployed in response to the World Trade Center attack and the anthrax attacks of fall 2001. In both cases, the delivery of NPS pharmaceuticals and medical supplies was made within the 12h goal and the missions were completed successfully. Conclusion: The US National Pharmaceutical Stockpile is a national asset that can effectively be used to respond to terrorism events or large-scale disasters.

49. GLOBAL SURVEILLANCE FOR CHEMICAL INCIDENTS OF INTERNATIONAL PUBLIC HEALTH IMPORTANCE

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Objective: Following a global consultation on the public health response to chemical incidents held at the headquarters of the World Health Organization in December 2001, the International Programme on Chemical Safety (IPCS) is in the process of developing a chemical incident surveillance and response program. This program has received the endorsement of Member States through a World Health Assembly resolution (WHA55.16) in May 2002. It is envisaged that the system will provide

early warnings or alerts, and will build on an existing global alert, verification and response system for illnesses of infectious aetiology. The objective of this presentation is to provide an overview of preliminary results from the first three months of a pilot study to develop and assess a global surveillance system for chemical incidents of international public health importance. Methods: The pilot study was carried out from August 16th 2002 through November 15th 2002. Four electronic databases together with other sources of information were used to prospectively identify chemical events on a daily basis. Criteria developed by the WHO Global Alert and Response team for screening communicable diseases to determine their international importance were adapted for chemical incidents. Results: During the 3-month pilot phase 80 events were selected for inclusion in the database. Of these 80 events, 43% occurred in the European region of WHO (EURO); 18% in the region of the Americas (AMRO); 17% in the Western Pacific region (WPRO); 11% in the Southeast Asian region (SEARO); 8% in the African region (AFRO); and 5% in the Eastern Mediterranean region (EMRO). Of the 80 events identified 12 met the criteria for chemical events of potential global public health importance (GPHI). The 12 events were identified in EURO (5/12), WPRO (3/12), EMRO (2/12), AFRO (1/12) and SEARO (1/12). No events were identified in AMRO. Information about the date of event was available for 68% (54/80) of all events in the database and was available for 83% (10/12) of the events of potential GPHI. In terms of timeliness, 23 of 54 (43%) of events were identified on the day they occurred, while 60% (6/10) potential GPHI were identified on the day they occurred. Conclusions: The data presented from the pilot study provide estimates of the occurrence of chemical incidents of public health concern and a number of weaknesses in available surveillance systems have been identified, for example, there are geographic gaps and the timeliness of event identification needs improvement. These data reinforce the need for a global surveillance system for chemical incidents of international public health importance.

50. PROGRESS IN POISONS CENTRE DEVELOPMENT SINCE THE RIO SUMMIT—THE ROLE OF POISONS CENTRES IN CHEMICAL SAFETY

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Introduction: The first poisons centers were established in the 1950s and their number grew rapidly during the 1960s and 1970s, particularly in North America and in Europe. The main stimulus for the development of these centres was a desire to reduce the morbidity and mortality associated with accidental poisoning in children, with the push coming largely from the health sector. By contrast in other parts of the world, particularly in developing countries, poisons centers are a relatively new concept and it is largely the chemical safety agenda that is driving their creation. Discussion: That poisons centers have a role in chemical safety was explicitly acknowledged at the United Nations Conference on Environment and Development (UNCED), held in Rio de Janeiro, Brazil, in 1992. The outcome of this summit meeting was a detailed and wide-ranging plan of action for sustainable development called Agenda 21, which was adopted by more than 178 Governments. Agenda 21 has a number of program areas: Chapter 19 concerns the environmentally sound management of chemicals and includes the recommendation that governments should promote the establishment and strengthening of national poisons centers. The momentum for the achievement of Agenda 21 is, in part, being maintained through a series of national, regional, and international review and planning meetings organized by the Intergovernmental Forum on Chemical Safety (IFCS). At IFCS Forum III, held in Salvador da Bahia in October 2000, governments agreed to a series of ambitious targets, including a commitment to establish poisons centers in 30 or more countries that did not have such centers and further strengthen them in 70 or more countries where they already existed, by the end of 2002. The IFCS Simple Indicators of Progress prepared for Forum III in 2000 revealed that more than half of countries worldwide did not have a poisons center and that provision was particularly weak in the African and Western Pacific Regions. A review of progress since 2000 reveals that the target is far from being achieved in the developing world, although some progress has been made. In particular innovative approaches are being explored, such as developing regional poisons centers to serve several countries. In fact, there are several program areas under Agenda 21 where poisons centres could potentially play a role, since underpinning many of the recommended actions is the need for information on chemicals and products, and on the health impact of exposure to those agents. The strength of poisons centers in this context is that they are essentially brokers of information, both providing and collecting information on chemicals and exposures. Indeed in some countries, poisons center data may be the only information collected about exposures to certain chemicals. Poisons centers are also uniquely well-placed to carry out toxicovigilance, and many consider this activity to be a core role. Information collected and generated by poison centers can be used in the furtherance of a number of chemical safety

objectives, e.g., setting priorities for national and regional chemical risk management strategies, mitigating and monitoring the health impact chemical incidents, the risk assessment of chemicals, assisting in the implementation of the Prior Informed Consent (PIC) Procedure under the Rotterdam Convention and assisting in the implementation of the Globally Harmonized System for the Classification and Labelling of Chemicals (GHS). Conclusion: While those who work in poisons centers know very well what their service is for and what its benefits are, outside the health sector the role of poisons centers is not necessarily well understood. The chemical safety agenda offers opportunities to poisons centers to raise their profiles in their own countries and to establish synergies with a wider range of entities, thereby strengthening their foundation of support. References: Agenda 21: www.un.org/esa/sustdev/agenda21text.htm; IFCS Forum III Priorities for Action: www.who.int/ifcs/forum3/f3-finrepdoc/priorities.pdf; IFCS Simple Indicators of Progress: www.who.int/ifcs/forum3/documents/f3-21-inf.pdf.

51. CENTRAL AND EASTERN EUROPEAN POISON CENTRES—EAPCCT SURVEY

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Objective: The EAPCCT Executive Board has established Eastern European Countries Committee to develop better relations with countries of Central and Eastern Europe. The aim of the survey was to collect data about Poison Centers in those countries, their activities and needs. Methods: The questionnaire was worked out and distributed by e-mail or regular mail to known Poison Centres (PC). The questionnaire consists of the following parts: general—name of the Centre, location, director, mailing address, telephone and fax numbers, e-mail, organization structure, and funding methods. In the second part—questions about activities undertaken by the Center, and the third—primary needs for the Center activity (training, support for scientific activity or financial aid). Results: The questionnaire was sent to 16 countries (Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Latvia, Lithuania, Macedonia, Poland, Romania, Russia, Slovakia, Slovenia, Yugoslavia-Beograd). There was no reply from Georgia, Kazakhstan, Macedonia, Slovenia and Yugoslavia. In Estonia PC is not yet established. The data from 10 questionnaires were analyzed. All PC have phones and e-mail addresses (personal or institutional). The organization and funding is different, most of them have support from government (9), part of them are financed also by local hospitals (4) and others—ministry of science, sponsors (2). Six PC are located in hospitals, as a separate unit in hospital, near to the clinical service, four PC are located in other sites (e.g., Department of Occupational Medicine, Institute of Public Health). A Poison Information Service for health professionals is provided in all PC, in eight an information service for the general public is also available. Clinical and laboratory services are provided in five PC. Other activities, like drug information, mycological expertise and legislative activities are undertaken in five PC. The third part of the questionnaire asked about the primary needs for the PC. The grading from 1 to 3 was suggested (1 = least important, 3 = most important). Training for people working in the center (non-physicians in well-organized PC, clinical toxicologists in well-organized PC and clinical units) was indicated by all PC, average of answers: 2.6. All respondents indicated that congress and scientific meeting participation was a useful scientific activity for the staff of the PC. A wish to participate in multicenter studies was declared by eight PC. The average of answers regarding required support of scientific activity was 2.5. All PC need financial aid, average of answers was 2.6. Priority was given to subscription of commercially available toxicological databases, toxicology manuals and tools helpful in the Center activity (computers and software). Conclusion: The primary need for Central and Eastern European Poison Centers is training for people working in PC in well organized PC in Western Europe and financial support for everyday PC activity. The collected data suggest that next steps for EAPCCT should include detailed analysis of needs, development of focused plan for financial aid, and identification of potential sources of funding.

52. ELECTRONIC INFORMATION RESOURCES FOR POISONS INFORMATION CENTERS

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Objective: To discuss the meaning of the term "Electronic Resources" in reference to Poison Centers' activity. To explore ways to find toxicological information on-line. To underline problems and difficulties in using the Internet to

retrieve toxicological data. To introduce some of the more useful Web-based resources for Poison Centers and clinical toxicologists. The term "electronic resource" is used to mean a wide range of different products sharing the common feature of being used and modified only by a computer or an electronic device. CD-ROMs, e-books, Web sites, data banks, mailing list, and electronic journalism are all called "electronic resources" or, sometimes, "digital resources." This all-inclusive terminology includes a great variety of entities extremely different from one another. The first distinction is the one between "local," off-line products ("direct access electronic resources," AACR2[1]; "local access electronic resources," ISBD[2]) and "remote," on-line products ("distant access electronic resources," AACR2[1]; "remote access electronic resources," ISBD[2]). This paper briefly introduces many of the useful on-line Web-based resources for Poisons Information Centers. The paper will not be encyclopaedic in listing Web sites but instead will outline the types of on-line resources available and provide examples and problems. The Internet offers a wide range of on-line resources for the field of Clinical Toxicology. The first task of the user is to find and classify the on-line resources. This could be done querying several Internet search tools such as Yahoo! (http://www.yahoo.com/), AltaVista (http://www.altavista.com/), and Google (http://www.google.com/). After developing a list of on-line resources, the user must visit and evaluate each Web site. The evaluation should ideally be based on some main criteria such as accuracy, currency, and authority. Sometimes it is not easy to find what one is looking for. Some Web sites have original content; others are "content aggregators" summarizing information and data from various sources. Some are devoted to specific toxicological subjects, others cover all aspects and fields. To find accurate and relevant data, users need effective strategies. They should learn in advance which Web sites cover a particular topic; which are best for Poison Centers; which contain updated archives; which sites are good for browsing, and which are good for searching. Any effort to list useful Web-based resources for clinical toxicologists is inevitably frustrated by the rapid pace of change in this topic, and the difference between editorial delays of publication and the Internet's uncontrolled evolution. Nearly all of the Web sites described in this paper are "stable" resources, with portals to reference materials not accessible through simple Web searches, and are likely to provide lasting significance to toxicologists who visit and query them. TOXNET® (Toxicology Data Network) is a group of databases, many of which are of particular interest to toxicologists (http://toxnet.nlm.nih.gov). TOXNET is maintained by the Toxicology and Environmental Health Information Program (TEHIP), (http://sis.nlm.nih.gov/Tox/ToxMain.html) within the Specialised Information Services Division (http://sis.nlm.nih.gov) of the NLM (National Library of Medicine). TOXNET contains 11 different databases organised into four groups according to whether the database provides toxicology data, bibliographic information, data on chemical releases to the environment, or nomenclature information on chemicals. The HSDB® (Hazardous Substances Data Bank) provides a comprehensive peer-reviewed database of human and animal toxicology data on over 4500 potentially hazardous chemicals. The database includes additional information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, and regulatory requirements. TOXLINE® is a bibliographic database containing over 3 million citations covering biochemical, pharmacological, physiological, and toxicological effects of drugs and other chemicals. MEDLINE® and PUBMED® remain the best source for web-based bibliographic references in the field of clinical toxicology. In 2000, and continuing into 2001, major changes occurred in the philosophy, structure and access to the NLM databases that MEDLINE users should be aware of. The Internet permits live e-mail discussions among the professional community of toxicologists. Electronic forums (founded and based in e-mail and then archived to the Web) provide interactive and dynamic opportunities for experts to share ideas and resources, and involve thousands of professionals world-wide. Subscription to these mailing lists requires a higher level of involvement than does the occasional visit to a Web resource, because participation is bi-directional and time-consuming. Messages from mailing lists accumulate quickly and can be overwhelming. Conversation via e-mail can be engaging but sometimes distressing. References: Greenberg G. Internet resources for occupational and environmental health professionals. *Toxicology* 2002;**178**:263. Young RR. Genetic toxicology: Web resources. *Toxicology* 2002;**173**:103–21. South JC. Online resources for news about toxicology and other environmental topics. *Toxicology* 2001;**157**:153–64. 1-AACR: Anglo American Cataloguing Rules. 2-ISBD: International Standard Bibliographic Description.

53. FIRST AID MEASURES IN THE SAFETY DATA SHEET—GOOD, BAD, OR JUST MISSING

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Objective: To investigate the quality of the first-aid measures recommended in the Safety Data Sheets required by the Chemicals Act. Methods: A random sample of first aid measures of 500 Safety Data Sheets from the Finnish Product register of the Chemical Register was evaluated by two Poison Information Center pharmacists independently using a structured evaluation form. After a pilot sample of 100 sheets had been evaluated, the evaluation form was revised. The recommended immediate first-aid measures at the site and instructions for further treatment were assessed separately for each route of exposure. Total amount of evaluated instructions were 3000. The information targeting different levels of medical care involved in first-aid, and the availability of important data for evaluation of acute toxicity were also assessed. Data was classified as missing, good instructions, insufficient instructions, incorrect instructions, and dangerous instructions. Results: In 50% of Safety Data Sheets, instructions (n = 1507) were missing. Most of the missing instructions were instructions on primary first aid. In 28.6 % (n = 859) the instructions were good, in 3.5 % (n = 104) insufficient, in 12.7 % (n = 382) incorrect and in 4.9 % (n = 148) they were considered as dangerous. Conclusion: Submission and quality of first-aid information in Safety Data Sheets needs improvement. Education of persons writing Safety Data Sheets and quality control of this aspect of submitted Safety Data Sheets is needed. Although our study was based on Finnish data, many of the Safety Data Sheets were from multinational companies, so the results may be generalizable.

54. POISONED PATIENTS IN SCOTTISH HOSPITALS—1. MANAGEMENT

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Objective: To investigate how adult-poisoned patients are managed in accident and emergency departments (A&E) and minor injuries units (MIU) in Scottish hospitals. Methods: 226 questionnaires were sent out in 2001 to doctors (consultants, specialist registrars, staff grade physicians) and nurse managers in all A&E and MIU in hospitals (91) in Scotland requesting information on policies on managing poisoned patients. Children's hospitals (3) are excluded from this particular study. For departments from which several replies were received staff members often had differing views of policy. Where multiple responses differed a mean score was calculated. These were summed to provide an overview of perceived policy. Results: 167 (77%) questionnaires were returned completed. For A&E (31) 111 replies (85 doctors, 26 nurses) were received; MIU (51) 56 replies (10 doctors, 46 nurses). An average of 3.6 replies (range 1–13) were received from A&Es; 1.1 from MIUs (range 1–3). Responses are shown by work location of individual responder. 95% confidence intervals are given where significant. Fewer than 5 poisoned patients/week were reported to be seen by 12.9% of A&Es; 5–10 by 9.7%; 10–50 by 67.7%; not stated 9.7%. All MIUs saw <5/week. Poisoned patients were managed in A&E;MIU (10.7%; 8.8%), acute admissions unit (36.4%; 2.0%), specialist poisons ward (2.2%; 1 hospital), general medical ward (27.3%; 5.9%), transferred to another hospital (0%; 60.8% ± 10.6%), combination (23.5%; 22.6%). 68.6% of A&Es and 11.8% of MIUs responses indicated *routine* checking of bloods on all poisoned patients for paracetamol, salicylate (68.6%; 8.2%), alcohol (29.6%; 5.9%) and 28.4% ± 15.9% and 88.9% ± 8.6% said they did not routinely check any bloods. 100% of A&Es and 76.5% of MIUs used activated charcoal; 55.2% and 32.0% gastric lavage; 8.9% and 36.3% ipecac respectively. Times for gut decontamination varied 1–4 hours. For consultants only (43), the figures were charcoal (100%), gastric lavage (65.1% ± 14.2%), ipecac (2.3% ± 4.5%). These compare with a 2000 study which found charcoal (76%), gastric lavage (90%), and ipecac (19%).[1] 6.8% of A&Es and 11.8% of MIUs reported nurse prescribing protocols (charcoal, N-acetylcysteine, naloxone, ipecac). Four MIUs said that psychiatric assessment was not available. For others, initial psychiatric assessment was carried out by some combination of psychiatrists (62.4% of A&Es; 10.8% MIUs), admitting doctors (27.1%; 36.6%) and psychiatric liaison nurses (47.7%; 14.7%). Conclusions: Variation in responses from the same departments indicated that staff working in A&E departments were not aware of protocols. Poisoned patients presenting to MIUs are less likely to have bloods checked, more likely to be given ipecac, less likely to be seen by psychiatric personnel, and are likely to be transferred to another hospital. There has been a change in consultant opinion on the use of charcoal, gastric lavage, and ipecac in Scotland. Reference: 1 McGuffie AC, Wilkie SC, Kerr GW. The treatment of overdose—time for a change? *Scot Med J* 2000;**45**;75–76.

55. ACUTE MANAGEMENT OF DRUG AND TOXIN-INDUCED HYPERTENSION

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Objective: Hypertensive urgencies and emergencies are routinely encountered complications following overdose or exposures to many drugs and environmental toxins. Many actions or mechanisms may result in hypertension. A review of many textbooks and manuscripts, however, universally only recommend a few treatment modalities. The lack of controlled studies on the management of toxin-induced hypertension results in some controversy on the management of sympathomimetic-poisoned patients. Discussion: Noradrenergic-induced hypertension has been the most studied. Many sympathomimetics act by direct stimulation of the alpha receptor which elevates intracellular cyclic AMP. Other sympathomimetics work more indirectly by promoting the release of norepinephrine, blocking its reuptake, inhibiting its breakdown or a combination of the above. Nicotinic and cholinomimetics enhance sympathetic ganglionic activity. Less well understood and studied is the hypertension that results from the anticholinergic and serotonin syndromes, although blood pressure elevations are usually less severe than that seen in severe sympathomimetic poisoned patients. The need to pharmacologically treat blood pressure elevations is individualized based upon age and prior history. A blood pressure of 160 mmHg systolic or 110 mmHg diastolic usually requires treatment in a teenager or young adult, as hemorrhagic strokes or myocardial injury may occur with sustained pressures above this range. Although not universally recommended benzodiazepines such as diazepam or lorazepam are probably the safest first line agents. The enhancement of gamma aminobutyric acid (GABA) neurotransmission centrally and peripherally will blunt sympathetic discharge and lower blood pressure. Nitroprusside, a vasodilator, is otherwise universally recommended as the agent of choice, because of the ability to titrate its effect. Phentolamine, another parenteral vasodilator, has been extensively studied for cocaine poisoning with excellent benefit and safety results. Nifedipine, a calcium channel blocker, has had much reported success. Nifedipine use in the elderly, however, is hazardous, because of occasional profound hypotension that may follow use in patients with atherosclerotic cardiovascular disease. Nicardipine has been suggested as a titratable alternative, but use and reports in the toxicology literature have been limited. Beta-blockers are controversial agents, because of the fear of inducing an unopposed alpha state that might actually worsen hypertension or cause coronary vasoconstriction. Labetalol, predominantly a beta-blocker with some alpha blockade, also has fallen out of favor, because of some reports of adverse outcomes. Propranolol also has studies that purport a benefit while others suggest risk. Propranolol may have potent central actions that affect peripheral effects. Hydralazine and clonidine likewise are now rarely used in hypertensive management. Enalaprilat has been used for other medical hypertensive emergencies, but safety, especially renal, has not been determined in toxin-induced hypertension. Conclusions: Toxin-induced hypertension of sympathomimetic origin often requires pharmacologic management. Benzodiazepines are a safe yet often underutilized antidote. Nitroprusside remains the universally recommended agent. Further research is needed to address the role of beta-blockers in symathomimetic poisoning, especially in combination with other agents. The use of titratable calcium channel blocker agents such as nicardipine also warrant further study.

56. THE MOLECULAR BASIS OF TOXICITY OF REVERSE TRANSCRIPTASE INHIBITORS

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Objectives: In 1994 the NIH halted a study of the nucleoside analog fialuridine for treatment of chronic hepatitis B due to severe hepatotoxicity. Five patients died. Since then numerous cases of liver injury attributed to nucleoside analogs that inhibit HIV reverse transcriptase have been recognized. Common clinical features include severe lactic acidosis with elevation of hepatocellular enzymes and bilirubin, and failure of hepatic synthetic function. Microscopic examinations show marked microvesicular steatosis with minimal necrosis. In addition to liver cell injury, myopathy that is histologically similar to rare myopathies associated with genetic disorders of mitochondrial function occurs in 10% of AIDS patients who take reverse transcriptase inhibitors. Electron micrographs of affected tissues demonstrate abnormal mitochondria. This presentation will review clinical manifestations of the toxicity of nucleoside analogs, and then discuss studies that define the molecular basis of this toxicity. Methods: Review of original case reports and basic science investigations of molecular causes of tissue induced by nucleoside analogs. Results: Lactic acidosis and impaired fatty acid metabolism suggest failure of mitochondrial energy production. Microvesicular steatosis is associated with

conditions attributed to mitochondrial failure such as Reye's syndrome and hypoglycin toxicity. In vitro studies demonstrate that HIV reverse transcriptase inhibitors inhibit mitochondrial DNA polymerase gamma and adenylate kinase, which is involved in the synthesis of ATP and translocation of nucleoside precursors of ATP. AZT depletes mitochondrial DNA by inducing DNA chain termination during replication. This is similar to the therapeutic mechanism of inhibition of viral DNA synthesis by reverse transcriptase. The toxicity of reverse transcriptase inhibitors correlates with their ability to inhibit polymerase gamma. Conclusions: There is mounting evidence that reverse transcriptase inhibitors also inhibit mitochondrial DNA polymerase, resulting in mitochondrial depletion and manifestations of impaired cellular energy production such as lactic acidosis, impaired B-oxidation of fatty acids, and myopathy. References: Chariot P, Drogou I, de Lacroix-Szmania I et al. Zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis, and mitochondrial DNA depletion. *J Hepatol* 1999;**30**:156–160. Chattha G, Arieff AI, Cummings C, Tierney LM et al. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993;**118**:37–39. Côté HCF, Brumme ZL, Craib KJP et al. Changes in Mitochondrial DNA as a Marker of Nucleoside Toxicity in HIV-Infected Patients. *N Engl J Med* 2002;**346**:811–820. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse tanscriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000;**22**:685–708. McKenzie R, Fried MW, Sallie R et al. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis. *N Eng J Med* 1995;**333**:1099–1105. Schafer F, Sorrell MF. Power failure, liver failure. *N Engl J Med* 1997;**336**:1173–1174.

57. METHOTREXATE TOXICITY: MECHANISM(S), SYMPTOMS AND TREATMENT

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Objective: Methotrexate (MTX) is a frequently used antineoplastic and immunosuppressive agent. Depending on the underlying disease, it is applied in low-, moderate-, and high-doses. Mortality from high-dose MTX is estimated around 6% demonstrating its high potential for systemic toxicity. Since rationale prevention and treatment measures are available, it is important to understand the most important features of MTX toxicity. Mechanism(s): MTX is a structural analogue of folate and competitively inhibits dihydrofolatereductase (DHFR). As a consequence folate cannot be reduced to tetrahydrofolate, which blocks the synthesis of purine nucleotides and thus DNA and RNA synthesis. Administration of reduced folate (= leucovorin) permits maintenance of DNA/RNA synthesis despite a blocked DHFR. With the exception of acute kidney failure due to MTX precipitation in renal tubules (acute tubular necrosis), the toxic manifestations result from MTX's pharmacological action. Pharmaco-/Toxicokinetics: Oral bioavailability of MTX is low because of rapid saturation of the intestinal organic anion uptake system(s). Thus, parenteral administration of high doses is necessary to achieve effective systemic drug concentrations. Volume of distribution is $\sim$0.7 L/kg. Total protein binding amounts to $\sim$50%. Plasma elimination half-life (T1/2β) has a short phase of $\sim$3h (renal elimination) and a longer phase of 8–10h (due to redistribution). Up to 90% of MTX are eliminated unchanged in the urine. Renal excretion is increased at high urine pH. Clinical symptoms: Signs of MTX toxicity include gastrointestinal mucositis, hepatotoxicity, myelosuppression, renal failure, and neurotoxicity (reversible arachnoiditis, irreversible leukoencephalopathy). The risk of manifest MTX toxicity is increased at plasma concentrations $>$ 1 μmol/L at 48h posttreatment. Risk factors for MTX toxicity include impaired renal function, extravascular fluid effusions (e.g., ascites), NSAID coadministration, advanced age and folate deficiency (e.g., alcoholism). With the exception of leukoencephalopathy, toxic manifestations are usually reversible within 1–2 weeks after MTX discontinuation. Treatment: Effective treatment measures of MTX overdose include 1) Early single- (oral overdose) and multiple- (systemic overdose) dose activated charcoal $\pm$ cholestyramine. 2) Saline diuresis and alkalinization of the urine (pH 7–8) in the presence of normal renal function. 3) Early high dose leucovorin rescue therapy (goal: plasma leucovorin conc. $>$ MTX conc.). In case of severe bone marrow toxicity leucovorin could be combined with thymidin and/or carboxypeptidase G2 (inactivates MTX) rescue therapy. 4) In case of renal failure, hemoperfusion or high-flux hemodialysis have been shown to be effective in some cases. 5) In patients with pancytopenia, "granulocyte colony-stimulating factor (G-CSF)" or "granulocyte-macrophage colony-stimulating factor (GM-CSF)" can accelerate neutrophil recovery with the time course of recovery depending on the presence (1–4 days) or absence (2–3 weeks) of myeloid precursors in the bone marrow. Conclusions: MTX overdose can lead to serious multi-organ damage due to its anti-folate activity. Its rationale management requires carefull consideration of the circumstances of poisoning (acute, chronic; oral, systemic), the pharmaco-/toxicokinetic

and pharmacodynamic properties of MTX, the clinical symptoms and the proven or potential efficacy of the various therapeutic possibilities.

58. CONTROVERSIES IN THE USE OF N-ACETYLCYSTEINE AS AN ANTIDOTE

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N-acetylcysteine (NAC) was introduced into clinical practice in the 1970s following a series of studies designed to determine the most effective sulfhydryl-donor in the management of paracetamol poisoning (1). Since that time it has become one of the most frequently used antidotes. Despite over 25 years of clinical use there is still uncertainty about certain aspects of this antidote's mechanism of action, clinical indications, and most appropriate treatment regimen. Original studies were based upon the dose of the antidote that could be tolerated by volunteers intravenously, and no formal dose-ranging studies of efficacy have been performed in man. In paracetamol poisoning specific markers were used to identify a sub-group of patients who may be at risk of liver failure. These markers have been applied in different ways. In some countries a single treatment line has been used (2), whereas in others normal and high-risk categories have been determined, the latter empirically (3). This means that it is difficult to compare therapeutic efficacy based on decision to treat. Furthermore the lack of routine use of intravenous NAC in North America, where a three-day oral regimen has been extensively used, has resulted in debate as to the most effective way to use the antidote. A 48h IV regimen has also been proposed (4). A meta analysis of treatments suggests that there is no difference in efficacy between IV and oral regimens in acute poisoning, though hospital stay is shorter with the IV regimen (5). The original data sets from which patient treatment lines were derived only extended to about 15h after paracetamol ingestion. This, and evidence from animal data that efficacy is lost with increasing interval from ingestion, led to uncertainty about the indications for treatment with NAC after this time interval. Subsequent data obtained in cohorts of patients referred for prospective liver transplant indicate that the antidote may be protective far later than originally considered (6). Adverse reactions to NAC are relatively common when the drug is given intravenously (7). Recent studies have shown that risk factors may include a history of asthma (8). Death from bronchospasm has been reported in a brittle asthmatic (9). The mechanism of these reactions is still not completely clarified but direct histamine release seems to play an important role, and to relate to plasma levels of the antidote. The potential to alter the infusion protocol to reduce this risk has not been properly evaluated. These reactions are usually easily treated however (10). Some workers have also questioned whether a 72h oral protocol is too long and could be replaced by a 48h period. Studies on this aspect are too small to be conclusive and likely to be made irrelevant if the intravenous protocol becomes accepted in North America (11). Conventional management following intravenous administration of a 20h protocol is to continue if there is evidence of clinically significant liver damage. Precise limits for this decision are not based on clinical trial data, and may be complicated by the fact that paracetamol and NAC may perturb clotting (12,13). Other aspects that need to be studied in more detail are the risk factors for increased susceptibility to paracetamol-induced damage, and the implication of these risk factors for NAC treatment intervention guidance. A clear example is the conflicting information on the role of ethanol in paracetamol induced liver damage. Despite its length of use very many different hypotheses have been advanced to explain the mechanisms of action of NAC particularly when used to treat other hepato-toxins and in the later stages of hepatic injury caused by paracetamol. NAC has been used in a variety of clinical situations, most frequently in amatoxin (14) and carbon tetrachloride poisoning (15) and radio-contrast nephropathy (16). The lack of good controlled clinical trials makes clear assessment of benefit in man difficult, and one is often left dependent upon animal data where there pattern of administration of antidote rarely mimics that seen in clinical practice. The challenge for the toxicological community is to mount effective clinical studies using suitable end points to clarify the questions that remain about the use and indications for this compound. References: 1. Prescott LF, Illingworth RN, Critchley JAJH, Stewart MJ, Adam RD, Proudfoot AT. 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59. TOXICOLOGICAL INFORMATION AND DATA NETWORK—A EUROPEAN CHALLENGE? RESULTS FROM A WORKSHOP, SEPTEMBER 2002, BERLIN.

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Objective: Poison information centers require high-quality data to give adequate advice. These data include product formulations, data about cases, and general toxicological information. In European states different approaches are taken to gathering this information, particularly product data. In some states the level of information about product composition is good, while in others it is inadequate. The use of electronic means for providing and exchanging information is becoming more widespread. However, although PCs use computers for their daily work, their use to exchange experience and knowledge is poorly developed. Method: To explore the desirability and possibility of improving electronic data exchange in Europe, a workshop "Toxicological Information and Data Network—A European Challenge?" was organized on behalf of the Research Project Toxicological Data and Information Network (TDI). TDI was initiated and supported by the Ministry of Environment, Nature Conservation and Nuclear Safety and realized by five German PCs, the BgVV, and the German Cosmetics, Toiletries, Perfumes and Detergents Association. Software was developed for electronic transfer from industry to poison centers, and other partners. This project was used as the basis for a discussion about the possible benefits of data exchange between European PCs and agencies involved in risk assessment, health policy and industry. Results: An overview about co-operation between the above mentioned Partners, and potential data needs was given. The approaches used for gathering product information in six different states showed broad heterogeneity. In some countries very strict regulations governed the notification of formulations. At a round-table discussion participants agreed that data exchange of information about products, cases, and substances was an important task. It was also noted that industry did not want to have multiple partners in different countries but ideally only one partner in Europe. This partner would ensure data would be transferred to others. It was felt that the development of a system for data exchange would be useful and would increase the quality of data. However, there were no common agreed standards for electronic data transmission between the European PCs. EAPCCT has already worked on data formats for products, and it was felt that EAPCCT should support an initiative for implementation of electronic formats. Conclusion: The workshop has clearly shown that there is a high degree of agreement that a co-operative approach is needed, and that EAPCCT as the representative association of poison centers and clinical toxicologists should play a major role in this process. This minisymposium was therefore organized to discuss how a common electronic data exchange format for products could be established which all poison centers can use and which considers all relevant information about products. A proposal for an electronic format and a transfer protocol will be presented and discussed.

60. CONCEPTS FOR ELECTRONIC DATA TRANSFERS FROM INDUSTRY TO POISON CENTERS—ADVANTAGES FOR INDUSTRY

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Objective: In several European countries the formulations of cosmetic products, detergents, maintenance, and cleaning products must be notified to poison control centers or national central agencies. Such notifications are partly made on a voluntary basis. An electronic notification format for cosmetic products is already recognized in various countries; relevant requirements for detergents and cleaning products have been harmonized in Germany. Methods/Results: For the collection of data on *cosmetic products* the IKW developed the notification program "SYSDECOS." This was done in cooperation with the former federal institute for the health protection of consumers and veterinary medicine—BgVV (now the Federal Institute for Risk Assessment—BfR). SYSDECOS generates notification files in the so-called KOS format. Currently files in the KOS format are accepted in Germany, Austria, Belgium, Finland, Norway, Sweden, and Switzerland. The advantage, especially for small and medium-sized enterprises, is that each formulation must be recorded only once (either as an EAPCCT/COLIPA frame formulation no. or with INCI names) and can be supplemented with country-specific information. For the collection of data on *detergents and maintenance and cleaning products* the "EMIL" program for the generation of so-called ROSETTA files defined by poison centres has been developed within the framework of the TDI-project in co-operation with German PCs. This uniform notification format makes it easier in Germany to change from notifications on paper to notification that is electronic. These can also be transmitted to the 10 poison centers and the BfR. Conclusions: As part of the development of a European internal market companies distribute their products not just in one, but to many, or all, Member States of the European Union. To facilitate notifications of formulations (on a voluntary or compulsory basis), companies should ideally record the same data (e.g., formulations) only once with the help of one program, enabling them to generate country-specific notification files. The long-term goal should be a single notification format.

61. ELECTRONIC DATA EXCHANGE AS A BASIS FOR COOPERATION OF POISON CENTERS IN EUROPE? ADVANTAGES FOR THE COMMUNITY

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Objective: Exposure to chemicals is part of daily human life. The prevention of human harm from chemicals during their occupation, as consumers and from exposure via the environment are major international challenges. It is of great importance that each institution that is involved in prevention, diagnosis and/or treatment of poisoning and its sequels must have appropriate information available. In the last two decades, electronic approaches have been developed world-wide for storing information, but only a few attempts have been made to exchange this information. This includes human epidemiological data, interesting cases of poisonings, and particularly data on product composition. The European states have differing approaches for the collection of composition data. Although industry is ready to support the needs of poison centers, it is interested in a uniform procedure. To utilize electronic measures for collaborative data exchange it is important to agree to a common standardized approach. In the past, some projects have shown that there is a great need not only for harmonization, but also for standardization of the approaches used. Important work that has been done on a world-wide level is represented by the IPCS/INTOX project. In this project, it has clearly been shown that all data that are stored in the system that is aimed to be available for numbers of partners should be well defined. Therefore, clear definition of all information is a crucial point of data management. For an international project dealing with data exchange there are two alternatives, (i) all partners would use a uniform system (like INTOX) or (ii) if not, they must speak the same language, which means that a standardized data exchange format and a standardized data exchange procedure must be developed. In several countries first approaches have been developed to exchange product data. Therefore there is an urgent need to use clear common definitions of terms to describe patterns (exact product names, manufacturer, distributor, ingredients, use classification, etc.) to start a co-operation of industry with poison centers and with other authorities. Some years ago the EAPCCT developed a paper-based data exchange format. This format should now be transferred to an electronic basis using commonly accepted standards and definitions to increase knowledge of product compositions and thus increase quality of poison center work. Conclusion: There is a great challenge to enhance the use of electronic data exchange for distribution and exchange of information between poison centers. This is

particularly relevant to product data, but also to human toxicity data and data on primary ingredient toxicity. For human health protection use of standardized data collection is essential and should be encouraged at the European and international level. Initially clear definitions and standard procedures have to be agreed upon.

62. A COMPARATIVE ANALYSIS OF THE ITALIAN EXCHANGE FORMAT FOR PRODUCTS IN ITALY

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The Italian government has enacted article 10 of the European Directive 88/379 (now updated with Dir. 1999/45/EC) on Dangerous Preparations, appointing a central body charged to collect information about all dangerous preparations present on the Italian market. A specific Decree was published in the year 2000 (19/4/2000) in which all the details of the project were reported. The National Institute of Health (ISS) was appointed as the central body responsible for the program and a fully computerized system was developed. A specific central database was defined together with client software, which was made available via the Internet Web site of the ISS, together with other complementary files (user instruction, etc.). The aim of the project is to create a central database containing a limited amount of information on the dangerous preparations present in the Italian market, with particular reference to the full chemical composition. Dangerous components have to be reported by chemical name and CAS number while non-dangerous components can be reported using a chemical family name. The companies responsible for putting a preparation on the Italian market (including companies located abroad) are requested to download the program (written in Oracle language) from the ISS Web site, install it in their PC, and fill electronic forms for all dangerous preparations actually put on the Italian market. At the end of the process the program can generate a compressed file which may be forwarded to the central database. The Italian Ministry of Health makes this database available via on-line connection 24h/day to all authorized PCs. Other countries have developed their own product registers, either in response to the EU Directive on Dangerous Preparations, or for other national purposes. Several EFTAC countries have previously developed internal product registers, where a variety of different information on Dangerous Preparation is collected: in addition to the full chemical composition they often collect information on dangerous preparations or on individual dangerous components. Often information contained in the MSDS is also centralized. France has partly applied the Dangerous Preparations Directive collecting information at a central level (ORFILA, under the sponsorship of INRS) on the preparations belonging to the most dangerous categories (very toxic, toxic, corrosive) while for the other categories industry is requested to keep information available upon request. Germany has developed different projects for different purposes for different categories of products at local level. Recently they have also produced specific projects (e.g., TDI) and are developing their own data entry screen (DES) for specific category of products. Similar approaches have been developed or are about to be developed in other countries (e.g., Spain and UK), but the general problem is that all these national systems are not compatible with each other having been developed on the basis of different legislative frameworks and for different purposes. It is now time to start a European project with the aim of developing an harmonized system finding a common format of the information, so as to be exchanged between member states and made available to all European PCs. The final goal could be to request industry to provide a minimum set of data to one Member State and granting the access of data via a European network to all National Authorities and PCs.

63. ROSETTA—ENHANCING DATA QUALITY BY STANDARDIZATION OF DATA ELECTRONIC EXCHANGE

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Objective: In 1996, EAPCCT and several European industry organizations have developed a paper form for exchange of product information in a harmonized manner (1) between companies and poison centers (PC). Since that time, this harmonized format has been used frequently in Europe and became a highly accepted standard for product data exchange. With increasing computer power in PC and companies and increasing opportunities of secure electronic data exchange a need for an harmonized electronic version of the format arises. Method: Embedded in the German national research project TDI (Network for information and cases documentation in German poison centers) a format describing product data and address data was designed. This was tested using a newly developed data acquisition program and an

import program connected to the project's product and address database, a copy of which has been installed in each of seven project centers. Results: A new data format XML ROSETTA was developed. XML language rules are used to describe the structural elements. Each ROSETTA data package consists of up to four main elements describing (a) the (whole) data package with its logistics, (b) product information (0, 1, or more products), (c) addresses (at least one address per package), and (d) evaluation parameters. Each main element is structured further up to three sublevels. Element (c) contains company address data, communication numbers, and an identification number for each company that links to external reference lists of addresses maintained by national institutions. The main element (b) contains the complete EAPCCT format for product information (1). Each product is linked to at least one company described in element (c), indicating authorship, producer of the product, or other relations. The complete format is published on the project's Web site (2) for easy access for all persons and institutions interested in harmonized product data exchange. Conclusion: All requirements for electronic product data exchange (in EAPCCT format) between several independent centers have been fulfilled. The system is ready and recommended for international data exchange. Reference: (1) Exchange of Information Between European Poison Control Centres And Industry (AIS:FIFE:FEA). EAPCCT Newsletter April 1996, pp. 3–13 (2) http://www.tdi-network.org.

64. CYANIDE POISONING: DIAGNOSIS AND ANTIDOTE CHOICE IN AN EMERGENCY SITUATION

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Objectives: Cyanide is a potent intracellular poison, due to its attachment to the ferric form of vital cellular enzymes. Cyanide quickly binds to cytochrome aa_3 inducing a noncompetitive inhibition of the mitochondrial cytochrome c oxidase, which inactivation reduces oxygen utilization by tissue. If left untreated, cellular poisoning results in a shift of aerobic to anaerobic metabolism, leading to cellular ATP depletion and lactic acidosis and death. Clinical features include coma, respiratory arrest and cardiovascular collapse. The biological hallmark is lactic acidosis. A plasma lactate concentration ≥ 10 mmol/L in fire victims without severe burns and ≥ 8 mmol/l in pure cyanide poisoned patients is a sensitive and specific indicator of cyanide intoxication. Many antidotes are available and efficient. However, therapeutic strategies are still debated. Our objective is to present briefly the different clinical features of cyanide poisoning and to analyze the different antidotal treatments in respect to their efficacy, their action rapidity, their availability, their cost and their side effects. Methods: Systematic review of the literature on cyanide poisoning treatments. Results: Cyanide poisoning may result from different exposures: residential fires, industrial accidents, drug and plant intoxication. The main clinical features of pure cyanide poisoning include dyspnea, restlessness, transient hypertension, mental confusion, coma, seizures, respiratory arrest, cardiovascular collapse with a paradoxical normal heart rate, and if treatment is delayed, a cardiorespiratory arrest. However, recognition of nonclassical situation of cyanide poisoning may be difficult. Confirmatory laboratory diagnosis may take hours to days, while early aggressive treatment with appropriate antidotes is essential. Immediate diagnosis of cyanide poisoning remains in fact elusive in spite of recent improvements in blood cyanide detection methods. The biological hallmark of cyanide poisoning is lactic acidosis. In fire victims without severe burns, a plasma lactate concentration greater than or equal to 90.1 mg/dL (10 mmol/L) is a sensitive and specific indicator of cyanide intoxication. Significant cyanide poisoning may also induce hyperglycemia, increased serum CPK activity, and acute renal failure. Conventional treatment of cyanide poisoning includes decontamination, supportive and specific treatment. Decontamination should be adapted to the route of poisoning and never postpone supportive treatment. Basic life-support includes immediate administration of high flow of oxygen, airway protection and cardiopulmonary resuscitation. Advanced life support includes mechanical ventilation, catecholamine and sodium bicarbonate infusion. Supportive treatment is efficient but does not modify the time-course or the body-burden of cyanide. Numerous antidotes are available. Oxygen counteracts efficiently cyanide action at the mitochondrial level. Sodium thiosulfate, methemoglobin forming agents and cobalt compounds act efficiently by complexing or transforming cyanide into non-toxic stable derivatives. However, regarding the main clinical condition of cyanide poisoning, i.e., smoke inhalation, we should take into account not only for the efficiency of antidotes but also for their safety. Sodium thiosulfate is both efficient and safe, but acts with delay. Methemoglobin forming agents are potent, but due to the transformation of hemoglobin into methemoglobin, they impair tissue delivery of oxygen. Experimental data showed increased mortality in carbon monoxide and cyanide poisoned rats treated with these agents. Cobalt EDTA and hydroxocobalamin are efficient and act immediately.

Cobalt EDTA is more potent on a molar basis; however, numerous side effects limit its use to evidenced cyanide poisoning. In a prospective study, hydroxocobalamin appeared safe in fire victims with or without cyanide poisoning. The only reported side effect was a red coloration of skin and urine. Conclusion: Antidotes are beneficial in cyanide poisoning. In suspected cyanide-poisoned patients, we recommend the use of hydroxocobalamin as first-line antidote, according to its safety. In massive cyanide poisoning, due to hydroxocobalamin limited potency, continuous infusion of sodium thiosulfate should be associated.

65. DESFERRIOXAMINE: FIVE CONTROVERSIES

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Introduction: For over 35 years desferrioxamine has been the antidote of choice for the treatment of iron poisoning. Despite this somewhat long history, many controversies and uncertainties persist regarding its optimal use. The purpose of this presentation is to review five desferrioxamine controversies: (1) Efficacy (2) Indications (3) Route of Administration (4) Dose (5) Duration of Therapy. Efficacy: The efficacy of desferrioxamine for the treatment of iron poisoning is unproved. There are no relevant randomized clinical trials. Furthermore, utilizing desferrioxamine/iron stoichiometry as the criterion for an effective dose, it is impossible to administer the dose calculated as being necessary for the treatment of a patient with a clinically significant iron ingestion. Therefore, the uncertainty regarding its efficacy goes beyond the absence of randomized clinical trial evidence. However there is other evidence, albeit not as compelling as RCT data, that supports efficacy of this antidote. This includes in vitro cell culture studies, in vivo animal studies and numerous descriptive reports of human iron poisoning cases. Furthermore, review of the pharmacokinetics of iron supports the notion that only a small proportion of the ingested iron is actually absorbed from the gut, thereby increasing the likelihood that the dose of desferrioxamine that can be administered is potentially efficacious. Thus a credible argument can be made to support the efficacy of this antidote for iron poisoning. Indications: There are no data that reliably link any criteria, be it dose, symptoms and signs of toxicity, serum iron concentration or other laboratory values with the need to administer this antidote. Suggested indications include the presence of significant clinical symptoms and signs, the presence of a metabolic acidosis or a serum iron concentration $>90\,\mu$mol/L. Historical indications no longer considered as valid include a serum iron concentration greater than the total iron binding capacity or the presence of the following panel of findings: hyperglycemia, leukocytosis, x-ray evidence of iron in the gastrointestinal tract, and a history of emesis. Route: The manufacturer recommends the intramuscular route unless the patient is in shock. However intravenous desferrioxamine has been shown to be more effective and because its half-life after bolus intravenous injection is short, 10–30 minutes, a constant intravenous infusion is the most rational method of desferrioxamine administration. Dose: There are no dose-response data describing the efficacy or the toxicity of desferrioxamine. Therefore the manufacturer's dosing recommendation is arbitrary. It is conservative. The recommended pediatric dose is 80 mg/kg/day to a maximum of 6.0 g/day. The recommended infusion rate is 15 mg/kg/hr. Therefore the entire day's dose would be administered in 5.3 hours. Clinical toxicologists routinely exceed the maximum daily dose by 3–4 fold for patients with moderate to severe iron poisoning. Duration of therapy: There are no reliable criteria for the duration of therapy. Serum iron concentration is of no use because it quickly falls after its peak and has no correlation with toxicity during the clinical course. Furthermore, the presence of desferrioxamine in the plasma can confound routine laboratory methods for the estimation of this value. Historically, the presence of vin rose colored urine was considered as a criterion for ongoing desferrioxamine administration, however this is unreliable and has never been validated. The presence of significant symptoms and signs or the presence of a metabolic acidosis unrelated to hypoperfusion are reasonable indications for the continuation of the desferrioxamine infusion. It is rarely needed beyond 24 hours. Conclusions: Because routine pharmacokinetic and pharmacodynamic data are lacking, optimal evidence-based recommendations for desferrioxamine therapy cannot be made. Personal recommendations include the initiation of an infusion of 15 mg/kg/hr of this antidote if significant symptoms and signs of iron poisoning are present, or if the patient has a metabolic acidosis or a peak serum iron concentration greater than 90 μmol/L. It should be continued until those symptoms and signs and the metabolic acidosis have abated. It is rarely needed beyond 24 hours. References: 1. Tenenbein M: Iron poisoning In Irwin RS, Cerra FB, Rippe JM, eds., Irwin and Rippe's Intensive Care Medicine. Philadelphia: Lippincott-Raven 1999;1666–1572. 2. Tenenbein M: Benefits of parenteral deferoxamine for acute iron poisoning. *J Toxicol Clin Toxicol* 1996;**34**:485–489. 3. Tenenbein M. Toxicokinetics and toxicodynamics of iron poisoning. *Toxicol Letters* 1998;**102–103**:653–656.

66. DMPS: THE NEW CHELATING AGENT OF CHOICE IN THE TREATMENT OF ARSENIC POISONING

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Objective: Since its introduction into civilian medicine at the end of World War II, dimercaprol has remained the chelating agent of choice for the treatment of arsenic poisoning in Western Europe. This is rather surprising, since dimercaprol has many disadvantages, e.g., high toxicity, low therapeutic index, unpleasant side effects, limited water solubility, instability in solution, the need to administer by intramuscular injection, which might be a problem when blood coagulation is compromised, and of paramount importance is the observation that dimercaprol might increase neurological morbidity in acute arsenic poisoning. In the search for better antidotes of arsenic, several experimental studies indicate a beneficial effect of DMPS in the treatment of arsenic poisoning. However, the clinical reports with this new antidote are extremely limited. Case series: The effect of the two antidotes DMPS and dimercaprol was compared in three severe cases respectively. The results were unequivocal. Out of the group treated with dimercaprol, two patients with maximum arsenic blood levels of 540 μg/l and 620 μg/l died within 34 hours and 6 days respectively. The third patient with a maximum arsenic blood level of 558 μg/l is still suffering from paraplegia caused by the intoxication. Two of the patients treated with DMPS including one with anuric renal failure left the hospital healed, despite extreme high maximum arsenic blood levels of 2240 μg/l and 4469 μg/l respectively, which is 7–8 times higher than in the cases treated with dimercaprol. The third case with a maximum arsenic blood level of 245 μg/l, which is also a severe intoxication, had a very mild course due to the early onset of DMPS treatment. For chelation therapy DMPS infusion of 100–500 mg/h with a starting bolus of 250 mg was used. The elimination half-lifetime could be reduced drastically using this dosage. In the dimercaprol-group the elimination half-lifetime was unmeasurable in 2 cases and 16 hours in the third case. In the DMPS-group the half-lifetime was 4 hours in 2 cases and calculated 5 hours in one case associated with acute renal failure. Conclusion: The recommendation of dimercaprol as the drug of choice in arsenic poisoning is obsolete. The combination of the chelation therapy with DMPS with an extracorporeal elimination technique including haemodiafiltration is only necessary when acute renal failure is present. Further clinical experience with DMPS in the treatment of arsenic poisoning is undoubtedly required, but the experimental and clinical results with this chelating agent obtained until now should encourage further use of DMPS in arsenic poisoning.

67. A CRITICAL REVIEW ON OXIMES IN THE TREATMENT OF ACUTE ORGANOPHOSPHATE POISONING

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Objective: Treatment with oximes capable of forcing reactivation of inhibited acetylcholinesterase (AChE) is thought to be mandatory (1), useless/contraindicated (2) or undecided (3). Since death rates from organophosphate (OP) poisoning are still significant, clinicians need to understand this controversy. Methods: Understanding the pharmacodynamics and pharmacokinetics of both OPs and oximes (4) is essential to assess conflicting observations as seen in case reports, case series, and randomized controlled trials. a) General mechanism. OPs react covalently with AChE by phosphorylating its catalytic centre with varying affinity constants, depending on the OP involved. The phosphorylated enzyme is stable and the rate of spontaneous reactivation depends on the chemistry and chirality of the attached phosphoryl residue. This rate should be considered in conjunction with that of a further reaction called aging which involves the loss of one alkyl group and leads to stabilization of phosphorylated AChE. Oximes remove the phosphoryl group from AChE, thus restoring its catalytic site. This antidotal reaction occurs only when the phosphorylated AChE has not undergone the intramolecular rearrangement of aging. Because aging is usually fast, oximes should be available at the synaptic cleft as long as there is newly inhibited AChE. b) OP pharmacokinetics and pharmacodynamics: Body clearance varies substantially among OPs and in some cases redistribution occurs. Moreover, some OPs are direct inhibitors of AChE whereas others require metabolic activation. Given these varying kinetics it is difficult to know if newly inhibited AChE is available to oximes at a given time. Rate constants for reactivation and aging of human AChE may not be known in all cases. c) Oxime pharmacokinetics & pharmacodynamics: The pharmacokinetics of oximes is influenced by changes in hemodynamics during OP poisoning. Each oxime has different reactivation power on a given phosphorylated AChE and different

phosphoryl residues attached to AChE are not equally susceptible to the same oxime. Results: Several clinical case studies and animal data indicate that oximes favor reactivation of AChE and have a positive effect on survival. On the contrary, some authors reported limited or no efficacy of oximes in individual cases and in two randomized controlled trials (3). In general, the assessment of oxime efficacy is difficult when key variables such as mechanical ventilation and multiple drug treatment are involved. In addition, OP identification in body fluids and chemical analysis of involved formulation are often missing and hemodynamic changes may not be comparable among patients. Several reasons have been identified to explain the failure of oxime therapy (1) including inadequate dose and duration of treatment. Recommended dosage schedules are aimed at achieving a plasma oxime concentration of 4 mg liter^{-1}, but higher concentrations may be needed in severe poisonings because effects of oximes depend on the plasma concentration of OPs. Long lasting OPs and prolonged release of stored OPs may require continous oxime therapy. Based on in vitro experiments it is believed that oxime therapy is useless on day 1 and day 5 after poisoning with dimethyl and diethyl phosphates, respectively. Whereas in vivo data supporting this suggestion are not convincing, other experiments indicate that in vivo reactivatability of AChE lasts for a longer period than expected from in vitro experiments (1) Conclusions: mechanistic studies strongly support the use of oximes in OP poisoning, although studies may be needed to refine dosing regimens. Empirical approaches to evaluate the need for oximes include the measurements of erythrocyte AChE before and after a bolus of oximes, or the in vitro reactivatability of erythrocyte AChE sampled from the patient. References: (1) Johnson MK, Jacobsen D, Meredith TJ et al. Evaluation of antidotes for poisoning by organophosphorus pesticides. *Emerg Med* 2000;**12**:22–37 (2) Peter JV, Cherian AM. Organic insecticides. *Anaes Intens Care* 2000;**28**:11–21 (3) Eddleston M, Szinicz L, Eyer P et al. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. *Q J Med* 2002;**95**:275–293 (4) Lotti M. Clinical toxicology of anticholinesterase agents in humans. In: *Handbook of Pesticides Toxicology 2nd edition* 2001;**2**:1043–1085 Academic Press, San Diego.

68. THE CURRENT STATUS OF OXIMES IN THE TREATMENT OF OP POISONING—COMPARING TWO REGIMES

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Background: Organophosphorus insecticides (OPs) are increasingly used worldwide, because they are rapidly degraded and do not accumulate in food chains. This advantage over organochlorines and pyrethroids is paid for dearly, taking into account the much higher acute toxicity of the OPs. While the number of victims from accidental intoxications is relatively low, their use for deliberate self-poisoning has reached epidemic proportions in some developing countries. OPs inhibit acetylcholinesterase (AChE) by phosphorylation of the active-site serine, thereby disturbing normal cholinergic transmission at nicotinic and muscarinic receptors. Standard therapy involves attempts to reduce absorption (gastric lavage, activated charcoal) plus atropine, sedation, and artificial respiration. The latter option, however, often remains an illusion due to shortness of the medical budget. Hence, administration of causal therapeutics aimed at reactivating the inhibited enzyme appears attractive. With the advent of 2-PAM nearly some 50 years ago, optimistic clinical reports on its benefits prevailed. Similarly, the introduction of obidoxime was attended with enthusiasm. It took, however, only a few years of broader clinical experience for the clinical merits of both oximes to be questioned. Even today two opposite parties exist: those who promote oximes as first-line causal antidotes and those who frankly deny any benefits. Obviously, such a dichotomy calls for an in-depth search for the underlying reasons for benefit or failure of oxime therapy that is sometimes observed. In studying reactivation kinetics of human erythrocyte AChE (Ery-AChE), which is derived from the same single gene as synaptic AChE, we observed marked differences in the potency and efficacy of 2-PAM and obidoxime, the latter being one order of magnitude more effective at the usually recommended dosage. This holds particularly true for AChE inhibited by diethylphosphoryl compounds, but also for the dimethylphosphorylated enzyme. While the former shows slow spontaneous reactivation and ageing, the latter is prone to either rapid spontaneous reactivation or rapid ageing resulting in an irreversibly inhibited enzyme. Hence, the type of

OP is of paramount importance in evaluating the effectiveness of oxime therapy. Lipophilic OPs such as the phosphorothioates (P = S) are prone to accumulate in fat tissue from which the OPs may be redistributed into the central compartment for days and even weeks. This behavior must be taken into account when considering the duration of oxime therapy. We have therefore thought it timely to monitor OP-intoxicated patients more closely and to follow the AChE status along with the oxime pharmacokinetics and the toxicokinetics of the poisons involved. Aim: To assess the effectiveness of oxime therapy in diethylphosphoryl vs. dimethyphosphoryl OP poisoning and to correlate the oxime and poison concentration with the Ery-AChE status and objective endpoints, such as improvement of neuromuscular function and survival. Methods: Two clinical studies were performed, one in Germany (1999–2001) using an obidoxime regimen and one in Sri Lanka (2002) adhering to the 2-PAM protocol that Senanayake argued was not effective. In Germany, primary care was given by emergency physicians, including oxygen and atropine administration, and in most cases gastric lavage and activated charcoal. The effectiveness of obidoxime was evaluated in 34 severely OP intoxicated patients (inclusion criteria: need for artificial ventilation) treated with a 250 mg i.v. bolus, followed by continuous infusion of 750 mg/24 h. The infusion was maintained as long as reactivation was possible, as determined by incubation of diluted patient's blood with 100 μM obidoxime (reactivatability). Blood samples were taken before obidoxime and at 15 min intervals after obidoxime up to 2 hours then in hourly intervals up to 8 hours, thereafter thrice per day. When obidoxime was discontinued, plasma samples for evasion kinetics were sampled in 30-min intervals. The following parameters were recorded in each patient: plasma concentration of obidoxime (HPLC) and atropine (radioreceptor assay), red blood cell Ery-AChE-activity referred to the hemoglobin content, reactivatability of Ery-AChE, inhibitory activity of patient plasma towards test Ery-AChE, plasma ChE-activity and muscle function (recording of the compound muscle action potential of M. abductor digiti minimi after stimulation of the N. ulnaris). Atropine was administered on clinical demand with the only recommendation to favor low atropine dosing. In Sri Lanka, 1 g of 2-PAM was administered i.v. qds for about 24 h. Blood samples were obtained before 2-PAM, 1, 4 and 12 h after 2-PAM and during the next days up to one week. Patients did not receive gastric lavage but were randomized to single or multiple dose activated charcoal or no intervention. All patients received sufficient atropine to keep the chest clear, pupils > 1 mm, pulse rate > 80/min, BP > 80 mmHg systolic, and axillae dry. As in the German study, blood was diluted bedside 1:20 in ice-cold saline, mixed and kept frozen at -20°C. Plasma of EDTA-blood was spun off within 15 min and stored at -20°C. Samples in dry ice were shipped in monthly intervals and arrived the Munich laboratories with dry ice present; they were kept at -20°C until analysis. Duplicates stored in Sri Lanka for longer periods and shipped at a later occasion turned out to give the same results. Hence, samples appear to be stable for 3 months when kept at -20°C. Results: In the German study, 34 patients were treated for 65 ± 53h (min: 16 h, max: 270h) with 2.4 ± 1.7 g obidoxime (min: 750 mg, max: 8.9 g). Seven patients died on about day 20 (min: 8 days, max: 38 days) after intoxication. Five patients died because of severe aspiration of the oil- and solvent-containing vehicle leading to ARDS and sepsis (3 parathion, 1 oxydemethon-methyl, 1 phoxime), most of these patients needed resuscitation at the spot; one patient died immediately before being discharged as cured because of pulmonary embolism; one died because of a penetrating gastric ulcer followed by overt peritonitis. With the obidoxime regimen used, the targeted effective plasma concentration of about 10–20 μmol/l obidoxime could be adjusted. Obidoxime was able to reactivate non-aged AChE, if the poison load was not too high and ageing was not complete. Based on their cholinesterase status patients were allocated to five groups. Group A: no detectable AChE/BChE inhibition; Group B: clinically insignificant AChE inhibition or BChE inhibition only; Group C: significant AChE inhibition followed by sustained reactivation; Group D: significant AChE inhibition, initially reactivated sufficiently, but not sustained; Group E: significant AChE inhibition, but insufficient reactivation. Table 1 shows the results. It is obvious that patients intoxicated with diethylphosphoryl compounds (13 parathion, 1 phoxim) had a good chance of reactivation. Only in those cases where the poison load was extremely high (n = 3) was

Table 1.

Group	Characteristics	Diethylphosphoryl-OP number	Dimethylphosphoryl-OP number
A	No ChE inhibition	0	0
B	AChE $> 50\%$	0	1
C	AChE $< 20\% \Rightarrow > 30\%$	11	2
D	AChE $< 20\% \Rightarrow > 30\% \Rightarrow < 20\%$	2	5
E	AChE $< 20\% \Rightarrow < 20\%$	1	12

Table 2.

Group	Characteristics	Diethylphosphoryl-OP number	Dimethylphosphoryl-OP number
A	No ChE inhibition 18	Not meaningful	Not meaningful
B	AChE $>$ 50%	5	2
C	AChE $<$ 20% $\Rightarrow$ $>$ 30%	11	2
D	AChE $<$ 20% $\Rightarrow$ $>$ 30% $\Rightarrow$ $<$ 20%	4	1
E	AChE $<$ 20% $\Rightarrow$ $<$ 20%	3	12

net reactivation too weak to hinder gradual aging. In contrast, reactivation did not occur with most dimethylphosphoryl compounds (12 oxydemeton-methyl, 6 dimethoate, 1 malathion and 1 methamidophos), except for those cases with low poison load and early treatment. In patients with parathion/paraoxon poisoning a quantitative correlation could be established between Ery-AChE activity and paraoxon concentration in plasma. In these patients Ery-AChE activity increased when paraoxon plasma concentration decreased. Generally, muscle function was severely disturbed, when Ery-AChE-activity was below 10% of normal. With increasing Ery-AChE activity disturbance of muscle function subsided and clinical conditions improved. At Ery-AChE activity of more than 30% muscle function was hardly affected. The data also demonstrate muscle function recovery by AChE reactivation is the main mechanism of obidoxime's therapeutic effect. Thus, data on reactivation obtained with human Ery-AChE are helpful for prediction of oxime efficacy in man. In the Sri Lanka study 57 patients were analysed, of which 2 died (1 chlorpyrifos, 1 dimethoate). Table 2 shows the allocation of the patients according to the above criteria: Remarkably, the proportion of patients with no significant AChE inhibition was quite high since persons were brought to the hospital by their relatives whenever someone was suspected of having taken an OP insecticide. The composition of group C and E was very similar to the corresponding German groups. The proportion of intoxications with diethylphosphoryl compounds (chlorpyrifos, quinalphos, diazinon) in group D was higher in Sri Lanka compared to the German group. This is probably due to the much longer treatment with obidoxime in the latter group whereby re-inhibition after oxime discontinuation was prevented. Again, dimethylphosphoryl OP poisoning (mainly dimethoate and fenthion) responded poorly to oxime treatment. Conclusions: The results with both oxime regimens show that effective reactivation can be expected primarily with the diethylphosphoryl compounds. In this group, oximes should be administered as long as persisting poison is to be expected. In megadose poisoning and/or when the toxicant is eliminated slowly, oximes will not be able to prevent aging. In practice, oximes are less effective in most intoxications with dimethylphosphoryl compounds. Hence, proper evaluation of the value of oxime therapy requires knowledge of the type of OP involved. Ery-AChE determination appears to be a reliable surrogate parameter for quantitative assessment of oxime effectiveness; its determination near the ward should be propagated. This may be possible in the near future when reliably functioning and cheap instruments become available.

69. AMIFOSTINE PROTECTS AGAINST ACUTE SOMAN TOXICITY IN RATS

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Objective: Highly toxic organophosphorus insecticides and nerve warfare agents produce their toxicity through the "irreversible" inhibition of acetylcholinesterase (AChE) and subsequent cholinergic overstimulation. Atropine, as an antagonist of cholinergic muscarinic receptors, an oxime, as a reactivator of inhibited AChE and dizepam, as an anticonvulsant, represent optimal antidotal therapy in poisoning with anti-AChE compounds. Amifostine (WR-2721) is a well-known radio- and chemoprotective agent. Its cytoprotective action appears to be mediated mostly by scavenging free radicals. However, it also produces a number of pharmacological actions (1). Some of them (e.g., antimuscarinic and calcium channel blocking activity) might be useful in protection against anti-AChE agents toxicity. Accordingly, the aim of this study was to estimate protective efficacy of amifostine against the acute nerve warfare agent soman toxicity in rats as well as its influence on efficacy of standard antidotes for anti-AChE compounds poisoning. Methods: Adult male Wistar rats (180–220 g) were used in experiments. Amifostine (300 mg/kg *ip*) was given either 30 minutes before or

Treatment	Time of administration of amifostine	LD50 (μg/kg) (95% confidence)	Protective index (PI)
None (the control)	—	98.98 (90.56–108.19)	1
Amifostine	30 min before soman	150.45 (104.90–215.80)	1.52*
	Immediately after soman	150.45 (104.90–215.80)	1.52*
Standard antidotes	—	186.10 (117.80–293.00)	1.88*
Amifostine + standard antidotes	30 min before soman	237.60 (148.50–380.10)	2.40*
	Immediately after soman	237.60 (148.50–380.10)	2.40*

PI = LD-50 value of soman in protected animals/LD-50 value of soman in the control; *$p < 0.05$ *vs* control.

immediately after soman (*sc*). Standard antidotes: atropine (10 mg/kg *im*), oxime HI-6 (10 mg/kg *im*) and diazepam (2.5 mg/kg *im*) were given simultaneously always immediately after the poison. The protective efficacy of amifostine and its combination with standard antidotes was estimated through the acute LD-50 values of soman given alone or in the presence of amifostine and/or standard antidotes. Besides, the influence of amifostine on the AChE activity of the intact and poisoned rats was also studied. Results: The results demonstrated that amifostine, regardless of the time of administration in relation to that of soman, produced significant protective effect in poisoned animals and enhanced efficacy of standard antidotes, too (see Table 1). On the other hand, it had no influence on the activity of AChE. Conclusion: Our results imply a potential use of amifostine in protection against acute soman toxicity. References:
1. Milovanović SR, Dobrić S. The effect of aminophosphate WR-2721 on the isolated perfused heart and isolated uterus of the rat. In: Nygaard OF, Upton AC, editors. Anticarcinogenesis and radiation protection 2. New York: Plenum Press, 1991:303–10.

70. ACUTE ORGANOPHOSPHATE INSECTICIDE POISONING: ANTIDOTES AND INTENSIVE CARE MANAGEMENT

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Objective: Early diagnosis and appropriate treatment of acute organophosphate insecticide (OPI) poisoning is life saving. As the clinical course of OPI poisoning may be quite severe, intensive care management is generally recommended. Treatment consists of specific, symptomatic, and supportive measures. We report our experience with intensive care management of serious OPI poisoning. Methods: A retrospective study was performed of patients with OPI poisoning, treated in the ICU of the Clinic of Emergency and Clinical Toxicology and Pharamacology, during a one-year period. For all patients the diagnosis was confirmed by a combination of clinical symptoms and signs of poisoning, pesticides detected in biological material, and depressed serum and red blood cell acetylcholinesteraze activity level. After gastric lavage, in all patients, activated charcoal was administered and if they had depressed level of consciousness and/or signs of respiratory insufficiency, intubation and mechanical ventilation was done. Careful monitoring of vital functions, including ECG and arterial pressure, respiratory frequency and quality of breathing, and temperature was performed. Antidotal therapy given included high doses of atropine, pralidoxime mesilate, as acetylcholinesteraze reactivator, and diazepam with sodium bicarbonate solution for prevention of seizures. Results: Fifty-six patients were treated for OPI poisoning and 38 (67.8%) of them were women. In all but two cases, poisoning was intended suicide. The cause of poisoning was malation in 34 (60.7%), dimethoate in 9 (16.1%), and diazinon in 4 (7.2%) patients, while other OPI were represented with single cases. According to the Poisoning Severity Score (PSS), the most severe poisoning (PSS 3 and 4) were registered in 12 (35.2%) patients with malation, 3 (33%) dimetoat, 1 diazinon, vetiol, and parathion poisoning respectively. Intravenous atropine and pralidoxime (in 41% of patients) for severe poisoning were administered as soon as possible. The highest recorded dose of atropine was over 2173 g for a patient with severe malation poisoning, who also needed mechanical ventilation for 12 days. About 25% of patients required mechanical ventilation and the mortality rate for them was above 50%, while the mortality rate for the whole group of patients was 23.2%. Complications were observed in 30 patients including acute respiratory insufficiency (32.1%), cardiocirculatory

failure (23.2%), aspiration pneumonia (10.7%), acute renal insufficiency (10.7%), and convulsions (3.6%). Conclusion: OPI poisoning is often severe, so rapid diagnosis and intensive care management is necessary. Respiratory insufficiency is the major reason for mortality, but careful monitoring, administration of antidotes, and mechanical ventilation may decrease mortality rate among these patients. References: Ballantyne B. Clinical and Experimental Toxicology of organophosphates and carbamates. Butterworth Heinemann Ltd, Linacre House Jordan Hill, Oxford 1992.

71. THE FETAL EFFECTS OF ANTIDEPRESSANT OVERDOSE DURING PREGNANCY

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Objective: To assess the fetal effects of exposure to antidepressant overdose in pregnancy. The tricyclic antidepressants (TCA), especially amitriptyline and dothiepin when taken in overdose can cause severe maternal toxicity including arrythmias and fits that may result in secondary toxicity in the fetus. The serotonin reuptake inhibitors (SSRIs) are of lower toxicity, but there are few data on fetotoxicity. Method: Using standardized procedures, NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 160 women who took an antidepressant overdose during pregnancy. Results: The results are shown in Tables 1 and 2. Multidrug overdoses were taken by 58.8%; the main categories involved were analgesics 38% (paracetamol 61%), benzodiazepines 11%, and alcohol 11%. The majority (85%) of overdoses occurred in the first trimester with only 15 (9%) reports of any significant maternal toxicity. Outcome of pregnancy was similar in those exposed to either a TCA or an SSRI. Overall, there were 12 miscarriages, 28 elective terminations, and 120 liveborn infants including 9 with neonatal problems and 9 with malformations. No pattern of defects was observed. The majority (92.5%) of liveborn infants were normal. Conclusion: The incidence of miscarriages (7.5% Vs 10–20%) and terminations (17.5% Vs 23%) is lower than expected. However, the incidence of malformations is higher than expected (9/120 = 7.5% Vs 2–3% expected), but no pattern of malformations was seen, and it is based on small numbers. No causal relationship could be established. In the majority of women who receive appropriate treatment at the time of the overdose the outcome of pregnancy is a normal baby.

Table 1. Outcome of pregnancy following TCA overdose.

Total number of overdoses (multi-drug)	Liveborn infants			Termination of pregnancy	
	Normal	Congenital anomalies	Neonatal problems	Miscarriage	Elective termination
Amitriptyline 20 (7)	15		3		2
Clomipramine 7 (4)	7				
Dothiepin 31 (20)	17	4		3	7
Imipramine 6 (4)	5			1	
Lofepramine 11 (6)	7	1		2	1
Mianserin 5 (3)	2				3
Total 80 (44)	53	5	3	6	13

Table 2. Outcome of pregnancy following SSRI-related overdose.

Total number of overdoses (multi-drug)	Liveborn infants			Termination of pregnancy	
	Normal	Congenital anomalies	Neonatal problems	Miscarriage	Elective termination
Citalopram 4 (2)	1		2		1
Fluoxetine 36 (20)	24	2	3	2	5
Paroxetine 22 (15)	14		1	1	6
Sertraline 9 (6)	6	1		1	1
Venlafaxine 9 (7)	4	1		2	2
Total 80 (50)	49	4	6	6	15

72. CHANGES IN THE APPROACH TO CHILDHOOD POISONING, 1993–2001. A MULTICENTER EXPERIENCE

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Objective: To describe changes in the approach to managing cases of childhood poisoning referred to the Emergency Room (ER) of Trieste, Genova and Padova Children's Hospitals in 2001 as compared to 1993. Methods: All referrals to the ER were prospectively registered in 1993 and 2001 as a part of national multicenter studies. Information stored in the database included epidemiological characteristics and clinical decisions. Severity was assessed according to MSPC score (*J Toxicol Clin Toxicol* 1995;**33**:223–31). For the present study, the 1993 and 2001 databases were reviewed. Statistical analysis included chi-square tests and multivariable logistic regression. Results: 306 subjects under 18 years were registered in 2001, 434 in 1993. Mean age increased from 2.8 in 1993 to 3.4 years in 2001 (p NS) with a significant decline in subjects aged 1–4 from 77.8 in 1993 to 65.2% in 2001 ($p = 0.004$). Slight changes in the substances implicated were observed with an increase in exposures to alcohol ($p = 0.054$) and cardiovascular drugs ($p = 0.021$), and decrease in caustic substances ($p = 0.014$). There was no difference in clinical outcome. Unconfirmed poisonings were 22.3 and 22.9%, asymptomatic treated cases were 50.5 and 47.1% in 1993 and 2001, respectively. Occurrence of symptoms increased from 27.2% in 1993 to 30.4% in 2001, without differences in severity. No deaths occurred. Significant differences were observed in decision making and treatment (see Table 1).

Table 1.

Decision making	1993	2001	p
Direct discharge	206 (47.5%)	76 (24.9%)	
Short observation	38 (8.7%)	141 (46.3%)	<0.0001
Hospital admission	190 (43.8%)	88 (28.8%)	
Treatment			
Activated charcoal	115 (27.6%)	110 (35.9%)	0.0173
Gastric lavage	33 (7.9%)	13 (4.2%)	0.0452
Ipecac emesis	65 (15.6%)	21 (6.9%)	0.0003
No. of cases	434	305	

In 2001 both direct discharge from ER and hospital admission decreased significantly because of the increase in short observation. The decision not to treat was made in 34.3% of the cases in 1993, 31.4% in 2001 ($p = 0.2126$). Use of antidotes increased from 3.6% to 5.2% ($p = 0.2877$). Gastrointestinal decontamination was carried out mainly by activated charcoal with decrease in use of gastric lavage and ipecac emesis in 2001 as compared to 1993. Moreover no case was treated by catharsis in 2001 as compared to 12 patients in 1993. Conclusions: The study points out significant changes and improvement in treatment and decision making in childhood poisoning in the more recent period. Supported by grant N9R/CM Istituto Superiore di Sanità, Roma.

73. TOXICOLOGICAL CRITERIA FOR THE SELECTION OF NON-RECLOSABLE CHILD-RESISTANT PACKAGES FOR PHARMACEUTICALS

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Objective: British and German standards for non-reclosable child-resistant packaging for drugs stipulate that packs should prevent children accessing more than 8 dose units. This paper assesses information available for 13 drugs on paediatric toxic dose and the risk from 8 units of solid-dose formulations, to test the feasibility of developing guidelines for selecting child-resistant packaging according to drug toxicity (described in a subsequent paper). Methods: Published literature, including American Association of Poisons Control Centres' annual reports, and National Poisons Information

Service (NPIS (London)) case files, were searched for reports of accidental ingestion of 13 drugs in solid formulations without co-ingested substances, by children aged 0–5 years, including estimated dose, clinical effects and outcome. The Poisons Severity Score (PSS) was applied to each case. These were compared with epidemiological data obtained from the NPIS (London), the UK Department of Trade and Industry's Home Accident Surveillance System (HASS), and mortality statistics for England and Wales. Results: For dothiepin and carbamazepine 13, and 9 reports, respectively, were found of children with serious poisoning (PSS 3 or 4), and 6 each for methadone and nifedipine. For each drug over half of these cases were reportedly due to 8 dose units or less. However most serious poisonings due to Lomotil® (diphenoxylate/atropine), quinine, and imipramine involved more than 8 dose units. There were only isolated reports of serious childhood poisoning from atenolol, propranolol, amoxapine, dapsone and hyoscine, and none for temazepam. UK mortality statistics included childhood fatalities implicating methadone, quinine, dothiepin, Lomotil,® imipramine, and amoxapine but none implicating the other seven drugs. In solid-dose formulations, dothiepin, temazepam and carbamazepine were more frequently recorded by HASS as a cause of admission to hospital from emergency departments than were the other 10 drugs. Conclusion: Serious poisoning was reported from less than 8 dose units of all drugs studied except dapsone and temazepam, but for only dothiepin, carbamazepine, methadone and nifedipine were there more than five case reports. Thus there is evidence that packaging allowing children access to 8 dose units would be an insufficiently effective preventive measure for these drugs. However, the evidence is limited, and although well-documented case reports provide key data for determining toxic dose, for most drugs additional measures of drug safety would need to be considered when determining the kind of packaging required. Reference: Tomlin S, Bara V, Bates N et al. Guidelines for predicting toxic doses of pharmaceuticals in children. (Submitted to EAPCCT Rome).

74. HEALTH RISKS OF OTC PREPARATIONS CONTAINING EPHEDRA

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Introduction: In 1998 we conducted a survey of "over-the-counter" (OTC) herbal products sold in "smartshops" in The Netherlands. One product category that seemed to be a potential health hazard was the energizers, especially those containing ephedra extracts. These preparations are mostly sold for the purpose of weight loss, bodybuilding, and enhancing stamina (partyscene, truckdrivers). Ephedra species are a group of plants containing efedrine-like alkaloids. The pure alkaloids, for example ephedrine and pseudoephedrine, are subscription drugs used mainly as bronchodilators and antihypotensive drugs and can only be obtained by presciption from a medical professional. The ephedra alkaloids are sympathicomimetics and in overdose they can cause serious health problems such as restlessness, agitation, tachycardia, hypertension, seizures, cardiac arrhythmias, cerebral hemorrhage and ischemia. The data presented here raises questions on the safety of these products. Methods: The number of inquiries about ephedra containing OTC preparations in the database of the Dutch National Poisons Information Centre was analyzed. Following the results of our survey, the Inspectorate of Public Health Protection decided to have a closer look at the ephedra products. During quality inspections in smartshops and manufactorier, they collected 202 samples. The Laboratory for the Quality Control of Medicines, part of our institute, analyzed the samples using TLC and HPLC-DAD techniques. Results: The number of calls to our Poison Centre about ephedra containing products increased from an occasional question in 1998 to about 43 in 2002. In the last year most questions concerned so called herbal ecstasies (capsules/tablets containing a combination of herbs supposedly imitating the effects of MDMA) and weightloss preparations often under the name of "stacker." Of the analyzed samples 77% contained more than the FDA standard of 8 mg per dose (vm.cfsan.fda.gov) for ephedra-containing products, 15% even contained more than 50 mg per dose. The highest reported content was 75.5 mg alkaloids per capsule with a recommended use on the label of three capsules per day. Besides ephedra 39% of the samples contained other stimulants, mostly caffeine. Discussion: The pharmacological activity of the constituents of the group of ephedra alkaloids as a whole is very similar. Hence for the purpose of risk assessment it seems reasonable to relate the total ephedra alkaloid content of OTC products to the therapeutic dose, which ranges from 12.5–50 mg for the treatment of bronchospasm. Two important risk factors need to be considered: 1. Combination of ephedra alkaloids with other stimulants can increase the adverse effects. 2. Improper use, caused by lack of proper user instructions on the label or by disregarding them. The intended users may consider overdosing in order to get better results more quickly. Even with

the fairly high limit of 50 mg per dose for OTC products, 15% of the analyzed samples exceed this limit. Health risks caused by overdosing with OTC ephedra containing preparations are evidently present and should not be underestimated.

75. COLONIAL ANSWERING SERVICE

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Objective/Introduction: In the latter half of 2002 the New Zealand National Poisons Centre (NZNPC) experienced an acute staffing shortage and approached the London center of the UK National Poisons Information Service (NPISL) for help handling calls from 23:30 to 07:30 New Zealand (NZ) time. The NPISL was chosen primarily because the 12h time difference allowed good coverage from London poisons information specialists and their associated clinicians. Method: Prior to this operation NZNPC provided NPISL with NZ formularies, pharmaceutical schedules, medicines guide, access to TOXINZ (the NZ internet poisons database), and contact details for NZ hospitals. Additionally an analysis of recent night calls received by the NZNPC was sent. This allowed NPISL to develop a standard operating procedure for handling enquiries and case referral, for mutual approval. From 29/7/02 night callers to the NZNPC received a recorded message advising their call would be diverted to London free of charge, before automatic transfer to a dedicated number at NPISL. For one week a pilot parallel service ran with calls directed to London but with NZNPC staff present at their center to help if required. From 5/8/02 NPISL handled enquiries unaided until 30/11/02. NPISL completed reports for all calls, submitting electronic copies promptly to NZNPC for audit and medico-legal purposes. Results: Call data from 29/7/02 to 31/10/02 inclusive are presented. 182 calls were transferred representing 2.9% of the NZNPC calls and 0.8% of the NPISL calls for the period. Calls were most frequently received in the first and last hours of each session. Most enquiries originated from the public (65.4%), or from medical personnel (35.2%). 99 enquiries concerned adults and 69 involved children. Seven hoax calls were taken. 95 enquiries concerned pharmaceuticals, for which 32 adults and 6 children required medical intervention. Household agents accounted for 55 enquiries—12 requiring intervention. Conclusions: Successful transfer of call-handling operations across continents occurs in other industries. We believe this is the first such calls between poisons centers. Although rare, occasional difficulties were encountered. These were sometimes linguistic or stemmed from NPISL unfamiliarity with NZ products, or from variations in management protocols between centers. Operational differences between centers concerned some NPISL staff who, unlike NZNPC staff, do not routinely answer medicines information enquiries or public enquiries. The hoax callers proved particularly troublesome. The operation was considered successful and mutually beneficial. We believe similar systems could be planned between sufficiently similar centers globally as a fallback security measure for implementation in times of emergency.

76. RELATION BETWEEN INITIAL RISK ASSESSMENT AND OUTCOME IN EXPOSURES TO NON-DRUG AGENTS

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Objective: As part of the quality assurance at the Danish Poison Centre, risk assessments done at the time of inquiry have been evaluated relative to outcome. Methods: A formalized risk assessment is routinely performed at the time of inquiry-in order to guide the advice given. The categories applied correspond to a modified poisoning severity score permitting a direct comparison of the prognostic risk assessment and outcome: 1) No risk. 2) Risk of minor and spontaneously transient symptoms (minor). 3) Risk of poisoning needing medical attention (manifest). 4) Risk of severe/life-threatening poisoning (severe). 5) Undetermined risk. Follow-up through hospital discharge records has been attempted for cases with a risk assessment indicating a clinically significant or more severe poisoning. Additional cases are followedup when judged relevant. Available hospital records have been used to evaluate outcome according to the poisoning severity scores. This assessment was blinded with respect to the initial risk assessment. Results: The poison

Table 1. Relation between risk assessment and outcome in cases with exposure to non-drug agents. Cells with corresponding risk and outcome and with estimated risk one level more severe than outcome are marked.

	Outcome					
Risk	No poisoning	Minor	Manifest	Severe	Death	All
Minor	1	12	3			16
Manifest	14	32	10			56
Severe	4	1	5	2	1	13
Unknown	7	4	1			12
All	26	49	19	2	1	97

center received a total of 2444 inquiries about non-drug poisonings in 2000. Follow-up was requested for 197 (8%) and succeeded for 101 (4%) cases. Matching risk assessment and outcome score was available for 97 (4%) of the cases. The relation between risk assessment and outcome is shown in the table. In the present study 3 cases had outcome more severe than the initial risk assessment. For 69 cases the relation was opposite-outcomes were more benign than risk assessment. Conclusions: Within this limited dataset the majority of inquiries had an outcome matching or less severe than the initial risk assessment. However 3 of 97 cases had more severe poisoning than predicted by the poison center. The method with comparison between a formalized risk assessment and outcome can be used as an easily applied tool for quality assurance of a core element in poison centers activity. An objective could be that no cases should have a more severe outcome than expected. If costs and risks associated with treatment should also be considered, an attempt to avoid risk assessments that exaggerates risk more than one level relative to outcome.

77. VALIDATION OF POISON CENTER PROTOCOLS AND GUIDELINES

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Objective and Background: This keynote presentation will review a validation process for protocols and clinical guidelines used in the telephone management of childhood poisonings in a poison center. Since 1997, the California Poison Control System (CPCS) has developed and utilized over 800 protocols and clinical guidelines that range from the identification of non-toxic products to clinical guidelines for the management of hospitalized symptomatic patients. The protocols and guidelines were developed through a process of reviewing and codifying standard practices, literature searches, pilot testing, and approval through a consensus process. Our current objective is to analyze our protocols and guidelines for pediatric ingestions and to determine their validity by a review and surveillance of medical outcomes from internal (poison center case records) and external (literature search) sources linked to substance-specific protocols and guidelines. The initial set of protocols analyzed included the "non-toxics," which were deemed as valid if they were not associated with a significant clinical outcome. A significant outcome was defined as an outcome that exceeded a "minor effect" or symptoms were more severe than self-limiting gastrointestinal irritation. The second set analyzed were the "send-in guidelines" or ingested dose thresholds for referral of patients to hospitals. The additional objective for this analysis was to identify determinants for triage patterns and utilize the results to guide future decisions for send-in guideline thresholds. Our intent was to implement an ongoing and efficient comprehensive surveillance net to identify outcomes associated with substances included in our set of guidelines and protocols as a means for consistent operational validation. Methods: A cross-sectional analysis was performed on computerized case charts of the CPCS for the calendar year 2001 that involved children less than 6 years of age. A search strategy was developed to link poison center cases to a protocol or clinical guideline. The analysis of "non-toxic" protocols involved grouping of cases by substance listed as a non-toxic and tabulation by outcome. This was coupled with a systematic literature search of 50 databases and Web sites seeking citations associated with childhood poisonings and hospitalization or deaths over the time period of 1997–2002, coincidental with the time period of utilization of the "non-toxic" protocols. We used acetaminophen as the prototypical substance to establish a process for analysis for our send-in guidelines. Our pediatric acetaminophen send-in guideline uses an ingestion threshold of 200 mg/kg or more for referral to a hospital. These cases were ranked by the amount of

acetaminophen ingested and stratified by patient flow (managed on site, referred to a health care facility, en-route to or at a health care facility). A secondary case review by poison center directors was employed for all cases with significant outcomes to ensure proper coding and causation analysis. Results: We identified 20,517 cases associated with 46 "non-toxic" protocols. There were an additional 68 "non-toxic" protocols for which a sensitive and specific computerized search strategy to retrieve protocol-related cases could not be achieved and were excluded from the analysis. For the cases identified, there were no outcomes coded as major effect or death. We found 9 cases coded with an outcome of "moderate effect," but a secondary review of the case notes revealed that 8 of these cases involved other substances (not part of the "non-toxic" protocols), and most had been inadvertently identified by our search codes for generic substances (e.g., Lye-containing crème relaxers were captured under cases listed for the "non-toxic" protocol, "Hair Conditioners"). There were only 6 cases found involving substances in the "non-toxic" protocols that were associated with an outcome of "potentially toxic effect," but all of these were lost to follow-up. Of note, 2 involved potential hypersensitivity reactions, 2 were cases with potential pulmonary aspiration, and 1 was a possible foreign body obstruction. A minor effect was coded in 334 cases. The systematic literature search, when limited to ingestions by children, unveiled 2,326 citations, of which 23 described a potential toxic effect from ingestion of one of our "non-toxic" protocol-related substances, but none of these described an outcome of death or hospitalization. Several of these citations were from non-traditional literature sources, such as newspapers and government rules, regulations and recalls. We identified 2,341 cases of pediatric acetaminophen ingestions. Of these, 1951(83.3%) were managed at home. Of 384 patients referred to or managed in a hospital, only 32 had ingestion amounts documented that exceeded the send-in threshold. Most referrals to hospitals were based on uncertainty of the amounts ingested by the patients. None of the patients had a documented toxic acetaminophen level. Conclusion: Our analysis provided validation for 46 "non-toxic" protocols. However, use of the term "non-toxic" in the protocol may bias the assessment, management, and triage of poisoning cases by poison center staff. A commonly utilized "Outcome" code for these exposures was "Judged as Nontoxic," which does not require a follow-up call to confirm ultimate outcome. Furthermore, ingestions of a few substances categorized as "non-toxic" resulted in clinical effects with varied severity, from mild gastrointestinal irritation to airway obstruction and hypersensitivity reactions. Our literature search located cases involving apparently "non-toxic" substances with the potential for toxicity (e.g., asbestos in crayons) foreign body and aspiration risk (e.g., aspiration of an ink pen). We suggest that alternative terminology be considered such as "minimally toxic" or "non-harmful" or "foreign body or aspiration risk" to reflect this small but not insignificant risk. Our difficulty with devising sensitive and specific search strategies to capture protocol-relevant cases highlights the need for an a priori link between the poison center case data collection system and protocols and guidelines. Furthermore, primarily due to miscoding, there should be a secondary review of the details of subsets of poison center cases with potentially significant and either unknown or deemed unrelated outcomes to verify outcomes from aggregate poison center data. For substances covered by send-in guidelines (i.e., acetaminophen), the ability to rank cases by ingestion amounts and stratify by patient flow, facilitates the assessment of determinants for staff triage decisions and compliance, and the potential impact of adjusting send-in thresholds. Notably, very few pediatric acetaminophen ingestions exceeded our send-in threshold of 200 mg/kg and if we were able to obtain more precise ingestion histories, our triage patterns for these ingestions could be further impacted. We feel that there is utility in prospective and periodic follow-up for a sample of protocol- and guideline-relevant cases, as well as continued surveillance of non-poison center databases and literature with a systematic search strategy, as keys to a validation process for poison center protocols and guidelines.

78. TRAINING METHODS TO IMPROVE POISON INFORMATION SERVICE

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Introduction: The demands made on poison centers in terms of accessibility, service continuity, and quality of information are increasing. A full 24-h telephone service is required and information must be provided instantly by adequately trained staff supported by clinical toxicologists. Queue lines, if occurring, should be as short as possible. Background documentation must be up to date. Additional demands are significant: patient follow-up, scientific research, and toxicoepidemiological studies should be carried out and published. More emphasis needs to be put on toxicovigilance and prevention of poisoning. The expansion of information sources must be faced with regard to

collecting and assessing data, as well as disseminating information to the customers of the poison information service. Furthermore, in this context medico-legal aspects are very important. The problem: Contrary to the often quoted statement that poison centers are a cost-effective part of health care systems, the centers themselves are frequently threatened by financial problems. How can poison centers deal with all above mentioned demands and challenges and handle, for instance, an increase in telephone calls without additional funding for extra staff? A contribution to a solution: Increasing the efficiency of poison centers infrastructure is of great value in solving a part of this problem. Within the individual poison center we should look for possibilities to deploy our staff and equipment more efficiently. Sometimes special equipment can be used as training tools, for instance voice recording systems of telephone inquiries and telephone management systems. Because of the possibility to reproduce the poison information provided and because of medico-legal aspects the Dutch Poisons Information Centre has voice recordings of all inquiries. Although these recordings contain confidential information, these recordings can be used for training purposes as all information specialists are bound by a duty of professional confidentiality. We have developed a training programme in which all 12 information specialists, their co-ordinator and a clinical toxicologist participate. In two-monthly 2h sessions several recordings are overheard. In each session emphasis is put on the efficient delivery of poison information and in addition specific items are trained as, for example, asking the relevant questions in order to explore the extent of the problem more effectively or, how to inform the customer adequately within a shorter time frame. The recordings are either chosen at random by the coordinator, or brought forward by the staff members themselves. All participants freely comment on the recordings with emphasis on constructive criticism. Nowadays these sessions are highly appreciated by all, but do these sessions contribute to diminishing the number of unanswered calls and in the duration of telephone calls? This is checked by using our telephone management system (Callscan) which records the duration of every telephone call as well as the number and duration of queue lines. We perform monthly overviews of the number of calls (about 3000 calls a month), but can also monitor the calls on an individual basis. Individual monitoring gives the opportunity to adjust the training program to individual needs in order to improve the quality of information service as well as to decrease the time involved in handling a telephone call. By doing so and overhearing the various recordings, it is our experience that in a much shorter training period than before, we have information specialists answering the calls who are tuned on the job. Conclusion: With the above mentioned approach, trained staff members are able to handle the inquiries more efficiently and have significantly shorter queue lines. The spin-off of this registration system is that a good foundation of arguments is provided for an extra staff claim when further efficiency gain is impossible.

79. A MULTI-CENTER FEASIBILITY STUDY FOR COLLECTING INFORMATION FROM POISONS CENTERS FOR RISK ASSESSMENT PURPOSES

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Objective: Few attempts have been made to use the information collected by poisons centers to help assign priorities for risk assessment work, to prevent unnecessary animal testing or to inform the risk assessment community about emerging concerns. As a first step to bridging this gap a multi-center feasibility study has been carried with seven poisons centers. The objective of the feasibility study was to find out whether poisons centers could identify reports of human exposure involving chemicals which have been concluded internationally as needing further assessment to protect human health. Methods: The six chemicals studied were: Ethylene Glycol (CAS No. 107-2-11), Methyl acetate (CAS No 79-20-9), Methyl methacrylate (CAS No 80-62-6); Cyclohexane (CAS No. 110-82-7); 2-(2-methoxyethoxy) ethanol (CAS No. 111-77-3); Hydrogen fluoride (CAS No. 7664-39-3) and Hydrogen cyanide (CAS No. 74-908). The poisons centers were asked to report on: the availability of information on the selected chemicals; the nature and extent of information available; how the information on each of the chemicals had been obtained. In addition they were asked whether risk assessment reports produced by the regulatory community were of use to clinical toxicologists and poisons centers. Finally they were asked about how chemicals rich in human data might be identified and characterized for future use in improving the methodological basis of risk assessment work e.g., to reduce the uncertainty of extrapolating from animal

toxicity data. Results: Almost 2000 reports involving the chemicals were identified. This showed that poisons centers are able to identify cases of specific chemical poisoning from their records, and that these have the potential to add to the information available to the risk assessor. The largest number of reports were retrieved for ethylene glycol (over 1000 reports) and the least for cyclohexane (16 reports). Only three centers reported cases with all six chemicals, showing the value in aggregating data from different centers. Chemicals commonly marketed in products proved the most difficult to identify. Incomplete information concerning product composition was a concern. The type of information available from the poisons centers varied greatly depending on the chemical and the type of poisons center involved. Poison centers found the international risk assessment reports of potential use but a little too detailed for emergency use. Sometimes the reports were found to be incomplete while in other cases the practical experience gained by clinicians provided a more solid basis for recommendations on first aid and safety directions. Conclusion: In light of continuing concern about gaps in basic information on the effects of chemicals on human health and the environment, poisons centers are in a unique position to monitor the pattern, incidence and severity of exposures to chemicals and to detect new trends and emerging patterns in human toxicology. Continued dialogue and joint projects are needed between the risk assessment and poison center community.

80. USING POISON INFORMATION CENTER DATA TO CONDUCT RESEARCH

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Linking the terms *poison information center data* and *research* are viewed by some as an oxymoron. The contention has been made repeatedly that poison information center data do not withstand scientific rigor and therefore, should not be the basis for research. The criticisms of poison center data focus on reliability and include, but are not limited to the failure to confirm the implicated poison through laboratory testing; reliance upon second-party observers to identify the poison and the quantity the victim was exposed to; the failure to determine the actual time of the exposure; reliability of reporting and assessment of symptoms by the lay public; the possibility that no exposure occurred; using retrospective data; poison center data are not inclusive of all poisonings (the denominator is unknown and true rates of exposure cannot be determined); poison center data represent passive surveillance; reporting bias; documentation and coding inaccuracies; the failure to determine the final patient outcome. Since one of the missions of the poison information center is to reduce unnecessary referrals to health care facilities and to manage exposures that are associated with low morbidity at the site of the exposure (e.g., home, work), these issues will never be resolved. While the criticisms of poison information center data are valid, do they negate the value of data derived from poison information center medical records? Clearly, research involving poison information center data is not classical bench science, but the same can be said about much of the clinical toxicology research that has been published and directs contemporary management of the poisoned patient. Understanding the limitations of poison information center data is the key to using it properly. Reliance on randomly collected patient information creates data voids that result in the collection of incomplete information and often the disqualification of many case records from data analysis. The development of well-designed prospective studies that capture essential information is the foundation of conducting robust research on poison information data and eliminating one of the major pitfalls of poison information center data research. This approach pertains to calls from the general public as well as those from health care professionals who are managing hospitalized patients. For example, the introduction of a newly approved prescription medication often presents a challenge to poison information center staff since little clinical toxicology information is available from clinical trials. The prospective collection of additional information such as blood concentrations, patient demographics, dosage, symptoms, laboratory values and outcome can help to characterize the clinical toxicology of the new medication and help to direct the management of future patients. The use of special templates in the electronic medical record system facilitates this process and reduces the incidence of documentation omissions, inaccuracies and coding errors—major criticisms of poison information center data research. Retrospective analysis of poison information center data should not be relegated to the status of being without value. An important application of retrospective data research is the use of poison information center medical records to data-mine for rare problems that cannot be studied prospectively. Furthermore, poison information center data can be used to characterize the toxicity profiles and outcomes from common exposures such as those involving analgesics, plants and household cleaning products—exposures where tens of thousands of medical records exist, thereby minimizing some of the limitations of poison information center data. Daily surveillance and retrospective analysis of drug identification

calls can help to identify substance abuse trends. Analysis of poison information data may identify adverse drug reactions that may otherwise take a longer period of time to identify. Understanding the limitations of poison information center data and maximizing the utilization of key elements of the poison information center patient medical record are critical to conducting successful research on poison information center data.

81. THE ROLE OF OXIMES IN THE TREATMENT OF NERVE AGENT POISONING IN CIVILIAN CASUALTIES

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Introduction: An important difference between on-target military attacks against relatively well-protected armed forces and nerve agent attacks initiated by terrorists against a relatively unprotected civilian population is the time after exposure when specific therapy is first administered. In a civilian context, even conservative estimates hint at a delay between symptomatic exposure and the first administration of atropine/oxime of 10–20 minutes. In the worst case scenarios this time delay may be in excess of 30 minutes. In addition, the question of which oxime to use to treat civilian casualties from nerve agent poisoning is an area of some controversy and international disagreement. The choice in current clinical practice is between the monopyridinium pralidoxime salts (chloride, iodide, mesilate [methanesulphonate; P2S] and methylsulphate), and the bis-pyridinium oxime, obidoxime, though the role of Hagedorn oximes, HI-6 (asoxime dichloride and dimethanesulfonate) and Hlö-7, will also be reviewed. Interpretation of experimental studies: Studies on the treatment of nerve agent poisoning have to be interpreted with caution for several reasons. Antidotal studies in animals have to be designed with great care or they may demonstrate the efficacy of antidotes in circumstances where they could not reasonably be used clinically. Thus, some studies have used prophylactic protocols, whereas the drugs concerned (atropine, oxime, diazepam) would only be given to a civilian population *after* exposure. The experimental use of pyridostigmine before nerve agent exposure, though rational, is not of relevance in the civilian context. Hence, these studies are difficult to interpret in relation to post-exposure treatment. Even those experimental studies in which antidotes have been administered after nerve agent dosing are not beyond reproach. In many studies antidotes were administered within a few minutes of, or even immediately after, exposure. Species differences and the importance of "aging": It has been assumed generally that monkeys would make a reasonable model for humans and it has also been suggested that guinea-pigs are good models for humans.[1,2] This was on the basis of similarity of protection ratios achieved for the treatment of soman-poisoned rhesus monkeys with atropine and oxime as compared with similarly poisoned and treated guinea pigs. However, these data on rhesus monkeys were not published in full and we have not been able to obtain the original data. There are major differences between the "aging" $t_{\frac{1}{2}}$ for soman-inhibited acetylcholinesterase (AChE) in primates (mean 0.88 − 1.4 min)[3] and man (1.3 min)[4] and in rodents (mean 7.6–8.6 min).[3] The rate of formation of "aged" enzyme in different species increases in the order: mouse $\ll$ rat $<$ guinea pig $<$ rabbit $<$ dog $<$ cattle $<$ monkey $=$ man.[3] This suggests that the guinea pig would not be a good model, even in soman poisoning. In vitro studies on human erythrocyte AChE have employed measures to prevent aging of the soman-inhibited complex. In vivo studies in rodents have employed protocols in which treatment was given before substantial aging would have occurred. Neither approach can be used to predict successful reactivation of the aged soman-inhibited complex. Hence, the results of such studies probably have little relevance to the management of human soman poisoning. It is probable that the claim that HI-6 can reactivate soman-inhibited enzyme only applies to unaged enzyme and there is no unequivocal evidence of reactivation of aged soman-inhibited AChE by any oxime in any species in vivo. However, other pharmacological effects of some oximes (i.e., those not mediated by cholinesterase reactivation), such as have been reported in the case of HI-6, may be important once aging of the agentenzyme complex is established, and therefore HI-6 may have some advantage in soman poisoning, though this is to be confirmed. Impact of a delay in administration of oxime: In experimental studies,[5] a delay of even 12 minutes in the administration of oximes reduced the protection ratio (LD_{50} with treatment/LD_{50} without treatment) substantially and it is therefore important that oximes are administered as soon as possible after exposure, even in the case of nerve agents other than soman. Which oxime should be employed? With the possible exception of the treatment of GF and soman poisoning, when HI-6 might be preferred, a review of available experimental evidence suggests that there are no clinically important differences between pralidoxime, obidoxime and HI-6 in the treatment of nerve agent poisoning, if studies employing pretreatment with pyridostigmine are excluded. Treatment of nerve agent poisoning outside hospital: Arrangements need to be in place to ensure that civilian casualties receive antidotal treatment

as soon as possible after exposure. This is of particular importance in the case of soman poisoning, as aging of the somanenzyme complex occurs very rapidly. Civilian casualties who have been exposed to nerve agents and who have developed rhinorrhea and bronchorrhea should be administered atropine as a matter of urgency. It is also recommended that the casualties should receive immediately whichever oxime is available, as it is very unlikely that the identity of the nerve agent will be known before the admission of casualties to hospital. This can be done most conveniently by the administration of the contents of an autoinjector, such as the ComboPen (the UK version contains atropine 2 mg, pralidoxime mesilate 500 mg and avizafone 10 mg) intramuscularly. Severely intoxicated casualties may require the administration of the contents of up to three ComboPens at 5–10 min intervals prior to admission to hospital. Casualties who do not develop the features of systemic toxicity, notably rhinorrhea and bronchorrhea, should be triaged but not given atropine and/or oxime. Treatment of nerve agent poisoning in hospital: If rhinorrhoea or bronchorrhea develops, atropine 2 mg in an adult (20 μg/kg in a child) should be administered intravenously every 5–10 minutes until secretions are minimal and the patient is atropinized (dry skin and sinus tachycardia). An oxime, such as pralidoxime chloride or mesilate, should be administered in a dose of 30 mg/kg body weight intravenously every 4–6h to patients with systemic features and who require atropine. Alternatively, an infusion of pralidoxime 8–10 mg/kg/hr may be administered, the infusion rate depending on severity. In the case of GF and soman poisoning, consideration should be given to the use of HI-6, if supplies are available. The duration of oxime treatment will depend on the presence of features, the clinical response, and the erythrocyte AChE activity. It is recommended that the oxime should be administered for as long as atropine is indicated. For the majority of individuals this will be for less than 48h; the exception would be individuals exposed dermally to VX where a depot of VX might result in prolonged intoxication. References: [1]Inns RH, Leadbeater L. The efficacy of bispyridinium derivatives in the treatment of organophosphonate poisoning in the guinea-pig. *J Pharm Pharmacol* 1983;**35**:427–33. [2]Leadbeater L, Inns RH, Rylands JM. Treatment of poisoning by soman. *Fundam Appl Toxicol* 1985;**5**:S225–S231.[3] Talbot BG, Anderson DR, Harris LW, Yarbrough LW, Lennox WJ. A comparison of in vivo and in vitro rates of aging of soman-inhibited erythrocyte acetylcholinesterase in different animal species. *Drug Chem Toxicol* 1988;**11**:289–305.[4] Harris LW, Heyl WC, Stitcher DL, Broomfield CA. Effects of 1,1′-oxydimethylene bis-(4-tert-butylpyridinium chloride) (SAD-128) and decamethonium on reactivation of soman- and sarin-inhibited cholinesterase by oximes. *Biochem Pharmacol* 1978;**27**:757–61. [5]Green DM, Inns RH, Leadbeater L. Unpublished observations on the consequences of delaying oxime administration.

82. ATROPINE THERAPY IN ORGANOPHOSPHATE INTOXICATION

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Objective: Overview of the use of atropine in the therapy of organophosphate (OP) intoxication. Introduction: Atropine, as a constituent of Atropa belladona, was used by women in ancient Greece to enlarge their pupils. In medieval Europe it is believed to have been one of the main ingredients of hallucinogenic brews. After the second world war, when nerve gasses based on OP compounds were developed. Atropine was used as an effective antidote for intoxication with OP insecticides or nerve gasses. The mechanism of the OP intoxication is based on the inhibition of acetylcholinesterase, leading to an abnormal accumulation of acetylcholine in the tissues. This causes symptoms of dysregulation of the autonomic nervous system. The signs and symptoms in organic phosphate intoxication usually appear in the following order: nausea, headache, vomiting, dizziness, weakness, sweating, abdominal cramps and diarrhoea, miosis, dim or blurred vision, muscle twitching, incoordination, slurred speech, confusion, oro-nasal frothing, excessive respiratory mucus, bronchospasm, difficulty in breathing, stupor, incontinence, random jerky movements, increasing respiratory failure, cyanosis, bradycardia, hypotension, convulsions, coma, death. Atropine: Atropine is a racemic mixture of d- and l-hyoscyamine. It is an organic ester. Both isomers bind to muscarinic receptors, but l-hyoscyamine is the pharmacological active isomer. Atropine is a muscarinic receptor antagonist that prevents the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors. These receptors are mainly located on the parasympathetic, postganglionic fibers on effector organs. The most important clinical effects of atropine in OP poisoning are the reduction of the excessive tracheo-bronchial secretions, to make either respiratory support or mechanical ventilation possible and to treat bradycardia, hypotension and convulsions. No good correlation between plasma levels and maximal pharmacological effect after intravenous injections of atropine is present, so the dosage is best titrated on the basis of clinical effects. Since atropine does not have an influence on the nicotinic acetylcholine receptors, ventilatory muscle

weakness remains and respiratory support is still needed. Atropine crosses the blood–brain-barrier and counteracts the convulsive effect of severe OP intoxication. Other antimuscarinic drugs such as glycopyrrolate do not cross the blood–brain-barrier, so then a benzodiazepine should be added for the central nervous effects. Atropine has different pharmacokinetic and pharmacodynamic behaviour in the very young and the elderly. In both groups relatively more atropine is needed to increase heart rate. In children under 2 years of age and in the elderly a prolonged elimination was found. In the elderly there also appeared to be a diminished cardiovascular response, compared to healthy adults. This suggests changes in cholinergic receptor sites in elderly persons. Therefore children and older people may need higher doses of atropine to antagonize the effects of intoxication with organophosphates. In a national survey in Israel of accidental injection of atropine in children by automatic atropine injectors, doses up to 17-fold higher than standard for age where seen. No seizures or life-threatening arrythmias were reported, and none of the 240 children died of atropine intoxication. Atropine in combination with cyanosis or an ischemic myocardium can, however, give rise to dangerous ventricular arrythmias. It is therefore important to improve oxygenation at the same time as atropine in patients at risk. Atropine treatment regimen in OP intoxication: The combination of atropine and oximes seems more effective than oximes with other antimuscarinic drugs. There appears to be "tolerance" for atropine in patients poisoned with OP agents, so relatively high doses of atropine may be necessary. There is debate whether you should titrate until signs of atropinization, such as flushing, dry mouth, changes in pupil size, bronchodilation and increased heart rate appear, with the risk of atropine intoxication. Suggested regimens for atropine should start as soon as possible with 2–5 mg (children 0.02–0.05 mg/kg), followed by repeat doses of 2-4 mg in adults or 0.015–0.05 mg/kg in children every 5 to 10 minutes until a sufficient antisialogue effect is reached. Furthermore, adequate reduction of bronchospasm and bronchosecretion, and a heart rate of circa 80–100 beats per minute should be targeted. Atropine therapy should be continued for at least 24 to 48h and be tapered before discontinuation. This is especially needed in case of intoxication with highly lipid-soluble organophosphates, because there may be redistribution of these compounds. Conclusion: As a muscarinic receptor antagonist, atropine is the first drug of choice in the therapy of organophosphate intoxication. It antagonizes the muscarinic effects of acetylcholine and passes the blood–brain barrier. It should be titrated on bronchosecretion and bronchospasm to make artifical ventilation possible and to achieve an adequate heart rate. In very high doses a continuous infusion might be necessary. The risks of atropine are allergic reactions (systemic and very rare) and toxic reactions (sometimes at therapeutic doses, large interindividual variation). In these cases atropine could be replaced by glycopyrrolate. Glycopyrrolate does not cross the blood brain barrier, so a central depressant, such as a benzodiazepine, should be added in cases with OP CNS toxicity. Following high doses of glycopyrrolate bromide, bromide intoxication is a theoretical risk. References: Freeman G, Epstein M.A. Therapeutic factors in survival after lethal cholinesterase inhibition by phosphorus insecticides. *New Eng J Med* 1955;**253**:266–271. Virtanen R, Kanto J, Iisalo E, Iisalo EUM, Salo M, Sjövall S. Pharmacokinetic studies on atropine with special reference to age. *Acta Anaesth Scand* 1982;**26**:297–300. Robenstock E, Luria S, Tashma Z, Hourvitz A. Adverse reaction to atropine and the treatment of organophosphate intoxication. *Isr Med Assoc J* 2002;**4**:535–539. Singh S, Batra YK, Singh SM, Wig N, Sharma BK. Is atropine alone sufficient in acutesevere organophosphorus poisoning?: experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995;**33**:628–630. Singh S, Chauddhry D, Behera D,Gupta D, Jindal SK. Aggressive atropinisation and continuous pralidoxime (2-PAM) infusion in patients with severe organophosphate poisoning: experience of a northwest Indian hospital. *Hum Exp Toxicol* 2001;**20**:15–8. Bardin PG, van Erden SF, Moolman JA, Foden AF, Joubert JR. Oraganophosphate and carbamate poisoning. *Arch Intern Med* 1994;**154**:1433–1441. Amitai Y, Almog S, Singer R, Hammer R, Bentur Y, Danon Y. Atropine poisoning in children during the Persian Gulf crisis. *JAMA* 1992;**268**:630–632. De Kort WLAM, Kiestra S, Sangster B. The use of atropine and oximes in organophosphate intoxications: a modified approach. *J Toxicol Clin Toxicol* 1988;**26**:199–208.

83. SYNERGISTIC EFFECTS OF GLYCOPYRROLATE, IPRATROPIUM, AND DIAZEPAM ON MORTALITY IN A RAT MODEL OF LETHAL ORGANOPHOSPHATE POISONING

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Objective: We have shown previously that diazepam, when used alone, offers significant but transient survival benefit in a rat model of organophosphate poisoning, likely due to its effects on the CNS respiratory center (1). Still unclear is whether peripherally acting anticholinergic agents offer survival benefit when combined with

Table 1. Survival by study group.

Group	10 min	p value	24 hr	p value 10'	95% CI 10 min survival
Normal saline IM	0	—	0	—	0.00 to 0.28
Atropine 5 mg/kg	100	<0.001	100	<0.001	0.72 to 1.0
Diazepam 1 mg/kg	38	0.001	0	1.0	0.12 to 0.68
Nebulized IB 75 mg	0	1.0	0	1.0	0.00 to 0.28
Neb IB + diazepam	88	<0.001	88	<0.001	0.55 to 0.98
GLYC 4.5 mg/kg ip	0	1.0	0	1.0	0.00 to 0.28
GLYC + diazepam	88	<0.001	88	<0.001	0.55 to 0.98

diazepam. The objective of this study was to evaluate the efficacy of glycopyrrolate, ipratropium, and diazepam alone and in combination in a rat model of lethal organophosphate (OP) poisoning. Methods: Male Wistar rats were randomized to one of 7 pretreatment regimens prior to poisoning with dichlorvos 25 mg/kg subcutaneously. 1) normal saline 0.3 cc IM; 2) atropine 5 mg/kg IM; 3) diazepam 1 mg/kg IM; 4) nebulized ipratropium bromide (IB) 75 mg; 5) nebulized IB 75 mg PLUS 1 mg/kg IM diazepam; 6) intraperitoneal (ip) glycopyrrolate (GLYC) 4.5 mg/kg; 7) GLYC 4.5 mg/kg ip PLUS 1 mg/kg IM diazepam. IM pretreatments were given 5 minutes before poisoning, and nebulized pretreatments were given continuously over 45 minutes prior to poisoning. Primary outcome measure was 10-minute survival. Secondary outcome was 24h survival. Data were analyzed using Kaplan–Meier test and Kruskall–Wallis one way ANOVA. Results: 10-minute and 24h survival for each group is presented in Table 1. Conclusions: Diazepam alone demonstrated a significant, but transient effect on mortality. Anticholinergic agents without CNS penetrance had no effect on mortality when used alone. The combination of a pulmonary or peripherally acting anticholinergic compound plus diazepam was as effective as atropine in preventing mortality in a rat model of lethal organophosphate poisoning. References: (1) Bird SB, Gaspari RJ, Lee WJ et al. Early death due to organophosphate poisoning is a centrally-mediated process. *Acad Emerg Med* 2002;**9**:485.

84. EFFECTS OF HIGH DOSES OF SODIUM BICARBONATE IN ACUTE ORGANOPHOSPHATE PESTICIDE POISONING

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Objective: Sodium bicarbonate infusion in an experimental organophosphate pesticide poisoning reduced morbidity and mortality (1). The previous sodium bicarbonate doses that have been used for the treatment of human organophosphate pesticide (OP) poisoning were not enough to achieve blood alkalinization (2). We therefore studied the effects of high doses of sodium bicarbonate in OP poisoning. Methods: Patients with moderate to severe OP Poisoning were divided randomly into two groups. The controls received the standard treatment but the test group was treated as the controls plus sodium bicarbonate infusion: 5–6 mEq/kg in 1h followed by 5–6 mEq/kg every 20–24h until recovery/death. Clinical features and Para clinical investigations were recorded on admission and at certain intervals. Acetyl cholinesterase (AchE) activity was estimated by Ellman method using a spectrophotometer (Perkin Elmer, Model 3030). Arterial blood gasses and pH were performed by a blood gas analyzer (AVL-995) on admission and at certain intervals (based on the severity of poisoning) to maintain the arterial blood pH between 7.45 and 7.55. The results were analyzed statistically, using SPSS (Student t-test, X^2 and Spearman's test). Results: The study was performed on 53 patients (30M and 23 F) aged 14 to 65 (mean 28) years, 26 in the controls and 27 in the test group. There were no significant differences on the clinical findings, AchE activities, arterial blood pH or any other biochemical and haematological investigations, on admission between the groups. The mean arterial blood pH of the test group (7.48 ± 0.04) was higher ($p < 0.001$) than in the controls (7.36 ± 0.05) during treatment. There were no significant differences on the atropine doses required on admission and during the fist 24h between the groups, but the total atropine used in the test group was significantly ($p = 0.048$) lower than in the control group (93.4 ± 59.1 and 129.5 ± 6.1 mg, respectively). The mean hospitalization period was also significantly ($p = 0.037$) lower in the test group than in the controls (4.33 ± 1.99 and 5.59 ± 1.97 days,

respectively). There were no statistically significant differences on AchE activity during treatment between the groups. All patients except two in the control group and one in the test group were recovered. Conclusion: Constant infusion of high doses of sodium bicarbonate appeared to be effective in human OP pesticide poisoning and thus, it should be added to the treatment regime of acute OP poisonings. References: 1. Palacio DC. New approach to treatment of organophosphate poisoning. *Ant Med Medelin* 1982;31:32–36. 2. Balali—Mood M, Salimifar R, Shahab-Ahmadi A. Effects of sodium bicarbonate in human organophosphate poisoning. Proceeding of CBMTS, Spiez, Switzerland, 7–12 May, 2000, 12–19.

85. ON THE ATROPINE DEMAND IN ORGANOPHOSPHATE POISONED PATIENTS

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Objective: Few data exist on the appropriate dosage of atropine in organophosphate poisoning, especially at the ICU setting. Therefore, a retrospective analysis of the atropine dosage was undertaken in patients with organophosphate poisoning who needed artificial ventilation and were enrolled in a clinical trial aimed at studying obidoxime effectiveness. Atropine was administered on clinical demands with the only recommendation to favor low atropine dosing. Methods: Atropine plasma levels were determined by a radioreceptor assay ($n = 33$). Activity of red blood cell acetylcholinesterase (Ery-AChE) was measured with a modified Ellman method. Muscular function was estimated electrophysiologically, by stimulating the ulnaris nerve and recording compound muscle action potential of the muscle abductor digiti minimi. To investigate whether the necessary atropine dose was dependent on the severity of cholinergic crisis, a correlation was assessed between atropine plasma level and Ery-AChE activity (AUCs from 12 h to 48 h after start of obidoxime treatment). Patient data were excluded when sampling was inappropriate or atropine administered in the absence of cholinergic dysfunction, i.e., when muscarinic symptoms were absent and neuromuscular function was not impaired with Ery-AChE activity exceeding 30% of normal. Results: Large atropine bolus doses during emergency care (up to 200 mg) resulted in plasma levels >100 nM (mean 259 nM) in 15 patients. During therapy at the ICU such high concentrations were observed only transiently; otherwise they ranged between 5 and 80 nM. Linearity was found between dosing and concentration at steady state (14 nM per 0.01 mg/h*kg; $r^2 = 0.90$; $n = 11$) and between amount administered (1 to 278 mg) and AUCs (100 to 6000 nM*h; 21 nM*h/kg per mg/kg; $r^2 = 0.88$; $n = 12$). A correlation between atropine concentration and Ery-AChE activity could be roughly described by a hyperbolic function ($r^2 = 0.42$). High concentrations of atropine were only necessary, when Ery-AChE was $<10\%$ of normal. At Ery-AChE activity between 10 and 30% of normal, atropine plasma concentration of about 10 nM appears sufficient. Elimination kinetics could be determined in 6 patients (amount administered between 5 and 200 mg, sampling between 1 and 24 hours after administration). One phase ($n = 3$; $r^2 = 0.974$; $t_{\frac{1}{2}} 1.2 \pm 0.44$ h) or two-phase exponential decay functions ($n = 3$; $r^2 = 0.985$; $t_{\frac{1}{2}}(1) = 1.7 \pm 0.2$ h; $t_{\frac{1}{2}}(2) = 13.9 \pm 4.9$ h) could be fitted to the data. Conclusions: For therapy of cholinergic crises in ICUs, atropine doses of more than 2 mg/h appear only necessary if Ery-AChE is completely inhibited. In turn, effective reactivation reduces drastically the atropine demand.

86. TOXICOSURVEILLANCE IN POISON CENTERS

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In a production model of poison center functions, data collection and analysis are outputs that, while not directly related to clinical care, nevertheless potentially have great value. There are both internal and external customers interested in such data. Poison centers find such data useful in monitoring quality and efficiency as well as to demonstrate needs or a level of effort to funding sources. Poison centers also use such data to inform their public and professional educational outreach efforts and their choice of poison prevention strategies. Poison centers also perform such data analyses for external customers and such activities can broadly be interpreted as

"toxicosurveillance." The objective of this presentation will be to discuss advances, problems, and prospects in using poison center data for toxicosurveillance. The Toxic Exposure Surveillance System (TESS), maintained by the American Association of Poison Control Centers (AAPCC), will be used as an example when discussing the systems characteristics outlined below. End-users for data on human toxic exposures have a variety of interests and needs that can be addressed by poison centers. External customers for such monitoring include companies interested in post-marketing product safety and/or effectiveness, government regulators monitoring industry compliance with safety standards, and public health policy makers investigating trends, clusters, and epidemics of poisonings and toxic exposures. Poison centers record *sentinel events* which, when recognized as potential threats to the public's health, can lead to corrective actions. One example of a sentinel event is that of a methacrylic acid-containing nail cosmetic, which was regulated only after TESS data revealed 759 product-related toxic exposures, demonstrating the product's hazard.[1] Poison center data can be used to identify new risks and previously unknown adverse reactions to pharmaceuticals.[2] Demographic profiles of toxic exposures can be used to define previously unsuspected populations who are vulnerable to toxic hazards in a variety of everyday circumstances and settings. For example TESS data was used to study 8779 occupational toxic exposures in U.S. children under 18 years old.[3] Novel uses for poison center data, such as surveillance for discreet events of chemical or biological terrorism, must be assessed within such a framework of resources and attributes as end-user needs are more fully defined. The Centers for Disease Control have outlined guidelines for monitoring surveillance systems. These guidelines include an assessment of the public health importance of the data, a definition of the system's objectives and usefulness, its resources and stability, and the configuration of its operations. Attributes assessed within the CDC's guidelines include: simplicity, flexibility, acceptability, sensitivity, predictive value positive, representativeness, and timeliness.[4] Special uses of data may also require additional attributes within the surveillance. For example, a system reporting data on medical errors requires such additional characteristics as: non-punitive reporting, confidentiality, independence, expert analyses, systems-orientation, and responsiveness.[5] Passive reporting systems also face limitations in the data that they can provide. Population-based rates are difficult to determine with reliability. The systems must have in place controls so as to insure the accuracy and validity of their data. Many poison center systems have limited resources to devote to quality control, advanced analyses, and results dissemination activities. In summary, poison centers have an important role to play as *agents of change* in monitoring the health of the populations they serve. Their continuous service generates a stream of clinical data on toxic exposures of all sorts, data that is a rich source of information important for the public's health. Poison centers have not in the past fully exploited the potential uses of their data for toxicosurveillance. New collaborations of stakeholder agencies, advances in computer technology, and improvements in data collection, harmonization, real-time analysis, and dissemination will yield important new capabilities in the field of poison control. References: 1. Woolf A, Shaw J. Childhood injuries from artificial nail primer cosmetic products. *Arch Pediatr Adolesc Med* 1998;**152**:41–46. 2. Litovitz T. The TESS database—use in product safety assessment. *Drug Safety* 1998;**18**:9–19. 3. Woolf A, Alpert HR, Garg A, Lesko S. Adolescent occupational toxic exposures—a national study. *Arch Pediatr Adolesc Med* 2001;**155**:704–710. 4. Klaucke DN, Buehler JW, Thacker SB et al. Guidelines for evaluating surveillance systems. Centers for Disease Control. *MMWR* 1988;**37**:S-5. 5. Leape L. Reporting of adverse events. *N Engl J Med* 2002;**347**:1633–8.

87. SURVEILLANCE MONITORING FOR EMERGING TRENDS IN DRUG ABUSE

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Introduction: It has long been held that poison center data could be used to detect changes in the pattern of human injury linked to specific exposures. Data utilization has been suggested to detect product tampering, food poisoning, new drug adverse effects, bad street drugs and emerging drug abuse. Unusual symptom clustering has also been touted as a screen for bioterrorist activity. Real time surveillance of poison center data to detect these events does not yet occur. Data from individual poison centers are uploaded to the AAPCC TESS database as cases close, but no computer programs are in use to automatically search TESS or individual poison center data to look for trends or symptom clusters. Currently recognition depends on a single severe event or one person noticing an unusual number of exposures or an unusual pattern of symptoms linked to a particular product. But human surveillance can fail. In April 2002 a single severe

incident of saxitoxin poisoning was identified by one poison center. Review of TESS data showed that two previous, less severe poisonings linked to the same estuary had been reported in January 2002 and March 2002 to two separate poison centers but these centers had not reported to public health authorities. In 1999–2000, experience at the Cincinnati Drug and Poison Information Center with a dramatic increase in teen abuse calls related to a dextromethorphan containing product, Coricidin HBP®, led us to identify an emerging epidemic of teen abuse/misuse of this product. Texas poison centers had also recognized the pattern, but peer communication occurred via the NAACT congress in late 2000. The pattern certainly emerged earlier and may have been recognized if local and national data had been scanned. Methods: To analyze this possibility and to understand how better to query the Toxic Exposure Surveillance Survey (TESS) database to detect shifting patterns of abuse, we looked at TESS data on dextromethorphan going back seven years and data on teen ADHD medication abuse for 5 years. Results: For all calls for dextromethorphan containing products (age 6 to 29 years), call volume was increasing slowly from a significant baseline. In contrast, intentional abuse calls for all Coricidin products rose significantly from a very low baseline as early as 1997. All Coricidin® specific product calls (age 6 to 29 years, all reasons) started to increase in 1998 and 1999. During 2000 Coricidin® products represented an increasing share of all dextromethorphan-containing product calls. On a month-by-month basis, teen only, abuse only calls for all dextromethorphan containing products and for Coricidin® in particular began rising in late 1999. Initially as Coricidin® product calls increased, the data suggested some miscoding of abuse calls as suicide and miscoding of specific products (specific codes for Coricidin HBP® were not available until 1999). This may have delayed detection in the narrowest product category but the trend was apparent. In contrast, when examining the call trend in teen only prescription ADHD medication abuse (limited to Ritalin®, generic methylphenidate and Adderall®) the total number of calls did not change, but the relative proportion of calls related to Adderall® increased. When specific subsets by site of original contact were examined (home or hospital), there was no earlier detection of this trend using either site. In this case the cause may have been related to market share replacement (and thus abuse of available drug) rather than preferential abuse. A pattern change was detected but the cause and response required may be different. Discussion: In the case of the OTC product Coricidin HBP®, diversion and abuse occurred following "underground" internet recommendation of this product. It occurred in the context of a rising trend in abuse of dextromethorphan. The rise in dextromethorphan calls as a whole may or may not have been above threshold for an alert. Even so, unless a subgroup product analysis was performed, the problem with diversion of Coricidin® products generally and Coricidin HBP® in particular would not have been detected. The Texas data suggests local clusters of specific product abuse were an early clue. A change in abuse calls for all Coricidin® products was the earliest indicator nationally. These data suggest the emerging teen abuse of Coricidin HPB® could have been detected earlier than our center perceived and certainly earlier than we communicated to others. Coding errors related to reason for exposure and to a specific formulation may have blunted early spikes above threshold. This concern highlights the importance of data quality and of multilevel screening. If the national scope of the problem had been recognized earlier, there may have been more opportunity to involve the company or government in curbing the trend, perhaps reducing the number of victims evaluated and treated for effects of the co-ingested anticholinergics and unreported personal injuries. Of course any proposed intervention would need to understand and consider the abuse in context and address alternative sources of the same components. Coricidin® abuse may simply represent a switch from Robitussin® to a more convenient OTC dextromethorphan source. Broad searches can provide such data once a narrower search indicates the relevance. Conclusion: Daily searches of last 24 h and last 7 days should occur. Product and outcome searches should include all branded and generic products, products containing a specific substance as well as substance classes (e.g., anticholinergics). Screens should occur by all calls as well as specific for abuse. Scanning programs should compare call volume and severity against time averaged baselines (weekly or daily substance specific call volume averaged from broader periods 3, 6 and 12 months before). System administrator alerts should be based on percent change relative to baselines. Shifts in the number of calls related to a particular product ought to be the easiest to recognize. Outcome severity screens by product (e.g., Coricidin HBP®), product group (Coricidin®) and substance class (e.g., dextromethorphan containing cough and cold medications) ought to occur. Daily and weekly individual center searches should also be performed as they may detect an abuse pattern or a cluster of death or severe outcome cases that might not yet cross alert thresholds nationally. Potential examples include identification of ecstasy related deaths suggesting PMA substitution or heroin related deaths suggesting more potent heroin. To be effective, surveillance searches should be run regularly without human prompting. Threshold alerts and special circumstances (e.g., death clusters) should always prompt human review. One problem in designing software is determining where to set a threshold to alert the system administrator for outcome alerts linked to specific centers. Two heroin-related deaths in one day at the NYC poison center may be unremarkable. In West Virginia it may be an epidemic. Thresholds will need to be reset as experience is gained. Another problem is in the interpretation of alerts. With OTC

products the sales data associated with total calls is less helpful in discerning abuse. Abuse may actually drive sales of OTC products. With prescription medications sales figures may help in discerning if a rise in call volume reflects a rise in absolute (prescribed) sales of the drug class, a rise in market share or a problem with growing abuse. For proper interpretation of prescription drug related data, sales data should be available. Calls per 100,000 prescriptions ought to be a better marker, although a fall may indicate less need for poison center advice for management rather than a decrease in misuse. In considering the potential relevance of the experience to European poison centers where reporting is primarily by physicians, it is encouraging that the teen ADHD abuse trends were detectable with either calls from home or calls from hospitals. Although European culture is more diverse than that within the United States, increasing European integration and use of the internet suggest a potential benefit of transnational data examination. References: Marcus SM, Wolf G et al. Neurologic illness associated with eating Florida Pufferfish, 2002. *MMWR* 2002;**51**:321–323. Simone KE, Bottei EM, Siegel ES, Tsipis GB. Coricidin® abuse in Ohio teens and young adults (abstract). *J Toxicol Clin Toxicol* 2000;**38**:532–533. Watson WA, Hellsten JJ, Fant PM, Shepherd JG, George DJ. OTC cough and cold medication abuse is infrequent and occurs in clusters: poison center data as a surveillance method (abstract). *J Toxicol Clin Toxicol* 2000;**38**:532. Baker SD, Borys DJ. Coricidin® use and abuse in Texas during 1998 and 1999 (abstract). *J Toxicol Clin Toxicol* 2000;**38**:533. Simone KE, Bond GR. Detection of unusual abuse patterns using broad searching of the Toxic Exposure Surveillance System (abstract). *J Toxicol Clin Toxicol* 2002;**40**:657–658. Simone KE, Bond GR. Dextromethorphan: a successful example of monitoring for emerging abuse using the Toxic Exposure Surveillance System (abstract). *J Toxicol Clin Toxicol* 2002;**40**:653–654. Bond GR. TESS and teen drug abuse: using prescription ADHD drugs to examine the utility of Toxic Exposure Surveillance System (abstract). *J Toxicol Clin Toxicol* 2002;**40**:652–653.

88. STRATEGY AND FOLLOW-UP OF THE NATIONAL POISONS INFORMATION CENTRE OF NORWAY

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Background and objective: As several Poisons Information Centres (PICs), also the National Centre in a small country with 4.5 million inhabitants felt a lack of resources. The Norwegian Centre is completely funded by the government, however, the increase in number of inquiries from the public and health services and other imposed tasks was not followed by the necessary funding. In 1999, a policy for long term strategy and planning to visualize the need for increased resources and follow-up of activities was established. The aim of this presentation is to report the methods and principles used for obtaining higher budgets and to try to establish a better matching of resources required and major tasks to be performed. Methods: Well-structured 5 years running strategy plans were worked out. Mission, main aims and main tasks were emphasized and related to resources. Explanations and reasons were focused. A man power plan was linked to the strategy plan. For each budget year, result-oriented activity plans and corresponding yearly reports were worked out. Number of telephone inquiries per information specialist was chosen as the most important steering parameter. A management tool, linking the various activities to the main tasks further anchored to their respective main aims was developed. A project trying to link the time used by the coworkers in PIC to the different activities was carried out. Results: Approval of mission, main aims and corresponding main tasks was easily obtained. Active arguing and written documentation based on strategy plans have resulted in an increase in budget from 9.8 million NOK in 1999 to 14.7 million NOK in 2002 plus 5.0 million NOK for projects. The corresponding increase in total man years (permanent and project engagements) was from 16 to 25. However, some of the positions are not filled due to maternity leaves and turn-over of staff. The number of telephone inquires was 28500 in 1999 and about 34000 in 2002. The theoretical figures of number of inquiries per information specialist was in November 2002 about 2000 compared to 2200 in 1999, leaving some time for other important tasks. The value of reported time by information specialist used to various activities was rather limited due to inaccurate completion of reporting. Our long term strategy and management of PIC are recently changed due to a political decision to incorporate PIC as a department in the newly established Norwegian Directorate of Health and Social Welfare. Conclusion: Efforts spent on strategy work and aim- and result-oriented planning and reporting resulted in 100% increase in total budget and 60% increase in man years from 1999 to 2002. The number of inquiries increased with 20%. The number of inquires per information specialist on telephone duty has decreased by 10% in the same period. This fact, combined with additional staff exclusively involved in project work, has increased our capacity for other important work outside telephone duties. However, due to 20% turn-over per year and several

maternity leaves, all positions are never filled. In order to increase budgets and better correlate tasks to resources available in PICs, it is recommended to give strong emphasis on strategy and documentation of consequences.

89. CAM: AN INTERDISCIPLINARY COORDINATING AND MONITORING AGENCY FOR NEW SYNTHETIC DRUGS OF ABUSE

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Objective: In 1999, the Dutch Public Health Care Inspectorate set up a coordinating agency for health and social risks, the Assessment and Monitoring of new synthetic drugs (CAM). This agency plays a key role in implementing the European Union (EU) recommendations for an Early Warning Mechanism on synthetic drugs. The central European drug agencies to which all Member States have to report are the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in Lisboa, Portugal, and, for criminal investigations, Europol in The Hague, the Netherlands. The mission of the EMCDDA is to provide the community and its member states with objective, reliable and comparable information concerning drugs and drug addiction, and their consequences. As input is provided by the national centres, these centres have to coordinate, assess and monitor drug trends at a national level. The key aim of Dutch drug policy is to reduce, to the extent possible, the hazards related to drug use for the users themselves and their environment, and the society as a whole. The government also strives to prevent a situation in which too strict judicial measures do more harm than the drug itself. Methods: The Dutch center is composed of experts from several scientific institutes that are involved in information, monitoring, research, and criminal investigation in the field of drug use. The institutes involved are for example the Trimbos Institute with a Drugs Information and Monitoring System (DIMS), the National Poisons Information Centre, the Forensic Institute, the Synthetic Drugs Unit, and departments of the Ministries of Health and Justice. These experts carry out risk assessments on new synthetic drugs, new drug combinations, smart-products or other substances. Following these risk assessments decisions are taken whether preventive measures should immediately be taken or whether judicial intervention or outlawing of the substance should be recommended, for example, whether or not to list the substance on schedule I (hard drugs) of the Opium Act, take repressive measures, or continue to observe and monitor. Results: The agency started with setting up criteria in order to perform the risk assessments. Items to assess the health and social risks are divided into several main categories: health risks to the individual and/or society; risks with regard to public safety, law and order; risks of criminal involvement, and remaining aspects, for example international political agreements. Since the setting-up of the agency several risk assessments of synthetic drugs have been carried out on hallucinogenic mushrooms, gammahydroxybutyric acid (GHB), ketamine, 4-methyl-thioamphetamine (4-MTA), paramethoxyamphetamine (PMA)/paramethoxymethylamphetamine (PMMA). Conclusion: The advantage of this approach of bringing together experts with different background for the risk assessment on drugs is that policy makers receive better balanced advice upon which to base decisions, and in particular whether to put specific substances under repressive control or to tolerate ("gedogen") these.

90. THE PRICE OF NON-TOXIC EXPOSURES TO THE IRISH HEALTHCARE SERVICE

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Background: Accidental exposure to non-toxic agents rarely results in adverse effects. Patients presenting to Emergency Departments (EDs) following these incidents will not usually require treatment. These patients must nevertheless be triaged and then discharged by a Medical Officer. Objective: To examine the cost to the healthcare service of patients presenting to EDs following non-toxic exposure. Methods: We retrospectively examined enquiries received from Emergency Departments between January and June 2002. We included only accidental incidents in our study. Cases were considered non-toxic if they involved (1) substances defined as non-toxic by Toxbase, Poisindex, and UKPID (e.g., silica gel), (2) non-toxic amounts of potentially toxic pharmaceuticals (e.g. <150 mg/kg of paracetamol), (3) "low toxicity

substances" associated with mild gastrointestinal upset (e.g., household cream cleaner). We noted the number of non-toxic cases. We obtained costings per patient from Crumlin Paediatric Hospital, and Beaumont Hospital in Dublin, and used them to estimate the total cost to the healthcare service. Results: 986 patients attended or contacted Emergency Departments following accidental exposure to various agents during the study period. 42% (413) of cases were considered non-toxic. 379 patients were asymptomatic, 28 had 1 episode of vomiting and 6 had mild nausea. No treatment was recommended by the Poisons Centre for any of these cases. 99% of patients did not contact the Poisons Centre before going to hospital. The top 5 agents involved were paracetamol suspensions, household cream cleaners, domestic bleach, antibiotics, and multivitamin tablets. 87% of patients were children aged under 5 years. 69 cases involved patients who remained at home but whose parents/carers contacted the ED by phone. After consultation with the Poisons Centre, the Emergency Department staff advised the callers that no treatment was required in these cases. While these patients have an impact on the activity of Emergency Departments, it was not possible to estimate their monetary cost to the health service and they are not included in further calculations. The cost of a patient who is triaged in a paediatric hospital and discharged without treatment is £200. The cost in an adult general hospital is £226. Assessment of patients following non-toxic exposures cost the healthcare service £69,762 during the first 6 months of 2002. An additional 366 patients consulted their General Practitioners following non-toxic exposure but were not included in this study because costing was unavailable. Conclusion: Inappropriate self-referral to Emergency Departments after non-toxic exposures generates unnecessary healthcare costs. Early contact with the National Poisons Information Centre (NPIC) by members of the public could result in reduced costs to the healthcare service and more efficient utilization of ED staff.

91. DRUG-INDUCED LITHIUM TOXICITY IN THE ELDERLY: A POPULATION-BASED STUDY

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Objective: Many commonly used medications have been suggested as possible precipitants of lithium toxicity, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). However, the risks associated with each of these drug classes are unknown. We evaluated the association between use of these agents and hospitalization for lithium toxicity in a population of 1.4 million elderly persons. Methods: This was a population-based nested case-control study set in Ontario, Canada between January 1992 and December 2001. We identified lithium-treated patients aged 66 and older using outpatient prescription records. Within this cohort, cases were those admitted for lithium toxicity (ICD-9 codes 969.8 and 985.9). Their prescription records were compared to those of randomly selected age- and gender-matched controls (4:1) to identify prescriptions for diuretics, ACE inhibitors, and NSAIDs in the preceding month. Mantel-Haenszel methods were used to estimate the relative risk of hospital admission for lithium toxicity, and conditional logistic regression was used to adjust for previous episodes of lithium toxicity, renal insufficiency, comorbidity, and other interacting medications. Attributable fractions were calculated using standard methods for case-control studies. Results: We identified 10,615 elderly patients treated with lithium between January 1992 and December 2001, of whom 413 (3.9%) were hospitalized with lithium toxicity. The simultaneous use of diuretics, ACE inhibitors, and NSAIDs was common. The adjusted relative risks of hospitalization for each drug class are shown in Table 1. Of the admissions for lithium toxicity in our cohort, approximately 13% were attributable to use of

Table 1. Risk of hospitalization for lithium toxicity within 28 days following concomitant treatment with potential interacting drug classes.

Drug class/subclass	Adjusted relative risk (95% C.I.) of hospitalization for lithium toxicity: *any use* in preceding 28 days	Adjusted relative risk (95% C.I.) of hospitalization for lithium toxicity: *new use* in preceding 28 days
Diuretics	2.2 (1.6 to 3.0)	4.5 (2.2 to 9.3)
Thiazide diuretics	1.3 (0.7 to 2.5)	1.3 (0.4 to 4.2)
Loop diuretics	1.7 (1.1 to 2.7)	5.8 (2.2 to 15.2)
ACE inhibitors	1.6 (1.1 to 2.3)	4.3 (2.1 to 9.1)
NSAIDs	1.1 (0.4 to 1.6)	1.5 (0.8 to 2.9)

a diuretic, 6% to use of an ACE inhibitor, and 1% to use of a NSAID. Conclusions: Among elderly lithium-treated patients, hospital admission for lithium toxicity is common. The simultaneous use of loop diuretics and ACE inhibitors increases the risk of lithium toxicity, particularly among naïve recipients. The co-prescription of NSAIDs likely poses minimal risk in most patients.

92. ACUTE POISONING IN ITALY: AN EIGHT-YEAR REPORT

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Objective: In 1990 the European Union (EU) promulgated resolution no. 90/C329/EEC on the subject of the prevention and treatment of acute human intoxication. One of the aims of the resolution was that of acquiring a Europe-wide overview of this phenomenon. To achieve this, the Resolution established that each member State should appoint a competent Authority to enforce, at a national level, the provisions contained in the Resolution. In Italy the competent Authority is the National Institute of Health. The tasks of the competent Authority include that of compiling, on an annual basis, a compendium of activity reports of national Poison Control Centres (PCCs), to be sent to the EU Commission, which then formulates the European compendium. Case report: The national compendium, is split up into 16 sections pertaining to the various parameters of the phenomenon. The Italian programme got under way in 1991 with the participation of 5 PCCs belonging to the following structures: the [1]Niguarda Ca Granda Hospital of Milan, [2]University of Rome "La Sapienza," [3]Catholic University of Rome, the [4]Careggi Hospital of Florence and the [5]University of Padua. This first compendium reported 37,922 cases of intoxication. In 1992 the Centres of the [6]Istituto Pediatrico "M. Gaslini" of Genoa and the [7]Cardarelli Hospital of Naples joined the programme, bringing the number of cases reported up to 42,839. In 1993 the Centre of the [8]Fondazione "S. Maugeri" of Pavia also joined, bringing the number of cases reported up to 47,691. In the years 1994 and 1995 there was a slight drop in the number of cases of poisoning reported yearly, with 45,908 and 45,587 cases respectively. In 1996 participation of the Centre of the S. Giovanni Battista Hospital of Turin helped raise the number of reported cases to 52,551. The growth trend continued over the following two years, with 56,378 and 66,770 cases respectively. With regard to characterization parameters, males were slightly affected more than women. Risk was greatest for the age classes 1–4 and 20–49. The most common etiological agents were medicines and household products. The home was the place where over 80% of cases occurred. Risk appraisal is highly variable over the years. Outcome however is favorable in almost all cases. Conclusion: the improved management of cases of poisoning requires an in-depth knowledge of the causes and circumstances of these events, as well as the rational organization of first aid facilities. The cooperation program between central bodies of the National Health Service and PCCs may be a valid instrument for achieving these goals. References: Resolution 90/C329/EEC. O. J. C329, of 31.12.1990.

93. EVALUATION OF THE NEW ZEALAND 0800 POISON HELPLINE

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Objective: A comprehensive review following the launch of the 0800 POISON free phone number (October 2001) for the National Poisons Centre (NPC) aimed to determine the following: 1. Quality of the service provided by the National Poisons Centre (NPC). 2. Effectiveness of the recently implemented 0800 POISON line. 3. Effectiveness of the campaign to raise awareness of the 0800 POISON line. Methods: Those who had called the NPC between 9th October 2001 and 28th February 2002 were randomly selected for telephone interview (general public callers, $n = 703$ respondents) or postal survey (health professionals, $n = 256$ respondents). Additionally, 568 members of the general public selected randomly from the telephone book agreed to a telephone interview and 171 members of organisations concerned with poisoning prevention completed a telephone interview or emailed survey. Results: Calls to the NPC from the general public sector increased by 18% following the implementation of the 0800 POISON line, with more than 60% of the general public knowing to call the NPC in case of poisoning. Awareness

of the services provided by the NPC was high. While relatively few respondents could cite the actual "0800 POISON" number, most knew where it could be found. Most respondents would still call the NPC if the 0800 POISON number was not available, reflecting the perceived emergency nature of a poisoning incident and the desire to access expert advice quickly. If the NPC service did not exist at all, most respondents would have sought alternative, possibly unnecessary and more costly assistance from the health care system. Nearly two-thirds of health professionals surveyed recalled situations where patients presented to the emergency department following a poisoning that could have been managed at home with simple advice and reassurance. The satisfaction of health professionals and general public callers with all aspects of the NPC service was extremely high. Respondents identified enhanced promotion of the NPC service and its 0800 POISON number as a key desired improvement. Conclusion: Based on the findings of this study, the following recommendations were made: 1. Continue the provision of the 0800 POISON number. 2. Develop and implement a strategy for regularly promoting through a range of media the services of the NPC, in particular the 0800 POISON number and the poisons information website. 3. Allocate funding to the NPC specifically for poison prevention initiatives, e.g., poisons prevention website, poisoning information brochures, poison prevention packs. 4. Develop service delivery methodologies and information resources targeting Maori and Pacific Islanders, and people with poor literacy or English competency. 5. Collect caller ethnicity data. 6. Undertake a cost-effectiveness study of the NPC.

94. TOXINZ: INTERNET-BASED POISONS INFORMATION DATABASE

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Objective: Since its establishment in 1964 the New Zealand National Poisons Centre has provided essential toxicology advice to both health professionals and the lay public via telephone consultations. Recognizing that information technology has advanced considerably during this period the center wished to develop a more efficient method for disseminating poisons information to healthcare providers. Methods: Software was developed to manage a product database maintained by the National Poisons Centre and to produce a CD-ROM based copy. This CD-ROM was distributed to select hospitals in 1997 for a two year beta-testing (user acceptance) phase. After enabling improvements recognized from feedback, and further developing information content, a CD-ROM was made fully available for use in New Zealand. Encouraged by wide acceptance and positive comment from clinicians, development began on an Internet accessible version (TOXINZ) which replaced the CD-ROM in 2002. Results: All public health service units and major hospitals in New Zealand now access detailed poisons information directly via TOXINZ. This database provides detailed information relating to 70,000 chemicals, pharmaceuticals, plants and hazardous creatures found in the Australasian region. Containing comprehensive clinical information regarding the advanced management of the poisoned patient, TOXINZ also provides an inexpensive less-detailed version for use by family doctors and other healthcare providers; and a free access first-aid site for public use. Information is supported with images and nomograms and reviewed by an editorial board of leading Australasian clinical toxicologists and toxinologists. The material is maintained on a 24 h basis by Poisons Centre staff, and the Internet based information updated weekly. Conclusion: The telephone consultation service provided by the New Zealand National Poisons Centre has been successfully augmented by utilising advances in information technology to develop TOXINZ—an Internet accessible poisons information database. Healthcare providers and public alike now have a greater range of access to poisons information.

95. POISONED PATIENTS IN SCOTTISH HOSPITALS—2. TOXBASE® AND OTHER INFORMATION SOURCES

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Objective: To investigate information sources used in Scottish hospitals for managing poisoned patients and to evaluate TOXBASE® use and satisfaction. Methods: 226 questionnaires were sent to doctors (consultants, specialist registrars, staff grade physicians) and nurse managers in Accident & Emergency departments (A&E) and Minor Injuries Units (MIU) of 91 hospitals in Scotland. 176 (78%) were returned completed from 82 hospitals (43 consultants, 17 specialist registrars, 40 staff grade physicians, 1 senior house officer, 75 nurse managers). 95% confidence intervals are shown where significant. Background: TOXBASE® (UK Internet poisons database) has been available free to UK National Health Service professionals since 1983. It was transferred to the Internet in 1999 and is used by all A&E departments and many MIU departments in Scotland. Results: Respondents were offered a number of options for information sources used and could select more than one. For the treatment of paracetamol (acetaminophen) poisoning respondents used: department protocol [doctors 27%, nurses 13%]; TOXBASE® [doctors 79%, nurses 75%]; paracetamol poster [doctors 76% ± 8%, nurses 37% ± 11%]; clinical experience [doctors 61% ± 10%, nurses 32% ± 11%]; British National Formulary (BNF) [doctors 35%, nurses 48%]. For aspirin, tricyclic antidepressants and opioids the percentages were respectively: protocol [doctors 9%, 8%, 6%; nurses 4%, 1%, 4%]; TOXBASE® [doctors 97% ± 3%, 96% ± 4%, 72% ± 9%; nurses 75%, 75%, 73%]; clinical experience [doctors 57%, 63%, 77%; nurses 33%, 35%, 40%]; BNF [doctors 34%, 24%, 28%; nurses 45%, 44%, 48%]. For other toxins respondents used TOXBASE® for *every* enquiry [doctors 51%, nurses 47%]; for *some* enquiries [doctors 48%, nurses 31%]; telephoned an NPIS centre [doctors 48%, nurses 63%]; clinical experience [doctors 53%, nurses 31%]; BNF [doctors 40%, nurses 47%] plus assorted books and posters. Only 12 respondents never used TOXBASE® (11 nurses, 1 doctor; all MIU). Of the rest, 8% of doctors and 19% of nurses said they *always* and 89% of doctors and 70% of nurses said they *usually* found sufficient information on TOXBASE®. Out of 158 replies to a question offering two TOXBASE® entries: a summary for nurse triage and/or a more detailed monograph for medical management 39% ± 10% of doctors and 89% ± 10% of nurses requested both; one nurse (MIU) wanted the summary only; 1 nurse and 5 doctors wanted the detailed entry only and 56% ± 10% of doctors and 8% ± 7% of nurses and were happy with the current version. Conclusions: TOXBASE® is used more frequently than other sources of information for managing most poisoned patients. Only for opioid poisoning were doctors were more likely to use their own experience. A&E and MIU respondents found TOXBASE® sufficient for most poisons enquiries. Nurses were more likely to want a triage summary on TOXBASE®.

96. EFFECT OF AVAILABILITY OF TOXBASE TO EMERGENCY DEPARTMENTS ON ENQUIRY NUMBERS TO THE NATIONAL POISONS INFORMATION CENTRE IN IRELAND

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Objective: To examine the impact of introducing an on-line poisons information database (TOXBASE®) to A + E Departments in the Republic of Ireland on enquiry numbers received by the National Poisons Information Centre (NPIC). Methods: For this study we examined the monthly enquiry numbers to the NPIC for the 18-month period immediately before TOXBASE® was made available to A + E Departments in the Republic of Ireland and compared these figures with those of the 18 month period after introduction. The enquiry numbers for each individual hospital registered for internet access to the database were analysed using a paired t test. Results: TOXBASE® is the first tier database used by the UK National Poisons Information Service to provide on-line toxicological information to A + E departments. This database was made available via the internet to Emergency Departments in the Republic of Ireland from 1st February 2001. There are 21 hospital A + E Departments registered to use TOXBASE®. The NPIC in Dublin received 7,803 enquiries from these hospitals in the 18 months preceding the introduction of the database. In the 18-month period after TOXBASE® introduction there was just 5,759 enquiries received from them. This represented a 26.2% decrease in the volume of telephone calls from these hospitals. We compared the call numbers from each individual hospital again for 18 month before and after TOXBASE® introduction using a paired t test. The decrease in the call numbers from these hospitals was found to be statistically significant ($P = 0.0007$). The NPIC received 21,869 enquiries in the 18 month period prior to the introduction of TOXBASE®. We received 23,260 enquiries in the 18 month period subsequent to introduction of this database. This represented a 6.4% increase in total enquiry numbers. Conclusion: 21 Irish hospital Emergency Departments registered to access TOXBASE® in the first 18 months of its availability. They have accessed it 2,013 times since then. The introduction of access to an on-line Poisons Information database for hospitals in the Republic of Ireland has resulted in a very significant reduction of enquiries to the NPIC from these Emergency Departments.

97. COMPARISON OF DIFFERENT HEALTH PROFESSIONALS' USE OF AN INTERNET-BASED POISONS INFORMATION DATABASE

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Objective: In the UK TOXBASE, an Internet-based database, has been designated the primary source of poisons information since February 2000, with the telephone service (comprising six regional centers) available for more complex enquiries. As part of the analysis of a quality assurance study[1], we wanted to determine whether there were differences in use of TOXBASE between different types of caller to NPIS (London). Methods: A questionnaire was sent to health professionals making an enquiry to NPIS (London), as described previously[1]. Results: 546 questionnaires were sent. Of the 244 (44.7%) received in time for analysis, 50.4% were from emergency department (ED) nurses, 9.8% from ED doctors, 10.2% from family doctors in general practice or out-of-hours services (GPs), and 17.2% from NHS Direct advisors (NHSD). NHS Direct is the nurse-led public-access medical advice helpline. 59.5% of NHSD had used TOXBASE prior to making their enquiry, but no GPs had. ED doctors were more than twice as likely to have used TOXBASE as ED nurses (17.4% vs 8.3%). 83.3% of ED doctors who had used TOXBASE first said they had telephoned NPIS (London) because the information on TOXBASE was insufficient, compared with only 50% of ED nurses and 48% of NHSD. This was the most common reason for each group. There were differences between groups regarding the most common reason why TOXBASE had not been used. For GPs it was that they had not heard of TOXBASE (84.0%), whereas for NHSD it was that they could not log on/the connection was not working (47.1%). ED nurses said they had not been trained to use TOXBASE (26.4%), and ED doctors that they were not trained yet or did not know what it was (35.3% each). Conclusion: Different user groups need to be targeted in different ways to increase their use of TOXBASE. NHSD were most likely to try to use TOXBASE, but problems with logging in or connections need to be addressed. If increased use by GPs, most of whom are likely to have easy access to the internet, is desired, they should be targeted with awareness, availability, and then training. ED staff need a combination of availability, awareness and training; the situation in individual hospitals needs to be determined. Reference: Bara V, Dines A. Users' experiences of internet and telephone poisons information services in the UK. *Submitted to EAPCCT XXIII International Congress, Rome 2003.*

98. USERS' EXPERIENCES OF INTERNET AND TELEPHONE POISONS INFORMATION SERVICES IN THE UK

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Objective: In February 2000 new arrangements were introduced for the provision of poisons information in the UK. TOXBASE, an Internet-based database, was designated the primary source, with the telephone service (comprising six regional centers) for complex enquiries. The take-up of TOXBASE is relatively low in the area served by NPIS (London). This quality assurance study aimed to determine levels of user satisfaction with the telephone service provided by NPIS (London), and to examine why TOXBASE had not been used, or why a telephone enquiry was necessary after accessing TOXBASE. Methods: A questionnaire was sent to every fifth caller requesting poisons information from NPIS (London) over a 15-day period. The accompanying letter gave sufficient details to remind the caller of the enquiry without breaching patient confidentiality. Exclusion criteria included calls from outside the UK, members of the public, non-urgent enquiries and calls referred to other departments. Results: Of 546 questionnaires sent, 44.7% were returned in time for analysis. Most respondents were from emergency departments (60.7%), NHS Direct, the nurse-led public-access medical advice helpline, (17.2%) or general practice (12.3%). 19.3% of callers or their colleagues had used TOXBASE prior to making their enquiry. The main reasons for calling NPIS (London) despite using TOXBASE were that TOXBASE provided insufficient (51.1%) or no (27.7%) information on the substance. The main reasons for not using TOXBASE before telephoning were that callers did not know what TOXBASE was (26.4%), it was not available in their department (23.9%), or they had not been trained on it (20.8%). For 9 of 11 statements measuring satisfaction, at least 90% agreed or disagreed with the statement to indicate satisfaction with that parameter. However 22.1% agreed the information was given to them too quickly and 14.3% agreed they had had to wait a long time for the Specialist in

Poisons Information (SPI) to answer the telephone. 94.7% marked very good or excellent for overall satisfaction. Conclusion: There was a high degree of satisfaction among users of the NPIS (London). However SPIs should ensure that information is always provided at an appropriate pace for the caller, although this may mean other callers having to wait longer before the telephone is answered. Awareness and availability of, and training on TOXBASE need to be addressed to increase its use. Further study into what information needs to be added to TOXBASE is necessary. Regular quality assurance studies should be carried out to monitor changes in satisfaction with NPIS (London) and use of TOXBASE.

99. CHANGE IN USE OF POISONS INFORMATION SOURCES BY EMERGENCY DEPARTMENTS

Bara V. *National Poisons Information Service (NPIS), Medical Toxicology Unit, Guy's and St Thomas' Hospital NHS Trust, London, UK.*

Objective: In February 2000 new arrangements were introduced for the provision of poisons information in the UK. TOXBASE, an Internet database, was designated the primary source, with the telephone service (comprising six regional centers) for complex enquiries. Use of TOXBASE in the 71 emergency departments (EDs) served by NPIS (London) had previously been limited. This study was designed to determine whether EDs had changed practice in line with the new arrangements. Methods: For each ED, the number of calls made to NPIS (London) and user sessions on TOXBASE per month were extracted from the appropriate databases in London and Edinburgh respectively. The results of two 12-month periods were compared: January to December 1999 (1999) and July 2001 to June 2002 (2001/2002). The analysis did not allow for factors influencing the need for poisons information (e.g., population served by the ED). It was assumed that each TOXBASE user session represented an alternative to using the telephone service since it was not possible to know the purpose of the user session (e.g. training, research, multiple patients). Results: The number of calls to NPIS (London) decreased from a mean of 978 per ED in 1999 to 764 in 2001/2002. 61 of the 71 EDs decreased their use of NPIS (London), including 14 EDs whose use had decreased by at least 50%. The median change was a decrease of 18.2%. In 1999 nine hospitals had used TOXBASE, rising to 60 in 2001/2002. However of these, only 28 had used TOXBASE more than 183 times in 2001/2002 (mean of once every other day), and 17 had used it fewer than 60 times (mean of 5 per month). Of the EDs whose use of NPIS (London) had increased, or decreased by less than the median of 18.2%, only three had used TOXBASE more than 183 times in 2001/2002. Comparing use of NPIS (London) with use of TOXBASE in 2001/2002 suggested that up to 17 hospitals were using poisons information sources in line with the new arrangements; 15 of these had not used TOXBASE in 1999. Conclusion: Some EDs appeared to have successfully introduced use of TOXBASE into the management of the poisoned patient, whereas others, despite having access, made no lasting changes to their use of poisons information sources. Therefore there must be a range of factors influencing these different responses to the new arrangements for provision of poisons information in the UK. As a result of these findings, a survey is under way to determine the most important barriers to use of TOXBASE, and factors that encourage its use.

100. QUALITY OF TOXICOLOGY INFORMATION ON THE INTERNET

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Objective: Rapid increase in availability of Internet access and growth in the number of medical Web sites results in use of the Web as a resource by laypeople and physicians. In this study, we obtained information from a sample of websites directed toward physicians regarding treatment of a toxicologic condition. The treatment recommendations were then evaluated to determine their quality. Methods: The Google search engine was queried using the terms aspirin, overdose or intoxication, and treatment. Google was used because of its method of ranking sites by number of visits. We felt this was the search engine most likely to find commonly accessed sites. Those which were clearly directed toward non-physicians were excluded. The first 10 Web sites which appeared to make treatment recommendations for aspirin intoxication were selected. The recommendations were abstracted and recorded on a standard form. The quality of the suggested treatments was scored by two toxicologists, blinded to source of the information, as either significantly substandard or meeting the standard of care. Results: With a high degree of agreement, (Kappa 0.85) raters found that

50% of the sites surveyed offered significantly sub-standard treatment recommendations. Two of the 10 Web sites did not mention dialysis as a therapy. Two did not mention alkalinization of urine as a therapy. Two of 10 Web pages were identified as peer reviewed. Both of these met the standard of care. Conclusion: While the Internet as a medical resource offers significant benefit to medicine overall, there are pitfalls for the unwary. This study shows that it is not only possible, but probable, that relying on a Web search for treatment recommendations on aspirin intoxication will result in substandard care. It is prohibitive to search the entire Web for all conditions and review all treatments proposed; however, we use the example of aspirin to illustrate our hypothesis. Information on the internet is not necessarily up to date or peer reviewed. It is not always possible to ascertain authorship. Thus, our recommendation for physicians who use the Web as a toxicology resource is to rely on expert authors and peer reviewed sources, or obtain specialist consultation. References: Wyatt JC. Measuring quality and impact of the World Wide Web. *BMJ* 1997;**314**:1879–81. Strauss K. Quality of medical information on the Internet [letter]. *JAMA* 1997;**278**:632. Wilson P. How to find the good and avoid the bad or ugly: A short guide to tools for rating quality of health information on the Internet. *BMJ* 2002;**324**:598–602.

101. BLINDNESS AFTER POISONING WITH SODIUM METAPERIODATE (SERISTRIP LIQUID)

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Objective: It is well known that iodate has a toxic effect on the retina, but poisonings with this substance is seldom reported. We describe a case of intentional ingestion of iodate. Case report: A 34-year-old man was admitted to hospital after drinking approximately 2 L Seristrip liquid. This is a cleansing agent used in the printing trade, containing considerable amounts of sulfuric acid and sodiummetaperiodate. The oral dose of iodate was estimated to 5100 mg/kg body weight. On admission he was unconscious, dehydrated, and hypothermic (rectal temperature 28.7°C). He had a metabolic acidosis, aniongap was 26 mmol/L (ref < 16) and the osmolar gap was normal. No toxic alcohols were detected, but a fully metabolised methanol intake could not be excluded as the anion gap was elevated. He developed rhabdomyolysis (maximum CK 18500 U/L, ref: 40–250) and anuric renal failure. He was treated five times with haemodialysis. The patient had major corrosive injuries in the oesophagus and stomach. Transient hyperphosphatemia and hypocalcemia was normalized on discharge. He also developed central amaurosis (blindness) on both eyes. Haemoglobin dropped to 9 g/100 ml (normal range 12.5–16.5), and increased to 11 g/100 mL on discharge from the Department of Medicine. After 1 month he had nearly recovered from the renal failure and corrosive injuries and was transferred to the Department of Ophthalmology. Examination of his eyes revealed atrophic pigmented changes in the central part of the retina with a normal peripheral retina. The patient had some peripheral vision on both eyes, and could detect movements and differentiate between light and darkness. He was able to walk around and manage daily care. Neurologic examination showed no other pathology. The blindness was probably caused by a toxic effect on retinal photoreceptor cells (retinopathy) and optic nerve injury. After four days at the Department of Ophthalmology the patient was discharged. Three weeks later his peripheral vision had improved. The same central retinal pigment changes were seen. He was lost to further followup. Discussion and conclusion: Various iodine compounds are known to cause local and systemic toxicity. Elemental iodine is the most toxic. Little is known about the human toxicity of iodates. Our case confirms the local and systemic toxicity of iodates and the potential for causing blindness. With intensive care treatment the patient can recover. Blindness might be permanent, but some improvement of the vision has been reported.

102. A YOUNG WOMAN SURVIVED A LETHAL DOSE OF ARSENIC TRIOXIDE DUE TO NEW THERAPEUTIC STRATEGIES

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Objective: This case report demonstrates that an acute poisoning with arsenic trioxide can be treated successfully with intensive therapy and close follow up. Case report: A case of a 27-year-old woman who intentionally ingested 9000 mg arsenic trioxide (As_2O_3) is reported. She presented herself with classical symptoms of an acute poisoning with arsenicum (As): gastrointestinal cramps, vomiting, diarrhea, ECG changes and disturbed liver function tests. The initial urine

concentrations were 6870 μg/L. The absorption of the ingested As was minimalized by continuous gastric irrigation with highly concentrated $NaHCO_3$ for more than 24 h [1]. Gastrointestinal cleansing with polyethyleneglycol was performed to limit absorption in the digestive tract. In addition, treatment with forced diuresis, BAL (2.3-dimercaptopropanol) and DMSA (meso-2.3-dimercaptosuccinic acid) was promptly started to increase As elimination. However, the patient deteriorated and in order to enhance the formation of methylated derivatives, which are potentially less toxic and can be excreted more easily, a cocktail—deducted from a recent in vitro study [2]—was administered. This therapy was started after permission of the local ethical committee and consists of HO-Vit B12, folinic acid, methionine and glutathion. In the urine analysis, As3+, As5+, as well as monomethyl arsenic acid (MMA) and dimethyl arsenic acid (DMA) levels were measured up to 6 months post incident. The patient survived this massive overdose of inorganic As and in the long-term follow-up only polyneuropathy occurred. Conclusion: This case report demonstrates that an acute intoxication with arsenic trioxide can be treated successfully with aggressive therapy and close follow up. References: [1] Michaux I, Haufroid V, Dive A, Buchet JP, Bulpa P, Mahieu P, Installé E. Repetitive endoscopy and continuous alkaline gastric irrigation in a case of arsenic poisoning. *J Toxicol Clin Toxicol* 2000;**38**:471–476. [2] Zakharyan R, Aposhian H. Arsenite methylation by methylvitamin B12 and glutathione does not require an enzyme. *Toxicol Appl Pharmacol* 1999;**154**: 287–291.

103. ACUTE GOLD CYANIDE POISONING

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Background: Potassium aurocyanide is a compound used for gilding goods. Poisoning after oral ingestion is rarely reported and little is known about the consequences of its ingestion. Case report: A 35-year-old man who had already attempted suicide with alcohol and benzodiazepine overdose, was admitted to the Toxicology Unit of AOC 2 h after having deliberately ingested about 50 mL of gold potassium cyanide in alkaline solution. He rapidly developed vomiting and on arrival at hospital he was conscious and only had a reddened face and epigastric pain. Gastric lavage was performed and a yellowish gold liquid was obtained. Activated charcoal was administered together with hydroxycobalamine (6 g i.v) and sodium thiosulphate (8 g i.v). Arterial blood exam was normal and a mild elevation of aminotransferases was present. Despite the therapy the patient was still suffering and agitated and developed tachycardia and tachypnoea. As laboratory tests showed increasing AST, ALT, γ-GT, bilirubin, CK, LDH, chelating therapy with dimercaprol (0.8 g i.v), and reduced glutathione (2.4 g i.v) was also initiated. Serum thiocyanate was detected and levels were similar to those found in smokers, while high levels of gold were detected in gastric lavage, in blood (1220 mcg/dL) and urine. The patient developed a rapid increase in liver enzymes, with features of cholestasis, which reached their maximum level on the second day after ingestion (AST 242 UI/L; ALT 278 UI/L; alkaline phosphatase 210 UI/L; total bilirubin 3.90 mg/dL; γ-GT 525 UI/L). Tests for hepatitis viruses were negative and liver biopsy was not performed. The patient also developed bilateral painful parotid swelling and a significant increase in amylase. Echographic examination of both liver and parotids showed no significative abnormality. From day 4 a persistent polyuria with protein, sodium, chloride and uric acid loss becomes evident. Full antidotal therapy was administered for 5 days and then reduced progressively: the patient received supportive therapy as his clinical condition kept improving. The patient was discharged from hospital on day 18 from intoxication in good condition. Follow up at 30 days showed that liver function was normal and urine and blood gold levels were undetectable. Discussion: Acute gold potassium cyanide poisoning is extremely rare but side effects of gold therapy for rheumatoid arthritis are known. In the stomach potassium aurocyanide forms CN^- and Au^+ ions. Organ toxicity due to these two ions is to be expected. Early antidotal treatment of cyanide toxicity probably prevented severe manifestations of cyanide poisoning. Though poorly absorbed from the gastro-intestinal tract, circulating gold is bound to albumin and has a half-life of approximately 7 days. Plasma gold level does not correlate well with its clinical toxic effects but we believe that specific antidotal therapy with dimercaprol contributed to the recovery of the patient despite evidence of transitory hepatic and renal injury.

104. ANTIMONY TOXICITY FROM THE USE OF TARTAR EMETIC FOR THE TREATMENT OF ALCOHOL ABUSE

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Objective: Antimony is a poisonous element with toxic properties that mimic those of arsenic. Acute oral exposures to antimony are uncommon as there are few remaining uses for this metalloid. Some trivalent and pentavalent antimony compounds are still used medicinally as both human or veterinary antihelminthic and antiprotozoal drugs. Additionally, antimony sodium tartrate (tartar emetic) was used previously to treat schistosomiasis infections and as an emetic and expectorant. Numerous reports describe gastrointestinal complications associated with antimony exposure including vomiting, diarrhea and stomatitis. However, antimony toxicity from the use of tartar emetic as a treatment for alcohol abuse has never been described previously. We report a patient who developed severe nausea, vomiting, diarrhea and subsequently transient renal failure after ingesting tartar emetic. Case-report: A 19-year-old man with a history of alcohol abuse ingested half of a 10 mL bottle of "Soluto Vital" (tartar emetic, 50 mg/mL), produced in Guatemala that is used for treatment of alcohol abuse. The recommended dose was 20–25 drops per dose after ingesting alcohol. He presented 60 minutes after ingestion with severe vomiting, abdominal cramps, soft stools and weakness. His vital signs were: BP 104/71 mmHg; pulse 96/minute, with notable orthostatic changes. His initial creatinine was 2.5 mg/dL, K+ was 6.1 mEq/L, and his hematocrit was 60%. He was given activated charcoal in order to reduce antimony absorption and supportive therapy including IV fluids and antiemetics. Over the next 48 h his creatinine normalized to 1.1 mg/dL and his hematocrit returned to 53%. He was discharged after 48 h of observation. His urine revealed antimony concentration of 1200 mcg/L (normal: less than 10 mcg/L). Conclusion: Although disulfiram is the most common aversive medication used for the treatment of alcohol abuse, and in combination with ethanol produces similar clinical effects, clinicians need to consider antimony toxicity when a patient presents with severe vomiting and diarrhea in this setting.

105. PHENAZOPYRIDINE-INDUCED SULFHEMOGLOBINEMIA

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Objective: Sulfhemoglobin is an abnormal form of hemoglobin formed by oxidant stress. Although incapable of binding oxygen to the affected hemoglobin subunit, the release characteristics of the other subunits are altered to allow easier release of oxygen than normal hemoglobin, producing less tissue hypoxia than expected. Though often assumed that any medication that can cause methemoglobinemia may induce sulfhemoglobinemia, this is a rare complication. We describe a patient who was taking phenazopyridine for an unusually long period of time and developed sulfhemoglobinemia. Case report: A 57-year-old woman presented to the ED with worsening shortness of breath. Her past medical history included hypertension, gastroesophageal reflux disease and chronic cystitis, for which she took amlodipine, cimetidine and phenazopyridine (pyridium), respectively. She has been on the phenzopyridine for several years. She developed cyanosis over a one-week period and had an extensive evaluation prior to being seen in the ED. Echocardiography revealed good left ventricular function and a computed tomographic scan of the chest was negative for pulmonary embolism. Her presenting vital signs were: blood pressure, 135/65 mmHg; pulse, 105 beats/min; respiratory rate, 22/minute; pulse oximetry 86% on room air. Her oral mucosa was notably cyanotic. The trachea was midline, no jugular venous distention and no stridor was noted. The lungs were clear to auscultation bilaterally with no wheezes, rales or rhonchi. The cardiovascular and abdominal examination were normal. Her extremities were markedly cyanotic, but there was no clubbing or edema. Her neurological exam was normal. Chest radiograph was normal. The electrocardiogram showed only sinus tachycardia. A complete blood cell count and electrolytes were all within normal limits. The blood was noted to be dark brown when drawn. The co-oximetry (Bayer 845 Blood Gas System) was initially reported as: pH, 7.43; pCO_2, 23 mmHg; pO_2, 85; oxyhemoglobin, 86.1%; methemoglobin, 0%; carboxyhemoglobin 0%. The patient was empirically treated with methylene blue (1 mg/kg) intravenously twice with no improvement. It was later noted that the sulfhemoglobin on the co-oximeter was reading a qualitative $>1.5\%$ concentration but was unable to report it since there was no quality assurance standard prepared. The patient was observed for seven days and did not receive any further interventions. She improved and was discharged without any sequelae. The sulfhemoglobin was later quantified as 13.9%. Conclusion: Since none of the other drugs that this patient used is known to cause sulfhemoglobin, it is likely that this patient had sulfhemoglobinemia likely secondary to prolonged phenazopyridine use. She improved with conservative management and did not require an exchange transfusion.

106. ACUTE FELBAMATE OVERDOSE WITH CRYSTALURIA

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Case report: A 3-year-old child ingested approximately 3.6 g of her sibling's felbamate elixir (232 mg/kg). She became restless and vomited pink liquid that smelled like the medicine at about 9 h after ingestion. In the emergency department she was restless, fussy and ataxic. The heart rate was 130–150/min. Serum chemistries were normal. Urine collected at 13 h after exposure contained numerous needle shaped crystals and 3–10 RBCs/hpf. The serum felbamate level at 15 h was 138 mg/L. After 12 h of intravenous hydration, the crystalluria and hematuria resolved, and BUN and creatinine remained normal. The ataxia fully resolved after 1 day. Conclusion: Felbamate is an anticonvulsant that is water insoluble and 90% cleared in urine. Felbamate renal stones have been reported with chronic human dosing and in animal studies. Crystalluria has been reported in one acute felbamate overdose, and that patient developed renal dysfunction. Our patient with felbamate induced crystalluria was successfully treated with intravenous fluid therapy.

107. REBOXETINE OVERDOSE

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Introduction: Reboxetine is a bicyclic morpholine derivative that acts as a selective norepinephrine reuptake inhibitor and an alpha-2 adrenoceptor antagonist. It has low affinity for alpha-1 adrenergic and muscarinic cholinergic receptors. Few case reports of reboxetine poisoning have been published up to now and here we describe one patient with high reboxetine plasma levels. Case report: A 32-year-old man, suffering from depression, came under our observation in the Emergency Department, after suicidal ingestion of reboxetine 80 mg, an unknown dose of lorazepam and ethanol. He presented with drowsiness and agitation, bilateral miosis, normal blood pressure (130/70 mmHg) and mild sinus tachycardia (102/min). Oral-activated charcoal 20 g and dextrose 5% infusion were administered and a cardio-monitor applied. Plasma levels of benzodiazepines, barbiturates and tricyclic antidepressants were negative, while ethanol was 184 mg/dL. In the following hours the patient was in a deeper coma but with good reaction to pain stimuli and with normalization of pulse rate. Plasma levels of reboxetine, analyzed by the Toxicological Laboratory of Forensic Medicine of Pavia, were 1,275 ng/mL, 1,060 ng/mL and 625 ng/mL after respectively 7, 12, and 31 hours after admission (half-life: 24 hours). Reboxetine therapeutic plasma level is between 50 to 150 ng/mL (half-life: 13 $\pm$ 5 hours). Therapeutic plasma level of methotrimeprazine (levomepromazine) was also found (35 ng/mL). After 10 hours the patient was more alert but still drowsy and with photoreactive minimal miosis. The patient was admitted to the internal division where he received activated charcoal and dextrose/normal saline infusions until complete resolution of CNS effects. No other cardiovascular effect was observed, in particular blood pressure increase. The patient voluntarily left the hospital the following day. Conclusions: As previously reported, our case-report confirms that reboxetine poisoning, also with high plasma levels, is not particularly dangerous, showing only moderate central nervous system effects (induced also by ethanol), without significant cardiovascular alterations other than mild sinus tachycardia and, in our patient, with an unexpected miosis.

108. SEVERE SEROTONIN SYNDROME DUE TO TRANYLCYPROMINE, THIORIDAZINE AND CLOMIPRAMINE POISONING WITH HEPATOCELLULAR INJURY AND RENAL FAILURE

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Introduction: Serotonin syndrome related to concomitant administration of monoamine oxidase inhibitors (MAOI) with tricyclic antidepressants (TCA) is a serious complication due to inhibition of serotonin and norepinephrine reuptake into the central nervous system and inhibition of their metabolism. There are few reports of the syndrome, complicated with kidney and hepatic injury and we report one after massive clomipramine poisoning plus tranylcypromine and

thioridazine (1,2). Case report: A 38-year-old woman with a long history of depression was brought to the Emergency Department comatose and nonresponsive with suspected clomipramine poisoning. Her body temperature was 41.8°C; blood pressure was not detectable and muscle tone was increased with masseter muscle rigidity and jaw clenching; lateral nystagmus was present. Endotracheal intubation and mechanical ventilation, facilitated by propofol and vecuronium, was started immediately and activated charcoal (2 g/kg/24 h) was administered. Initial laboratory tests were normal apart from creatine phosphokinase 524 IU/L and creatinine 2.69 mg/dL. On the second day, disseminated intravascular coagulation (platelets 12,000/mm^3, prothrombin time 42%, fibrinogen 269 mg/dL, fibrin degradation products 4.5 mcg/dL) with hepatic injury (aspartate transferase 8,240 IU/L, alanine transferase 4,140 IU/L), metabolic acidosis, rhabdomyolysis (creatine phosphokinase 56,585 IU/L) and renal failure (creatinine 3.4 mg/dL) were observed. Serotonin syndrome after clomipramine poisoning was postulated, but no other drugs were reported and serotonin syndrome secondary to clomipramine treatment, complicated by hepatocellular injury and renal failure is very rare. Venous serum levels were sent to the Laboratory of Forensic Medicine of Pavia and clomipramine levels were 1,250 ng/ml (therapeutic level less than 200 ng/ml) on the first day and 1,800 ng/ml on the second day. The next day her psychiatrist reported previous therapy with tranylcypromine (serum level found 35 ng/ml, therapeutic less than 30 ng/ml) and thioridazine. Haemodialysis was started and continued for 33 days, due to severe renal failure. Cerebral magnetic resonance imaging (on day 9) detected multiple ischemic areas and renal biopsy confirmed the presence of severe tubular necrosis. After 3 weeks the patient was extubated with apparently no neurologic damage and partial remission of renal failure. She was transferred to a psychiatric department. Conclusion: Combined poisoning from MAOI and TCA can often induce serotonin syndrome and should be suspected when clinical symptoms are not compatible with pure TCA intoxication. Serotonin syndrome can rarely be complicated by hepatocellular injury and renal failure. References: 1. François B, Marquet P, Desachy A et al. Serotonin syndrome due to an overdose of moclobemide and clomipramine. *Intens Care Med* 1997;**23**:122–124. 2. Prueter C, Schiefer J, Norra C et al. Ping–Pong gaze in combined intoxication with tranylcypromine, thioridazine and clomipramine. *Neuropsychiatr Neuropsychol Behav Neurol* 2001;**14**:246–247.

109. ANTICHOLINERGIC SYNDROME AFTER ISOLATED OLANZAPINE OVERDOSE

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Objective: No manuscripts exist describing the anticholinergic effects of the atypical antipsychotic olanzapine. We present a case of isolated olanzapine overdose presenting with progressive central and peripheral anticholinergic syndromes. Case report: A 25-year-old man who was just discharged from an inpatient psychiatric facility presented 2 h after taking 15 sample tablets of olanzapine (20 mg each) that he was given upon discharge. His other medications included only trazodone as needed for sleep. His initial heart rate (HR) was 125 beats per minute, blood pressure (BP) 138/81, and temperature 38.1 degrees centigrade. Electrocardiogram demonstrated a sinus tachycardia at 117 bpm with QRS duration of 82 msec, QTc of 407 msec, and no ischemic changes. Physical exam was essentially unremarkable and not consistent with any toxidrome. The patient received 50 g of activated charcoal and basic chemistries were sent. Within 90 minutes of presentation the patient's HR increased to 150 bpm. He became agitated, delirious, had dry skin and mucous membranes, and minimally reactive pupils. Repeat ECG showed a sinus tachycardia at 139 bpm with a QRS of 76 msec and QTc of 426 msec. A test dose of 0.5 mg of physostigmine was given without any effects. A further 1.5 mg of physostigmine was given 5 minutes later with a gradual improvement in the patient's delirium. Due to the patient's partial response, another 1 mg of physostigmine was given, with resultant clear sensorium and mentation. The patient required no further physostigmine or other pharmacotherapy. A comprehensive urine toxicology assay demonstrated olanzapine, physostigmine, and possibly trazodone. Conclusion: We present a case of isolated olanzapine overdose with progressive anticholinergic syndrome. Delirium or other findings consistent with an anticholinergic state in the setting of olanzapine overdose should prompt the clinician to consider physostigmine therapy, provided contraindications to its use do not exist.

110. VALIDATION OF A DECISION-MAKING ALGORITHM TO DECIDE THE INDICATED METHOD OF GUT DECONTAMINATION IN PATIENTS WITH ACUTE THERAPEUTIC DRUG OVERDOSE

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Objective: In light of the current controversy on the indications for gut decontamination in patients with acute therapeutic drug overdose, we decided to design and validate an algorithm to choose the best method to prevent absorption of the toxic agent. Methods: An algorithm was designed to choose between syrup of ipecac (initial dose: 30 mL), gastric lavage, activated charcoal (initial dose: 25 g) or no treatment, according to the type of therapeutic drug ingested, the dose, the time from ingestion and the clinical condition of the patient. The algorithm was incorporated into the daily clinical practise of the Emergency Department. To validate the algorithm, epidemiological, clinical and toxicologic variables of all drug overdoses were collected prospectively during three months. The evolution of patients following the algorithm was compared (using the SPSS statistical package) with those in which alternative courses of treatment were followed. Results: One-hundred and seventeen patients were included. The average age was 35 years, 65% were females. Ingestion was voluntary in all cases, with benzodiazepenes being the drug group most often involved. In 84 cases the algorithm was followed (Group A) and in 33 another course of decontamination was pursued (Group B). Both groups were comparable on arrival at the emergency department with regard to sex, age, time from ingestion, type of medication ingested, level of consciousness (according to Glasgow Coma Scale) and vital signs. Twelve percent of patients in group A and 21% in group B presented a clinical deterioration after admission; 2 and 6%, respectively, were admitted to the intensive care unit; the average time until discharge was 15 and 52 h, respectively, and it was considered that 73% of the cases in group A and 69% in group had a totally satisfactory evolution, although none of these differences was statistically significant. The adverse effects most often observed were vomiting following administration of activated charcoal (11%) and bronchoaspiration following gastric lavage (1/10). There were no deaths in either of the two groups. Conclusions: Using a specifically-designed algorithm to decide on priority methods of digestive decontamination is associated with a more satisfactory clinical evolution of acute therapeutic drug intoxications, although the differences were not statistically significant.

111. SEVERE METHANOL POISONING TREATED WITH FOMEPIZOLE AND HEMODIALYSIS: REPORT OF TWO CASES

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Objective: Methanol poisoning is a medical emergency characterised by metabolic acidosis, visual disturbances and circulatory and respiratory collapse. Recently, the new antidote fomepizole has been approved as an antidote in this poisoning by inhibiting the continuous metabolism of methanol to formic acid. Arguments in favor of fomepizole (as compared to ethanol) are less side effects and easier administration. We present two cases of severe methanol poisoning where rapid treatment with fomepizole and hemodialysis were associated with a favourable outcome. Case reports: *Case 1* (F 54) was admitted because of severe dyspnoea and "almost blindness" several days after ingestion of a methanol/ethanol mixture. Upon admission her S-methanol was 15.6 mM (50 mg/dL), pH 6.91, pCO_2 1.9 kPa, HCO_3 2.8 mM, base deficit 39 mM, osmolal gap 16 mOsm/kgH_2O and anion gap 40 mM. S-ethanol and S-ethylene glycol was zero and S-formate 6.4 mM 3 h after admission. Fundoscopy revealed the typical 'pseudopapilitis' seen in severe methanol poisoned subjects. She was immediately treated with bicarbonate (750 mmoles) and fomepizole twice. Hemodialysis was initiated 2 h after admission and continued for 5 h. S-half lives of methanol and formate during dialysis were approximately 3.2 and 2.8 hrs, respectively. Acid-base status normalized within 3 h and visual disturbances also regressed completely. She was discharged on day 3 following a complete normal ophthalmologic exam, including perimetry. *Case 2* (M 42) was admitted because of dyspnoea and blurred vision several days after ingestion of a similar methanol/ethanol mixture. Upon admission his pH was 6.87, pCO_2 2.9 kPa, HCO_3 3.8 mM, base deficit 29 mM, anion gap 43 mM and osmolal gap 61 mOsm/kgH_2O. S-methanol level was 32.5 mM (104 mg/dL) and S-formate was 11.6 mM 3 h after the admission. Fundoscopy revealed typical 'pseudopapilitis'. He was immediately treated with bicarbonate (750 mmoles) and fomepizole four times. Hemodialysis was initiated 2 h after the admission and continued for 8 h. S-half lives for methanol and formate during dialysis were 4.0 and 2.3 h, respectively. Because of respiratory arrest 30 min after admission he was intubated and treated with mechanical ventilation for 25 days, also due to pneumonia and sepsis. Cerebral CT and MRI showed typical hemorrhagic necrosis of the basal ganglia. He is still in hospital and will be discharged with permanent sequelae. Conclusion: The present cases demonstrate that rapid treatment with alkali and fomepizole may reverse the metabolic disturbances of methanol poisoning, whereas haemodialysis is associated with

a rapid elimination of methanol and formate. Rapid initiation of treatment also reversed the pronounced visual disturbances seen in case 1.

112. IN VITRO BINDING OF LITHIUM CARBONATE TO PRUSSIAN BLUE AND ACTIVATED CHARCOAL

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Objective: Prussian Blue (potassium ferric hexacyanoferrate) has been described as an effective chelating agent for thallium. By mechanism of potassium ion-exchange, Prussian Blue might serve as an ion-exchange adsorbent for elements other than thallium. Lithium has similar chemical properties to potassium. The purpose of this experiment was to determine if Prussian Blue has any binding affinity for lithium. Methods: A standard aqueous solution of lithium carbonate was agitated at 25°C with Prussian Blue at lithium:adsorbent ratios ranging from 1:100 to 1:100,000 as well as a solutions of 1:1000 with 50 g of activated charcoal and 1:1000 plus 18.7 mg activated charcoal added. After thorough agitation, the mixtures were suction filtered. Supernatant lithium concentrations were measured by atomic absorption spectrophotometry and compared to the prepared lithium standard curve. Results: The adsorptive capacity of Prussian Blue can be seen by measuring the decrease of absorption values. The lithium:Prussian Blue of 1:100,000 and 1:1000 plus 50 g activated charcoal both showed a decrease in absorbance readings of 89.9%. The lithium: Prussian Blue of 1:100, 1:1000, and 1:1000 plus 18.7 mg of activated charcoal demonstrated a range of only 4–7% decrease in atomic absorption values. Conclusion: This in vitro study demonstrates that Prussian Blue with or without activated charcoal has some binding affinity for lithium which is concentration-dependent. The quantities of Prussian Blue necessary for binding are greater than would be physiologically feasible to administer in vivo. The decreased atomic absorption of the solution containing activated charcoal may represent a synergistic effect of charcoal and Prussian blue or may represent an ability of charcoal to bind lithium independently.

113. THE USE OF PHYSOSTIGMINE IN ANTICHOLINERGIC SYNDROME

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Aim of study: The use of physostigmine in treatment of the anticholinergic syndrome is common, but controversial because of the well-known severe side effects of the drug. We performed an explorative data analysis on the indication of its use. Patients and methods: Drug exposures reported to the Poison Control Center Mainz/Germany are documented with the ADAM documentation and evaluation system. We focused on drug exposures where physostigmine was given or recommended in cases of an anticholinergic syndrome in the period from 1.1.1995–30.6.2002. Initially we assessed whether physostigmine was indicated due to the ingested drug or the appearance of symptoms. Secondly we evaluated cases of amitriptyline or diphenhydramine poisoning with a poison severity score 2 and 3, where physostigmine was not recommended by the Poison Control Center. Results: 7107 cases were analyzed according to these criteria. In 96% of the cases physostigmine was indicated due to the type of drug to which the patient was exposed. The administration of physostigmine was reported in 471 cases. Physostigmine was mistakably given in 10% of 160 of these cases, where it was given prior to the call at the Poison Control Center. The mistake rate was 5% in those cases where physostigmine was given following the call at the Poison Control Center. We found that in 50% of the cases with written follow-up ($n = 436$), the use of physostigmine was not indicated due to a lack of severe symptoms. In 1.1% of the amitriptyline and in 0.8% of the diphenhydramine poisoning cases, with poison severity scores 2 and 3, it was, in our view mistakenly, not recommended by the Poison Control Center. Conclusion: The use of physostigmine should be carefully considered. It should be restricted to the treating severe symptoms in anticholinergic poisoning, such as severe tachyarrhythmias and seizures non-responsive to conventional treatment.

114. HOW AVAILABILITY AND ACCURATE USE OF ANTIDOTES CAN BE ACHIEVED BY USING A NATIONAL ANTIDOTE DATABASE

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Objective: To describe the development of a national system, ensuring adequate availability and accurate use of antidotes. Methods: Since it's start the Swedish Poisons Information Centre has taken on the responsibility to evaluate and, whenever appropriate, introduce new antidotes into the country. To implement an optimal antidote program, considering medical, practical and economical aspects, the following strategy has gradually been developed. (1) The information on antidote use, given by the PC to doctors handling acute cases, has been completed with two publications (one for pharmaceuticals and one for other kinds of poisoning) updated every one–two years and distributed to all doctors in the country. These texts inform about indications, dose and administration of all antidotes currently recommended. (2) A national list of antidotes that is evaluated by the PC is regularly distributed to all hospital pharmacies and responsible clinicians. This list also includes recommended quantities to be stored and the indications. (3) A separate list of recommended antidotes has been prepared for use in major chemical accidents to be kept in hospitals and mobile units. (4) The antidotes are classified in terms of urgency: (A) immediate access, e.g., naloxone; (B) access within 2 h, e.g., antidigoxin Fab; (C) access within 4–6 hours, e.g., octreotide. This classification will allow a regional planning, so that certain antidotes (e.g., those rarely used or expensive) can be stored in a cost-effective way. (5) The most recent component in the antidote system is a centralised antidote database, operated by the PC. It contains exact information on all antidote stocks kept in Swedish hospitals (around 85 emergency hospitals): antidotes currently stored, quantity, shelf life, where in the hospital the stores are located, indications and administrative aspects (e.g., legal status). Antivenoms for both indigenous and exotic snakes are also integrated into this system. Any changes of the stocks are reported directly by the hospital pharmacist to the PC and entered into the database. Results: The integration of an antidote database has completed and strengthened the national antidote system, that now instantly can tell the PC and its customers where and in which quantity a certain antidote can be found. This database is a good tool for making decisions on cost-effective regional storing of antidotes. Conclusion: The antidote system currently used has proven efficient in providing instant information, around the clock, on medical and administrative aspects, ensuring accurate antidote use.

115. A PROSPECTIVE EVALUATION OF ABBREVIATED ORAL N-ACETYLCYSTEINE (NAC) THERAPY FOR ACETAMINOPHEN (PARACETAMOL) POISONING

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Objective: Standard oral NAC therapy in the U.S. consists of a 140 mg/kg loading dose followed by 17 doses of 70 mg/kg every 4 h. However, a significant minority of these patients never develop even mild hepatotoxicity (1). If patients at no risk of hepatotoxicity were treated with an abbreviated course of NAC, substantial savings in resources may be realized. Our objective was to prospectively evaluate the efficacy of short-course oral NAC therapy in acute acetaminophen poisoning. Methods: Since July 1997 we have treated patients at our institution with serum acetaminophen concentrations above the Rumack-Matthew nomogram treatment line (150 μg/mL (990 μmol/L) at 4 hours post-ingestion) with 24–48 h of oral NAC, provided that LFTs are within normal limits and serum acetaminophen concentration is below 10 μg/mL (60 μmol/L) at 24 h post-ingestion. If either of these conditions is not met, the patient receives standard NAC therapy. Only those patients admitted to our University hospital within 24 h of ingestion were included. Primary outcomes were death at 30 days or need for liver transplantation. Secondary outcomes were severe hepatotoxicity (ALT or AST $>$ 1000 IU/L), or any AST or ALT value of $>$2 times upper limit of normal. Abbreviated NAC therapy was defined as $\leq$12 doses. Patients were followed up by phone, computer search of hospitalizations and lab values, or contact with primary physician. Massachusetts' death and transplant records were also queried to identify any patient not accounted for. Results: Summary data are presented in Table 1. Two patients were lost to followup. No deaths or transplants were discovered upon transplant center or death certificate review. One patient had mild elevation of ALT (111 IU/L) during NAC therapy that returned to

Table 1. Patients treated with abbreviated NAC.

# Patients abbreviated NAC:	33
# (%) men/women:	6 (18)/27 (82)
Mean age (range):	21.2 years (7–58)
Mean # NAC doses (range):	7.1 (4–11)
# with 30 day followup:	31
Complications:	Death or liver transplant: 0
	Severe hepatotoxicity: 0
	Any LFT > 2 X normal: 1

normal by hospital discharge. Conclusions: Abbreviated NAC therapy (≤12 doses) appears safe and effective for those patients with acetaminophen poisoning who have normal LFTs and serum acetaminophen concentrations of less than 10 μg/mL 24 h after ingestion. A larger prospective investigation of this therapy is warranted. References: 1. Woo OF, Mueller PD, Olson KR et al. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med* 2000;**35**:363–8.

116. ARTIFACTUAL ELEVATION OF PLASMA L-LACTATE IN THE PRESENCE OF GLYCOLATE—A POTENTIAL FOR MISDIAGNOSIS

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Objective: Glycolate can cause large artifactual elevations in plasma L-lactate measurements when measured by the L-lactate oxidase enzymatic method because of structural similarities between them. This has a potential for misdiagnosis of lactic acidosis in the work up of an anion gap acidosis, and unsuspected ethylene glycol poisoning. We report a case of ethylene glycol overdose with high lactate levels because of this interference. Case report: A 66-year-old male was found to confused, on his bedroom floor, by his daughter. He had a history of paranoid schizophrenia, and previous stroke. The family reported that he had depressive symptoms since the death of his wife and had been newly prescribed risperidone. On physical examination he was noted to be somnolent and confused but in no acute distress. He was afebrile. His vitals showed HR 113/min, BP 180/90 mm/Hg, RR 26/min(deep), SaO_2 96% on 2 L NC. Exam was non-focal, and abnormal only for altered sensorium, dry mucous membranes, and tachycardia. His laboratory revealed: Na 139 meq/l, K 3.7 meq/l, Cl 105 meq/l, HCO_3 12.8 meq/l, BUN 11 mg/dl, Cr 0.8 mg/dl, Glu 184 mg/dl, Osm 349 mOsm/L, and Ethanol 0 mg/dl. His arterial blood gas showed: pH 7.14/PCO_2 21.5 mmHg/PO_2 93.4 mmHg, SaO_2 96%. The lactate was 22.5 mmol/L. His ethylene glycol level was 141 mg/dl. An initial diagnosis of sepsis was made, but once the ethylene glycol level came back he was started on an alcohol drip, given thiamine and pyridoxine, and sent for hemodialysis. The ethanol drop was stopped when fomepizole became available. The lactate level normalized with treatment. The patient did well and was transferred to psychiatry. Conclusion: Physicians need to be aware of this potential interference by glycolate so that they are not misled. However, this information can be a useful clue for suspected ethylene glycol intoxication and help to make an early diagnosis. The artificially elevated lactate can be used as a surrogate marker for high glycolate levels.

117. ETHANOL ELIMINATION FOLLOWING MASSIVE INGESTION IN A CHILD

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Objective: At low to moderate levels, ethanol elimination follows zero-order kinetics. It is not known, however, whether renal, pulmonary or other first-order pathways become significant in patients with very high serum ethanol levels. Additionally, it is unclear if and when ethanol naïve subjects are able to abruptly induce their metabolism during acute intoxication. We present the pharmacokinetic analysis in a child with a massive ingestion of ethanol.

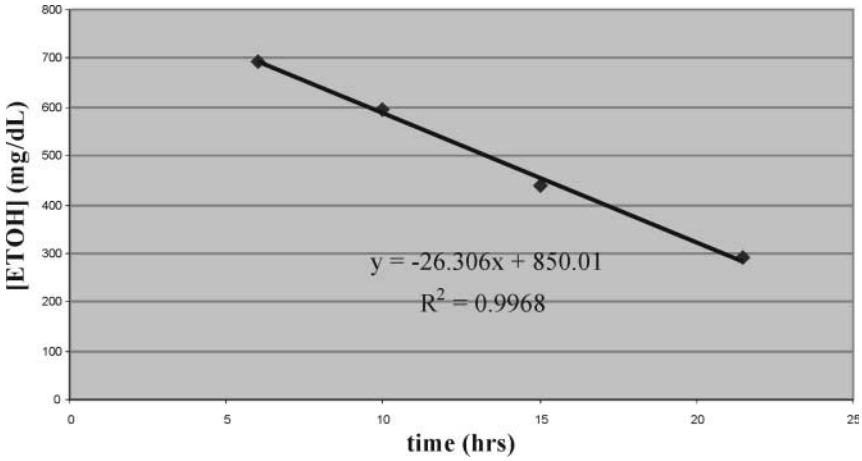

Figure 1. Post-absorptive phase ethanol levels.

Case report: A 15-year-old girl without significant past medical history presented to the Emergency Department after drinking 24 ounces of tequila. She was found unresponsive at home with a Glasgow Coma Score (GCS) of 3. Her presenting vital signs were: blood pressure, 118/69 mmHg; pulse, 88/min; respirations, 20/min; pulse oximetry 96% on room air. Other than obtundation, the remainder of her physical examination was normal. She was intubated for airway protection and admitted to the intensive care unit. Her initial serum ethanol level was 543 mg/dL (118 mmol/L). A repeat level 3 h later was 722 mg/dL (157 mmol/L). Post-absorptive ethanol levels decreased from 624 mg/dL (136 mmol/L) to 291 mg/dL (63 mmol/L) over the following 15.5 h. The patient had spontaneous eye opening 24 h after presentation. Her projected serum ethanol level at that time was 215 mg/dL (47 mmol/L). She was extubated 2 h later and had an uneventful recovery. Results: Starting from a level of 694 mg/dL, the elimination of ethanol in the post-absorptive phase remained zero-order at a rate of 26.3 mg/dL/hr (5.7 mmol/L/hr) with an R^2 of 0.9968 ($p < 0.01$). There was no evidence of induction. Conclusion: Even at very high ethanol levels in ethanol naïve subjects, elimination of ethanol is well-described by a zero-order pharmacokinetic model.

118. A CASE OF SEVERE METHANOL POISONING REFUSED FOR ORGAN DONATION, WITH ALMOST NORMAL POST-MORTEM PATHOLOGIC FINDINGS. ORGAN DONATION SHOULD BE CONSIDERED

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Background: kidney, liver and lung transplantation with grafts obtained from methanol poisoned donors have been performed successfully[(1,2,3)], although our transplantation centre was very reluctant to use organs from a man with severe methanol poisoning. We subsequently investigated the post-mortem pathology changes in the heart, kidneys, pancreas, lung, and liver. Case report: A 42-year-old man was admitted comatose with suspected methanol poisoning. Blood pressure was 77/33 mmHg, pulse 56/minute, rectal temperature 32°C. Lab results: pH: 6.74, base deficit 30.6 mmol/L, bicarbonate: 5.2 mmol/L, lactate: 6.6 mmol/l, creatinine 2.9 mg/dL and potassium 8.6 meq/L. Methanol level was extremely high: 463 mg/dL. ECG showed signs of hyperkalemia. Cardiac echocardiography was not performed. Nonoliguric renal failure was present. Despite therapy with haemodialysis, bicarbonate, ethanol and inotropic support (severe acidosis and shock) the patient was pronounced brain dead 10 h after admission. Organs were refused for donation because of severe methanol intoxication. Autopsy showed: normal macroscopic findings of the heart, kidneys and liver and pulmonary oedema. Pancreas inspection was suggestive of acute pancreatitis. Microscopy showed: heart: normal findings, lungs: normal alveolar structure, intra-alveolar fluid and capillary congestion, pancreas: autolysis but no signs of acute pancreatitis, liver: minimal and focal centrilobular necrosis and kidneys: normal findings. Conclusion: Despite a severe poisoning with methanol presenting with acute renal failure, severe metabolic acidosis, shock and mild

cardiac failure post mortem microscopy did not reveal pathologic changes in the heart, liver, pancreas and kidneys. Organ donation in severe methanol poisoning should be considered. Based on theoretical consideration kidney and heart donation was an option. References: 1) Hantson Ph, Vanormelingen P, Squifflet JP, Lerut J, Mahieu P. Methanol poisoning and organ transplantation. *Transplantation* 1999;**68**:165–166. 2) Evrard P, Hantson P, Ferrant E et al. Successful double lung transplantation with graft obtained from a methanol-poisoned donor. *Chest* 1999;**115**:1458–1459. 3) Radam M, Hamza A, Landgraf B, Fornara P. Succesful multiorgan transplant after donors death caused by suicidal methanol ingestion. Abstract EAPCCT XXII International congress.

119. APPLICATION OF BLOOD METHANOL AND ACETALDEHYDE CONCENTRATIONS MEASUREMENT AS MARKERS OF ALCOHOL DEPENDENCE

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Almost all alcoholic drink contains acetone, methanol and other alcohols as impurities. These allow for the presence of acetone, acetaldehyde, methanol, isopropanol and n-propanol to be detected in the blood of alcohol addicted patients. In addition to liver enzymes (SGTP, SGOT, GGTP, CDT) some volatile compounds (e.g., methanol) are used as the markers of alcohol addiction. Objectives: The aim of the study was to compare the usefulness of measurement of methanol and acetaldehyde concentration in blood as markers of alcohol addiction. Methods: 48 alcohol addicted and acutely poisoned patients in the Detoxification Unit, Toxicology Clinic, Jagiellonian University, Krakow, with a history of alcohol abuse for more than three years, participated in the study. The control group was social drinkers accidentally poisoned by ethanol (in psychological and psychiatric examination alcohol addiction was excluded). Blood samples for toxicological study were taken in heparinized tubes just after admission to the clinic and later three times during 24 h of treatment. The ethanol concentrations in a series of whole blood samples were measured by enzymatic method (ADH) and other compounds (methanol, acetaldehyde, acetone, isopropanol and n-propanol) using headspace gas chromatography. Results: The results have shown a four times higher concentration of acetaldehyde (6 mg/L) and five times higher concentration of methanol (30 mg/L) in blood of ethanol addicted patients than was found in accidentally poisoned patients. Also the elimination rate of the studied compounds was slower in addicts than in social drinkers. These results show good correlation with psychological and psychiatric tests of alcohol addiction recommended by the WHO. Conclusions: Our study suggests that measurement of methanol and ethanol can be used as markers of alcohol addiction. Further studies using more accurate markers (ethyl glucuronide) of alcoholism should validate the usefulness of the proposed as a simple, inexpensive method of proving the alcohol addictions.

120. ETHYLENE GLYCOL POISONING IN A CHILD: EFFICACY AND SAFETY OF FOMEPIZOLE TREATMENT

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Introduction: Ethylene glycol (EG) is used as an antifreeze in cooling and heating systems, in hydraulic brake fluids and as a solvent in the paint and plastics industries. Its sweet taste results in a very high risk for ingestion and poisoning in children. Fomepizole is an alcohol dehydrogenase inhibitor for treating EG and methanol poisoning. Case report: A 3-year-old child, 13 kg weight, was admitted in the pediatric ED 2 h after ingestion of diluted antifreeze (EG 50%). Somnolence and mild metabolic acidosis (venous pH: 7.29, HCO_3: 17.8, BE: −7.7) were the only symptoms observed in the child. Gastric lavage and activated charcoal decontamination were undertaken, oral ethanol 40% was administered as antidotal therapy and a fluid infusion commenced. EG plasma and urine levels (70 mg/dL and 835 mg/dL, respectively) were rapidly obtained. In view of the EG plasma level, the spontaneous correction of metabolic acidosis, the resolution

of somnolence and the low ethanol plasma level obtained (less than 50 mg/dL), fomepizole administration without hemodialysis was started 8 h after ingestion. Fomepizole dosage regimen was selected based on the EG plasma level: 15 mg/kg as the first dose, followed by a second dose of 10 mg/kg after 12 h and a third dose of 7.5 mg/kg after another 12 h. No side effects were observed during or after fomepizole infusion. EG plasma level lowered to 12 mg/dL 22 hours after the ingestion and was undetectable after 46 h. The child was discharged without other clinical effects of EG poisoning 48 h after admission. Conclusions: Fomepizole can be safely used in the EG poisoning in children, and may avoid the necessity of hemodialysis in patients without renal impairment or significant metabolic acidosis.

121. METHANOL OUTBREAK IN RURAL AREAS: USE OF ANION AND OSMOLAL GAPS IN THE DIAGNOSIS OF METHANOL POISONING

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Objective: Despite effective treatment with alkali, antidotes and dialysis morbidity, and mortality in methanol poisoning is still considerable because of delayed diagnosis. Although not without controversy, the use of the anion (AG) and the osmolal gaps (OG) has been recommended as diagnostic tools in patients presenting with metabolic acidosis of unknown origin. We have evaluated this tool in 16 patients poisoned with methanol. Patients and methods: The present patients were all part of a methanol outbreak where patients mainly were admitted to hospitals without methanol analyses available on a 24 h basis. In the acute setting, the triage and treatment decisions were mainly based upon the values of the OG and AG upon admission. Blood samples were sent to larger hospitals for methanol determinations, which were helpful in the further treatment of the patients. In retrospect, these methanol levels were compared to the OG and AG in 16 patients and the correlation is presented here. Results: The regression line between the OGs (ordinate) and S-methanol concentrations ($y = 1.041x + 10.31$) showed an excellent fit with $R^2 = 0.943$, indicating a reference value of OG of 10 $mOsmkgH_2O$ in this series of patients. There was also a good fit to the identity line of ($y = x + 5$) based on the previously published reference value for OG of 5 ± 20 $mOsmkgH_2O$ (mean ± 2SD). The AGs correlated well with the values of the base deficits, as could have been expected. There was no correlation between the AGs and the S-methanol concentrations ($y = -0.0279x + 38,069$, $R^2 = 0.0133$). Unexpectedly, there was no inverse relation between the OG and AG. Even if one outlayer value with the highest OG was removed, such an inverse relation could hardly be demonstrated ($y = -0.1118x + 41,185$, $R^2 = 0.1536$). Both gaps were elevated in 10 of the 16 subjects. Six patients had a normal OG (because of low S-methanol), but elevated AG because of formate accumulation. One patient with concomitant ethanol ingestion had a high OG and a normal AG. Conclusion: The present data illustrates that these robust laboratory parameters were useful in the diagnosis and triage of methanol-poisoned subjects. Confounders were low S-methanol and concomitant ethanol ingestion. References: Aabakken L, Johansen KS, Rydingen EB, Bredesen J, Ovrebo S, Jacobsen D. Osmolal and anion gaps in patients admitted to an emergency medical department. *Hum Exp Toxicol* 1994;**13**:131–4.

122. CHEMICAL POISONINGS IN KRAKÓW POPULATION AND AGE RELATION (1997–2001)

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Objective: Each Kraków resident older than 14 stated or suspected to be poisoned is served by the Department of Clinical Toxicology Jagiellonian University Medical College. This enables a precise recording of all medical intervention related to poisonings. A contribution of Forensic Medicine Department enables also on the spot victims recording, so full epidemic analysis of poisonings among adult Kraków residents can be done. The aim of the study is to present the pattern (frequency, poisoning type, toxic agent involved) of adolescent and adult poisonings in Kraków in 1997–2001. Material and methods: The analysis included 17931 patients: 6016 (33.5%) women and 11915 (66.4%) men treated at the Kraków Department of Clinical Toxicology and 582 victims on the spot. The frequency of cases was expressed by incidence rate per 10000 of Kraków inhabitants. Data concerning the number of population was obtained from the City Statistic Office in Kraków. Results: Incidence rates per 10000 were 46.9, 43.7, 43.6, 52.4, and 55.4 in the analyzed years respectively.

The rate of patients between 20–39 years old was highest however downward trend was noticed through the period. The upward tendency was noted in older group of poisoned patients. A suicidal poisonings were predominant in 1998 and 1999 in the youngest and oldest groups: 37.1%, 37% in 1998, and 25.5%, 22.2% in 1999 respectively. The medication drugs were mostly involved in adolescent acute intoxication. The highest rate of ethanol poisoning was found in male patients between 40 to 59 years old. A fatal outcome was noted in 89 hospitalized cases, so the average mortality rate was low (0.5). A medication drugs (30.4%) followed by ethanol (17.4%), carbon monoxide (13%) and solvents (13%) were involved in lethal poisonings in the oldest group of patients. Significant increase in mortality rate (average 3.5) while including the victims on the spot was caused mainly due to ethanol, carbon monoxide, and drug poisoning.

123. ACUTE POISONING IN OCCUPATIONAL SETTING: A UNIQUE MODEL FOR ANTIDOTE AVAILABILITY

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Background: It is well known that many hospitals have insufficient antidote stocks, defined as the complete lack of the antidote or the presence of an inadequate amount to treat one seriously poisoned 70-kg patient. Acute occupational poisonings usually involve more than one patient, with subsequent need of larger amount of antidotes. Objective: To create a model to ensure prompt antidote availability for toxicologic emergencies in industrial setting, through the constitution of an antidotes stockpile in chemical plants. Methods: Thirty-six petrochemical plants, widespread all over Italy, were included in the study. For each plant, working processes were analyzed in order to identify chemicals involved and risks of acute poisoning. Accidental non-occupational poisoning occurring at the workplace was also considered. Potential antidote use during emergencies was assessed, according to factory size and workers number. Minimum antidote stocking was defined as the amount needed to treat three severely poisoned patients; the possibility to get additional doses of a given antidote from other plants was also considered. Operating procedures to ensure the proper use of antidotes were prepared. Information of nearby hospitals was considered. Results: For the management of the chemical emergencies in petrochemical plants 18 antidotes were identified. Each plant was given non-specific antidotes (syrup of ipecac, activated charcoal, simethicone, liquid paraffin) and antidotes for pre-hospital management of fire victims (amyl nitrite, oxygen, hydroxocobalamin). Other antidotes (folic acid, ethanol, methylene blue, calcium chloride, calcium gluconate, calcium disodium edetate, calcium gel, N-acetylcysteine, polyethylene glycol, penicillamine, sodium thiosulfate) were supplied according to specific risks in single plants. Antidote stocking and replacement, when needed, was considered a Poison Center (PC) responsibility. In order to avoid antidote misuse, in the operating procedures it was clearly stated that antidotes have to be used under the advice of the PC physician both in pre-hospital and hospital setting. Special attention was addressed to make sure the antidote is brought to the Emergency Department (ED) with the patient. EDs, intensive care units and hospital headquarters were repetitively mailed and kept updated with the activities accomplished. Discussion: Insufficient hospital stocking of a variety of antidotes is a worldwide problem. This unique procedure for the management of antidote stockpiles in industrial plants under the PC responsibility, together with 24 h clinical advice from PC physicians, should allow a timely and proper management of cases of acute occupational poisoning. Moreover, through PC intervention, antidotes may be made available for other cases of poisoning presenting in the EDs of the hospitals close to the plants.

124. ACUTE OCCUPATIONAL POISONING BY CYANURYL CHLORIDE: A CASE REPORT

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Background: Despite its extensive use as a atrazine precursor, poisoning by cyanuryl chloride is rarely observed. Case report: A 45-year old male was accidentally exposed to cyanuryl chloride dust by inhalation and skin contact. The accident occurred at work, during the transfer of product into a storage container. The patient developed severe bronchoconstriction followed by severe respiratory failure and cardiac arrest. Life support measures were started at the scene. Due to the pre-dispatch of possible cyanide poisoning, the patient was given hydroxocobalamin 5 grams

intravenously. The patient was brought to the intensive care unit (ICU). On admission, he was comatose (GCS 3) without focal neurological deficit, and hypertensive. Symptomatic and supportive treatment was started. Cyanide was negative in patient's blood and urine samples. Treating physicians noticed that the skin was diffusely reddish, without signs of thermal or chemical burn, and ordered a skin biopsy. During the following 24 h the patient regained spontaneous respiratory activity and consciousness. Thirty-six hours after poisoning, the patient had a generalized seizure. EEG exam showed left hemisphere abnormalities, and phenobarbital was started. Severe myoclonus, interfering with voluntary movements, became evident 48 h after poisoning. The clinical picture partially improved when clonazepam 4.5 mg/day was added to therapy. One week later, the patient still had mild dysarthria, dysmetria, dysdiadocokinesia, slurred speech, and moderate intention tremor. Standing was not possible due to sustention tremor and balance deficit, leading the patient to fall to the right. Abnormal synergies during voluntary movements, pyramidal tract deficits, and limitation of joint movements were absent. MRI revealed the presence of a slight, focal hyperdense signal, localized into the right and left middle cerebellar peduncles, extending toward the left corticospinal tract. A diagnosis of anoxic encephalopathy with post-anoxic action myoclonus was made. The patient was started on a rehabilitation program. Two months after poisoning, a balance deficit is still present. The incisional skin biopsy performed in the ICU failed to demonstrate hydroxocobalamin epidermal or dermal deposits. Discussion: Cyanuryl chloride is a strong airways irritant, not leading to direct organ toxicity. However, the severity of early respiratory impairment may cause anoxic sequelae, as in the case presented. Undetectable cyanide levels in patient's blood and urine confirm that cyanuryl chloride is not a cyanide-releasing compound. However, emergency team associated the name "cyanuryl chloride" to cyanide poisoning. The patient did not suffer any relevant adverse effect from hydroxocobalamin administration. In a suspected cyanide poisoning, hydroxocobalamin administration seems reasonable, because of its safety profile.

125. STUDENTS SAFETY DURING LABORATORY TRAINING—EXAMINATION OF WORKING ENVIRONMENT

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Students of many faculties (e.g, chemistry, pharmacy, agriculture, biology) spend a large amount of time in chemical laboratories. A guarantee of safety conditions of university laboratories is an obligation of the faculties and should be periodically checked. Objectives: Different countries adopt different methods of checking the students working conditions during laboratory exercise. The legal regulation of checking university students' working conditions varies between European countries. The differences will be discussed. In particular we will discuss the approach taken in examining the working conditions in the laboratories of two polish medical schools in Poznan and Krakow. Methods: The following chemicals were studied in the laboratories of both schools: acetone, methanol, ethanol, butyl alcohol, chloroform, xylem, ethyl acetate, hydrochloride, sulphur dioxide, diethyl ether, phenol, formaldehyde and acetic acid. All chemical assays were performed according to the polish rule of law. Results: generally the examinations of air pollution in chemical laboratories were performed every two years. In laboratories where threshold limit value-time weighted average (TLV-TWA) was exceeded the next measurement was carried out within six months. When the measured value was 0.5–1.0 TLV-TWA, further inspection occurred after one year. The results of 10 years study of air pollution in the students chemical laboratories have shown that TLV-TWA was exceeded in only a few cases. These cases mainly involved air contamination by formaldehyde. The initial high formaldehyde fell by over 50% by the time of repeat measurement at one year. There was no difference between the two polish university schools studied. Conclusion: The obligatory Polish system of checking working condition in student research laboratories helps to create a safe working and teaching environment in university medical schools.

126. INTRAVENOUS AND SUBCUTANEOUS INJECTION OF MERCURY

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Background: Parenteral mercury intoxication is rare. We report the case of a 40 mL metal mercury intentional injection in the arm which required surgical incision and caused significant contamination of surgical instruments. Case report: A 44-year-old gold washer amateur was admitted 48 h after an intravenous and subcutaneous injection of 40 mL of mercury in the back of his left hand and left elbow fold, in a suicide attempt. He had an edematous, painful arm, with blisters and paresthesias, biological inflammatory syndrome, without rhabdomyolysis. Radiologicaly, mercury was visible all along the external radial venous segment. The patient was given a surgical exerese of mercury and antibiotherapy by amoxicilline-acid clavulanic and metronidazole. The development was favorable without pulmonary, neurological or renal complications after only a 5-month period passing by. The functional forecast of the arm is more reserved with ankylosis and fibrous retraction of the elbow. The mercury maximal rates observed are 504 μg/l in blood and 1550 μg/l in urines (standards < 10 μg/l) at Day 12. The patient did not receive chelation. The problem of the mercurial contamination of the operating room was also raised. The average mercury concentration in the air was 7.50 ± 1.50 μg/m3. The surgeon's urinary mercury concentration was 4 μg/l. As for the material used, the average mercury concentration was 49.5 μg/m3. The surgical instruments were decontaminated by absolute alcohol and bisulfite. The decontamination of the operating room and of the instruments was done by a chemist team specialized in environmental pollution. Conclusion: Parenteral elementary mercury injections are serious because of the local complications observed (necrosis, fasciite, functional after-effects) and possible chronic mercurial intoxication requiring a long-term toxicological follow-up of the patient. Contamination of the personnel and surgical buildings is a problem that should not be neglected.

127. PROFESSIONAL CHLORINATED HYDROCARBONS: OCCUPATIONAL VERSUS HOME POISONINGS

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Introduction: The chlorinated hydrocarbons are volatile non-inflammable chemicals extensively used in industry due to their excellent solvent properties and low cost. These products can be employed as cleaning agents; degreaser, solvents, chemical intermediates, aerosol propellants, refrigerants, fire extinguishers, and fumigants. Exposures may occur both at the workplace and at home. The acute toxic effects are CNS depression and skin, mucous membranes and respiratory tract irritation. These may be followed by hepatic and renal toxicity. We examined referrals associated with occupational and home acute poisonings by these substances made to our Poison Control Center (PCC). Methods: From January 1997 to December 2001, all intoxications with industrial products containing chlorinated hydrocarbons at $>50\%$ concentration were tabulated. Data on site of intoxication, aetiology, age, gender, toxic substance, exposure route, clinical manifestations and severity were analysed. Results: Of 219 exposures to these substances, 51.6% occurred at the workplace. Sixty-eight percent of them were male. All the patients were adults. There was no effect of age on agent type. The chlorinated hydrocarbons more frequent involved were: trichlorethylene (36.2%), perchlorethylene (23%) and methylene chloride (19.5%). The main exposure route was inhalation in 54.8% of cases, followed by ocular (18.5%), oral (13.2%) and dermal (10.6%). For trichlorethylene, perchlorethylene and methylene chloride intoxications, CNS symptoms were present in 53.8%, 53.8%, and 66.6% of cases, and respiratory symptoms in 38.4%, 38.4% and 40.9% of cases respectively. Of all cases 42.4% resulted in moderate and 8.8% in severe clinical features. 42.4% chlorinated hydrocarbons poisonings occurred at home. 94.6% were accidental and 5.4% were suicidal attempts. Children less than 24 months old represented 7.5%, children more than 24 months 13.9%, and adults 78.4% of cases. Fifty-eight percent were male. The principal route of exposure was ingestion (53% of cases), followed by inhalation (16.1%), ocular (16.1%) and dermal exposure (5.3%). Trichlorethylene poisonings accounted for 38.7% of cases, followed by methylene chloride (25.8%) and perchlorethylene (16.1%). Moderate clinical manifestations at home occured in 43% of exposures and severe ones in 7.5%. Conclusions: Trichlorethylene poisoning was more common than other chlorinated hydrocarbons both at home and at work. CNS depression and respiratory tract irritation were the clinical manifestations more usually observed. More effective methods of prevention should be implemented in all environments in order to reduce intoxication risks. PCC is able to detect work-related complaints and help in co-worker prevention. PCCs and occupational health care organizations should interact more frequently in order to assess worker population for these kind of exposures.

128. CHEMICAL BURNS IN JAMAICA: FEATURES AND MANAGEMENT

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Objectives: Caustics and corrosive injuries are frequent in Jamaica[1]. Criminal acts remain the principal source of these chemical burn injuries. Incidence is increasing rapidly, particularly among young adults, due to rising violence. Chemical burns may lead to dramatic social, economic, and medical problems, because of the lack of availability of specific antidotes. The objectives of this study were to describe the circumstances, the characteristics, and the treatments of chemical burn injuries in Jamaica, in order to improve the management and to give recommendations for prevention. Methods: A retrospective study of the medical records of all patients admitted from January to December 2001, in the Emergency Department of the Regional Hospital in Montego Bay, Jamaica, for various chemical burn injuries. Results are expressed as median [extremes]. Results: Twenty-six patients (age: 26 years [3–49], 14 women and 12 men) were included in our study. All cases resulted from a criminal action (assault weapons, intentional violence, and revenge) at home or in the street, but none of them from an accidental contamination. Chemicals involved sulfuric acid, gasoline, hydrofluoric acid or alkali, but in the majority of the cases, the circumstances and the pattern of injury make difficult the precise identification of the toxicant. The burn surface areas involved the face (10 patients), the upper limbs (9 patients), the lower limbs (9 patients), the thoracic area (2 patients) and the back (1 patient). The majority of patients developed severe pain and itching. Despite frequent occular injuries (5 patients), no case of blindness was found. Ophthalmologic consultation was recommended for all patients with ocular burns. Skin decontamination, analgesics, antibiotics and antiseptic ocular drops were the most important aspects of the treatment in the Emergency Department. No antidote was administered. Ten patients (38%) developed extensive severe burns, requiring admission to the surgical wards. Three patients (12%) required skin grafting. No chemical burn patient died. Conclusion: Chemical burns represent an increasing health problem in Jamaica. The majority of the cases were violence-related and involved sulfuric or hydrofluoric acid assaults. Health education, prevention and legal restrictions on the sale of those products should be undertaken to reduce violence and crime in the Jamaican society. Reference: 1—Branday J et al. Chemical burns as assault injuries in Jamaica. *Burns* 1996;**22**:154–5.

129. PERCUTANEOUS HYDROCYANIC ACID POISONING

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Case reports: We describe two cases of life-threatening hydrocyanic acid (HCN) gas poisoning. In at least one case the uptake was strictly percutaneously, as a self-contained breathing apparatus (SCBA) had been used. A stream of gas containing 19% of HCN was released from a leaking flange. One worker collapsed and was treated on site with 4-dimethylaminophenol (4-DMAP). At the same moment a fire fighter wearing SCBA collapsed, was unconscious and had foam in front of his mouth and nose. He also immediately received 4-DMPA. Upon arrival in the emergency room the cyanide levels were 5.3 and 6.75 mg/l respectively in whole blood (after the application of 4-DMAP). Methemoglobin was 5.5 and 16.2% respectively. After decontamination both patients received 50 and 150 mg/kg b.w. N-acetylcysteine (NAC) respectively, as a parallel acrylonitrile poisoning had to be suspected. In addition 30 and 40 mL sodium thiosulfate 10% respectively were given. In both cases the cyanide levels dropped significantly to 0.035 and 0.036 mg/l on the following day, and both patients survived without sequelae. Conclusions: HCN gas can easily penetrate the skin and give rise to possibly fatal cyanide poisonings. If work in contaminated areas is necessary, a chemical protection suit has to be used, normal fire fighting equipment has been shown to be insufficient for protection. The immediate application of 4-DMAP at about 50% of the recommended dose has been shown to be life-saving, even though met-hemoglobin levels remained relatively low. The high cyanide levels after 4-DMAP treatment show, that there is no definitely lethal cyanide concentration. It might be possible, that the rapidity of increase of the cyanide levels may play a greater role. The application of NAC plus sodium thiosulfate seems to be an efficient treatment of cyanide poisonings and should be evaluated further.

130. CHEMICAL PNEUMONITIS CAUSED BY LAMP OILS: PHYSICO-CHEMICAL PROPERTIES AND POSSIBLE MODE OF ACTION

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Objectives: According to surveys conducted by the BgVV, since 1970 there has been an increased number of dangerous lamp oil ingestions in infants and small children. The cases indicate that there is a high risk of aspiration, often followed by a chemical pneumonitis. Between 1990–2000 the BgVV and the Poison Information Centres documented three deaths in children and more than 150 serious injuries. Not only detergents, but also volatile hydrocarbons (VHC) have been involved in aspiration. Among these VHC, ingestions of kerosene, lamp oils, charcoal lighter fluids, furniture polishes, thinners etc. have been most frequent. Physico-chemical properties: The "dangerous" lamp oils are exclusively highly purified petroleum distillates such as kerosene or isoparaffins with a hydrocarbon chain length between C8 and C16. From 1990 onward, lamp oils were pure C8–C14 paraffins. To better understand the aspiration hazard of the VHC, we estimated several physico-chemical properties (HPLC, viscosity, surface tension, density, vapour pressure, water solubility). An aspiration hazard was associated with: very low viscosity (≤ 2 mPa × s), low surface tension (≤ 25 mN/m) and low volatility (≤ 5 kPa), minor water solubility and a short-chain composition ($\leq$C16). Of these the low volatility was considered most important. This pattern was found only in lamp oil, kerosene, and charcoal lighter fluid. Possible mode of action: The very low viscosity/surface tension and the low volatility promote the spreading of the lamp oils deep into the respiratory system. Even small amounts can pool in the epiglottis in the "recessus piriformis." This concords with the clinical observation that children develop prominent coughing within a short time of ingestion. After penetrating the larynx/pharynx area, the lamp oils spread to the alveoli due to their low surface tension. Through a direct disturbance of surfactant lamp oils appear to produce a diffusion barrier, resulting in severe disturbance of gas exchange. This is consistent with the clinical course of the three children who died and other severe cases where IPPV with 100% oxygen had little effect on blood oxygenation. The amounts ingested can be very small with about 600–800 mg of lamp oil leading to the death of a 16-month-old boy. Conclusions: The chemical pneumonitis caused by lamp oils can be explained by the physico-chemical properties of paraffin and kerosene preparations. The hypothesis is, that very low viscosity (≤ 2 mPa × s), low surface tension (≤ 25 mN/m) in connection with low volatility (≤ 5 kPa), minor water solubility and a short-chain composition ($\leq$C16) promote the aspiration process. The minimal evaporation allows entry into alveolar tissue with resultant severe disturbance of gas exchange due to interactions with surfactant.

131. EXPOSURE TO ORGANIC SOLVENTS IN RESTORATION WORK AND THE EFFECT ON OCCUPATIONAL HEALTH

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Objective: The aim of the study was to evaluate the exposure to certain organic solvents used in the restoration work and their effects on occupational health. Owing to their toxicity, some chemical substances may present a health risk for workers; we investigated this specific risk and the atmospheric concentrations reached by these substances, when they were eventually released in air. Methods: A preliminary analysis was carried out to evaluate the most common substances used during some specific activities such as restoration of mosaic, woodwork, and paint. Air samples were taken and measured to determine the atmospheric concentrations of frequently used chemicals under normal working conditions and, therefore, the likely exposure levels of these chemicals. Results: The table shows the frequency of use of these chemicals and the associated risks as described in standard Risk (R) and Safety (S) phrases. Conclusion: The investigation highlighted the presence of chemical substances generally considered dangerous for workers' health and safety. The indoor nature of the work, the wide range of substances used during the normal workday and the corresponding variability in the duration and level of exposure were shown to present a health risk for those engaged in restoration work. Moreover the lack of systems for controlling gaseous emission could result in problems of air pollution affecting those living in the surrounding areas. References: Orecchio S, Prodotti chimici ed attività di restauro. *Boll Chim Igien* 2001;**52**:25–28. Stanley E. Manahan Environmental Chemistry CRC The Merck Index 11° ed., Merck and CO inc.

Chemical substances	CAS	Weight %	Usage frequency	TLV-TWA (ppm)	TLV-TWA (mg/m^3)	R	S
Acetone	67-64-1		High	750	1800	11	9-16-23-33
Ethyl alcohol	64-17-5		Very high	1000	1900	11	7-16
Permethrin	52645-53-1	20	Very high			20-36-37-38	
solvent naphtha	64742-95-6	80					
Nitrous	108-88-3	50–100	Very high			11-20-21-22	9-16-23-29-33
diluting solution	64742-82-1	5–7					
	78-83-1	3–5					

USA 1989. Plenderleith HJ, Werner AE. The conservation of antiquities and work of art (treatment, repair and restoration) Oxford University Press.

132. OCCUPATIONAL AND NON-OCCUPATIONAL LEAD POISONINGS

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Objective: To describe scenarios of severe intoxications with lead from occupational settings and non-occupational environments in order to inform about less common ways of intoxication. Case series: Typical occupational intoxication: 35-year-old worker from a battery plant with six weeks history of loss of appetite, constipation, paleness and anaemia was treated with antacids and prokinetics for the abdominal colic. Then lead intoxication was diagnosed and four doses of EDTA (disodium dicalcium edetate) were given. Mixed intoxication with lead: 46 year-old employee of a glass factory with symptoms of severe lead intoxication and repeated EDTA treatment had persisting symptoms 9 months after his occupational exposure ceased. X-ray examination of abdomen confirmed granulated lead red (lead oxide) in rectum. This person was under control during 25 months; treated with 56 doses of EDTA and excreted about 210 mg of lead in total. Non-occupational intoxications: A 17-year-old student ingested 500 pellets of lead shot. After two weeks she was admitted to hospital because of abdominal discomfort, only admitting the ingestion to the doctor after another two weeks. Severe anaemia and colic in the abdomen were present. Removal of the lead shot by gastroscopy was not successful; after diet with large amount of vegetables the lead shot was eliminated naturally. The young woman was treated both with EDTA and DMSA (dimercaptosuccinic acid), total 13 doses, complete recovery lasted about 6 weeks. A 50-year-old woman was treated by a preparation recommended by an astrologist to improve diabetes compensation. Treatment resulted in normocytic anaemia with saturnine colic, nausea, and constipation, which complicated the treatment of diabetes and led to two blood transfusions. Abdominal surgery was already planned, but in the meantime lead intoxication was proven and classical treatment with two doses of EDTA led to a fundamental change and gradual improvement of the condition. A mother (44 years) and daughter (24 years) had been drinking lemon tea prepared in an old glazed ceramics jar and after two months both developed typical symptoms of lead intoxication. Treatment with EDTA was started one month later. The lead content measured in the lemon tea was 2.02 mg l^{-1}. Conclusion: Intoxications with lead are very rare in the Czech Republic and the physicians underestimate this diagnosis. In most of the patients the antidote treatment was started with several weeks delay after the typical symptoms developed. These case reports should serve as examples of possible ways of intoxication and as a warning against ignorance of the typical symptoms. Acknowledgement: Supported by MSM J13/98 111100002 and 111100005.

133. POLYMER FUME FEVER AFTER USE OF A HOUSEHOLD PRODUCT

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Objective: Polytetrafluoroethylene (PTFE or Teflon®) is a commonly used compound that may result in polymer fume fever (PFF) when heated in poorly ventilated conditions. PFF in persons smoking contaminated cigarettes is an

occupational hazard in industries where these products are used. To our knowledge, this is the first report of PFF associated with the use of a consumer product. Case report: A previously healthy 40-year-old male developed fever, chills, cough, and progressive dyspnea after using Elmer's Slide-All® dry lubricant for the first time. After extensive hand contact with the micronized PTFE product at room temperature, he hand-rolled and smoked a hash-tobacco "joint." He noted that symptoms began with a vigorous cough after a few "tokes." He presented to the ED 8 h later with coughing and dyspnea at rest. Temperature was 39.4°C, HR 80, RR 24, and pulse oximetry was 90% on room air. Exam revealed retractions and expiratory wheezing. Chest radiograph showed bilateral alveolar infiltrates. Peak flows improved from 200 L/min to 450 L/min with 3 albuterol treatments. Pulmonary function tests 16 h after exposure revealed moderate airway obstruction that was reversed with albuterol. He improved over 48 h without further therapy and was asymptomatic at 7 days and at 3 months after exposure. The discharge diagnosis was PFF. The MSDS and the product label did not indicate a risk of PFF in association with use of smoking materials and this was reported to the manufacturer and OSHA. Conclusion: PFF should be considered in the differential of influenza-like illnesses when an occupational and smoking history is suggestive of the disease.

134. HIGH-PRESSURE INJECTION OF NAPHTHA AND LIMONENE—A CASE REPORT

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Objectives: We describe a case of a high-pressure injection injury with a cold cleanser containing naphtha (>50%) and limonene (2.5–10%). High-pressure injection injuries to the hand are rare but particulary dangerous. Because of their initial benign aspect they are often underestimated[1]. To a large degree the outcome is dependent upon the injected material[1,2]. When injected subdermal hydrocarbons can produce an intense inflammatory response and sterile abscesses. Limonene is a skin irritant in humans. There are no data about tissue toxicity after subdermal injection. This is the first published case limonene was injected subdermal. Case report: A 37-year-old man presented after high-pressure injection injury of the second digit of his left hand. A few minutes after the accident he felt pain. At admission in hospital 20 min after injury the finger was slightly swollen and reddened. A small wound at the distal segment was visible. The next day pain increased. Index finger, palm and dorsum of left hand were swollen and erythematous. The injured finger had reduced sensibility. The patient was admitted to a Trauma Centre. Surgical intervention included debridement, removal of the cold cleanser, decompression of the median nerve and fasciotomy including forearm. Two days later the patient was taken again to surgery for debridement. At day 5 after injury the index finger was amputated. Fourteen days later hand and forearm were treated with skin grafts. Systemic intoxication was not observed. Conclusions: In the presented case the high-pressure injection of a mixture of naphtha and limonene caused an intense inflammation and resulted in amputation. Even if systemic intoxication was not observed, its occurrence after high-pressure injection is described[3]. Rate of amputation is higher if surgical intervention is delayed (>4–10 h after injury) as in the reported case (24 h after injury). Poison centers must be aware that early and extensive surgical removal of foreign material and debridement of the injured tissue are important in preventing amputation. Therefore patients should be transferred to a center with a hand unit. The danger of a systemic intoxication should not be overlooked. References: [1]Mizani MR, Weber BE. High-pressure injection injury of the hand. The potential for disastrous results. *Postgrad Med* 2000;**10**:183–5. [2]Rappold G, Rosenmayr E. High-pressure injection injuries of the hand. *Handchir Mikrochir Plast Chir* 2001;**33**:332–41. [3]Lilis R et al. Paint spray gun injury of the hand. *JAMA* 1981;**246**:1233–5.

135. PHOSGENE POISONING

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History: In the 1960s and 1970s within Bayer AG, Leverkusen, the course and treatment of phosgene poisoning were thorougly researched resulting in the development of the phosgene badge and a treatment regimen. The badge allows an estimation of the phosgene exposure dose (as ppm*min), which in turn allows determination of a definitive therapeutic

regimen for the specific dose range: 1. No symptoms, dose <25 ppm*min: no specific therapy necessary. 2. Symptoms possible, dose >25 and <150 ppm*min: clinical observation, X-ray after 2–4 hours, inhalation of corticosteroid spray every 5–10 minutes, corticosteroid i.v. (e.g., 250 mg methyl-prednisolone) 3. Imminent or manifest lung edema, dose >150 ppm*min: inhalation of corticosteroid spray every 5–10 minutes, corticosteroid i.v. (e.g., 500–1000 mg methyl-prednisolone), immediate transfer to ICU, CPAP/PEEP ventilation. Case report: To illustrate the course of a severe phosgene poisoning with less than perfect treatment a case from 1990 is reported. A 59-year-old patient, who had thrown his badge away, was treated with repeated corticosteroid spray inhalation. Four hours after inhalation he developed a slight pulmonary wheeze, and the X-ray revealed an early perihilar lung edema. He was immediately hospitalized after injection of 1 g methyl-prednisolone, but the hospital did not follow the therapy suggestions. The patient was kept on the normal ward overnight, and was found with fully developed lung edema the next morning. Even after transfer to the ICU and repeated steroid injections, no positive pressure ventilation was done. Accordingly a series of X-rays showing the course of toxic lung edema can be shown. The patient can be considered lucky to survive. Conclusions: From animal experiments and our experiences a therapeutical regimen has been developed according to a dose range of phosgene estimated from a badge. If no badge is present, a higher inhalation dose should be assumed. Clinical (auscultation) and technical (resistance, oxygen saturation) observation of the patient is mandatory, as is an X-ray of the chest in more severe inhalations and suspected cases. When a search of the literature for evidence based proof of the effectiveness of corticosteroid spray alone for the prevention of pulmonary edema was undertaken no publications could be found in animal experiments nor man. Thus we recommend spray only as additional therapy or as first measure in larger incidents. Sequelae like ARDS or decreased lung function have been seen in very few cases. More common are both acute and prolonged psychological sequelae of inhalation accidents with phosgene. These have to be considered and managed appropriately.

136. IS N-ACETYLCYSTEINE AN EFFICIENT CYANIDE ANTIDOTE?

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Case series: We have treated two patients with acute, yet prolonged inhalative acrylonitrile poisonings with the German standard regimen for such intoxication using N-acetylcysteine (NAC) as in paracetamol poisonings: Slight poisoning: (patient not unconscious, few central nervous symptoms): NAC 150 mg/kg b.w. during 15 minutes undiluted or in 250 ml glucose 5% i.v. Severe poisoning: (patient unconscious, or severe central nervous symptoms): NAC 300 mg/kg b.w. i.v.: 150 mg/kg b.w. as above, 50 mg/kg b.w. in 500 ml glucose 5% during 4 hours,. 100 mg/kg b.w. in 500 ml glucose 5% during 5–40 hours. It was only subsequently, from our biomonitoring, that we learned oft significant cyanide levels in these cases that reach life-threatening ranges. Therefore in one case sodium thiosulfate at a dose of 10 ml 10% i.v. was applied some hours after the intoxication. Biomonitoring results showed a significant drop in cyanide levels before the sodium thiosulfate application suggesting an effect of NAC alone on cyanide detoxification and blood levels: Case 1: cyanide 3.8 mg/l, dropping to 1.0 mg/l after 90 minutes, NAC 150 mg/kg b.w. Case 2: cyanide 3.4 mg/l, dropping to 0.5 mg/l after 100 minutes, NAC 300 mg/kg b.w. Conclusion: Looking at the published literature there are no reports on the use of NAC in human cyanide poisoning cases, but there have been animal experiments with the very closely related cysteine, showing a clear efficacy of cysteine against cyanide poisoning. The mechanism involved is identical to sodium thiosulfate via increasing the sulfur stocks needed for endogenous cyanide detoxification. Cysteine showed a better effect than sodium thiosulfate, perhaps in part due to better intra-mitochondrial penetration. Our results with NAC indicate falls in cyanide levels in whole blood and should prompt further research into the possible use of NAC as cyanide antidote. This is particularly relevant in view of the lack of a "perfect" cyanide antidote. Sodium nitrite and 4-dimethylaminophenol cause a decreased oxygen transport capacity by forming met-hemoglobin, dicobalt edetate has intrinsic toxicity, and hydroxocobalamin is expensive and possibly insufficient as the only antidote in severe cyanide poisoning.

137. INADVERTENT POISONING DUE TO DECANTING OF SUBSTANCES FROM THEIR ORIGINAL CONTAINERS

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Objective: To analyse the epidemiology of inadvertent poisoning due to decanting of substances from their original container. Background: Decanting of substances into beverage containers is a common practice but there is little

epidemiological data in the medical literature, concerning subsequent inadvertent poisoning, as determined by a Medline/Pubmed search. Most citations described individual case reports or advice on accident prevention. Methods: A prospective study was carried out to determine the incidence of accidental poisoning, as reported to the National Poisons Information Centre (NPIC), where the caller specified that the agent had been decanted from its original container. Information on the substance involved, caller identification, patient age, sex, clinical features, and route of exposure was collated. Results and case reports: From February 2000 until November 2002, the NPIC received 149 enquiries relating to 100 incidents of inadvertent poisoning, involving 112 patients (55 adults, 55 children, 2 unknown). Overall, males were more likely to be poisoned and the male:female ratio was 1.3:1. 75.8% of enquiries originated from health-care professionals, 18.8% from members of the public and 5.4% others. 92/100 incidents involved ingestion of substances, there were 4 dermal exposures and 4 inhalation exposures. The identity of the decanted substance was known or suspected in 94 incidents, identified by analysis in 4 incidents, and unknown in 2 circumstances. Household products (39%), industrial chemicals (29%), car products (15%), cosmetics (7%), and pesticides/herbicides (7%) were the principal categories of chemicals decanted. 32% of all decanted products were corrosive in nature. The 10 most frequent products decanted were industrial cleaners, bleach, ethylene glycol, hydrogen peroxide hair dye, white spirit, car oil, floor polish/cleaner, furniture polish, drain cleaner, and beerline cleaner. 79 patients (70.5%) were symptomatic, 27 (24.1%) were asymptomatic, and symptoms were unknown in 6 patients. The predominant clinical features were vomiting, a burning sensation in the mouth or stomach, pharyngitis/dysphagia, swollen lips/tongue, buccal burns. One fatality occurred following ingestion of paraquat, 3 incidents resulted in severe symptoms in 6 patients after ingestion of sodium hydroxide (1 incident involved drain cleaner, 2 involved beerline cleaner), and 1 incident resulted in multiple paediatric cases presenting to a hospital emergency department, post-inhalation of an unknown substance, subsequently identified as an organophosphate. Conclusion: Significant morbidity and death can occur following inadvertent poisoning resulting from the inappropriate practice of decanting substances from their original containers. Members of the public should be alerted to the dangers of decanting substances into unlabeled bottles, particularly into beverage containers.

138. SOME CASES OF NON-OCCUPATIONAL PLEURAL MESOTHELIOMA: COULD THE NON WORK ENVIRONMENT BE RESPONSIBLE FOR THE DISEASE?

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Objective: The aim of the study was to determine the environmental conditions responsible for the development of pleural mesothelioma in patients who were not occupationally exposed to asbestos. Case series: Three cases of frank pleural mesothelioma were studied. In each case the possibility of occupational exposure to asbestos fibers, even in small concentrations, was excluded by investigation of work practices and targeted inspections in the workplaces. Sporadic exposures reported by the patients themselves have not previously been taken into account by Inail (Italian Workers' Compensation Authority) as possible causes for the development of cancer, but clinical evidence of the disease together with the well-known association between the development of pleural mesothelioma and exposure to asbestos prompted a more in-depth investigation. The non-work environment and lifestyle were screened from medical and technical points of view in order to determine whether they could be responsible for the disease. Environmental air sampling was conducted in the workers' domestic environment and immediate surroundings where the presence of asbestos was known or strongly suspected. Results: No consistent evidence was found that exposure to asbestos in the domestic environment was a major influence by comparison with the occupational environment. Nevertheless some measurements showed concentration values (up to 10 ff/l) higher than the background norm. This supports the suspicion that, in the studied cases, the exposure to asbestos played anyway a more important role in mesothelioma development than other non-occupational factors such as age, gender and lifestyle. Conclusion: The study highlights the need to consider the contribution of the environment outside work to asbestos exposure in order to determine the origin of the disease. The Insurance Institute considers it vital to commence collaboration with other public institutions involved in health protection, even in those cases where occupation is not the predominant means of exposure.

139. METHYL BROMIDE POISONINGS

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Objective: Methyl bromide is a colorless gas used by fumigators to eradicate insects, fungi, and nematodes. It has a very high olfactory threshold so it provides little warning of its presence. We report two cases with different outcomes after methyl bromide exposure and present an estimated elimination profile of inorganic bromide in serum. Case reports: *Case 1*: A 32-year-old male was found unconscious 4 hours after entering a mill that had been fumigated with methyl bromide 24 h earlier. Upon admission, the patient was comatose with generalised seizures. Arterial blood gas showed pH 6.92, pCO_2 10.6 kPa, pO_2 22.7 kPa, HCO_3 16 mM and base deficit 18.2 mM. He was intubated, mechanically ventilated and treated with diazepam, morphine, and muscle relaxant. Initial blood analysis showed leucocytes 34.5, K^+ 5.7 mM, CPK 395 U/L, ALAT 91 U/L and creatinine 173 uM. Chest X-ray demonstrated signs of alveolar oedema. Echocardiography showed well-filled, well-contracting left ventricle. Extensive amounts of IV fluids and very high doses of vasopressors were needed. The patient developed acute myocardial infarction and acute renal failure. His condition gradually deteriorated and he died in multiorgan failure on day 6. *Case 2*: This 35-year-old male entered the mill together with case 1. After 2 h he left the building as he felt nauseous, was vomiting and experienced a burning sensation in his eyes and throat. The face and throat was swollen. Upon admission 36 h later his face and upper body was erythematous. He had a slight metabolic alkalosis in his blood gas analysis; otherwise the lab results and chest X-ray were normal. The hospital course of 1.5 days were uneventful and he was discharged without sequelae. Results: Serum inorganic bromide levels are usually used to indicate methyl bromide exposure. Cases of human fatalities have been reported from as low as 40 mg/L (0.50 mmol/L). The inorganic bromide concentration of case 1 was 735 mg/L (9.20 mmol/l) at hospital admission and a preliminary kinetic study indicates elimination according to 1. order kinetic model with a serum half-life of 2.5 days. Elimination data for case 2 follow. Conclusion: The concentration of inorganic bromide observed in case 1 is among the highest level reported after methyl bromide exposure. The elimination of serum bromide indicates a 1. order kinetic model and a serum half-life of 2.5 days. Pulmonary complications and death in multiorgan failure are typical findings also reported by others. Reference: Horowitz BZ et al. An unusual exposure to methyl bromide leading to fatality. *J Toxicol Clin Tox* 1998;**36**:353–357.

140. OCCUPATIONAL EXPOSURES TO FUMIGANTS

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Objective: A description of incidents involving fumigants reported to the chemical incident response service. Case 1: A cargo vessel, radioed ahead to the Port of Liverpool to advise that 5 of the 6 members of crew were unwell. The affected crew members complained of various combinations of muscle aches, cramps, headaches, nausea and mild respiratory symptoms. One crew member lost color vision while retaining black and white vision. The Captain reported a smell of garlic or onions in the bridge area of the ship at the same time as the crew experienced symptoms. On arrival at Liverpool a doctor examined the crew, but by this stage the crew was asymptomatic. It is suspected that a fumigant (phosphine), which had been used on departure from the previous port could have entered the bridge area and caused the symptoms. Case 2: Three port workers attended an Accident and Emergency (A&E) department complaining of mild respiratory and throat irritation. The workers had opened and entered a sealed container, spending 2–3 minutes inside. The airtight container had been fumigated with methyl bromide then sealed. On arrival in the UK the containers are vented for 48 h and port workers are not permitted to enter without a venting certificate which had not been issued in this case. The workers were assessed clinically and advised not to work for 48 h in case of delayed symptoms. Case 3: An A&E department was contacted by a local furniture store regarding five of their employees who had been unloading a container imported from Vietnam. The staff had broken a packet of aluminium phosphide releasing the dust, which had then been swept up and placed in a bucket of water. The bucket started to "fizz" as phosphine was released. The staff left the container, closed the door and changed their clothes. The staff were assessed at the local A&E as a precaution although they remained well. However 9 containers had been supplied to stores across the UK, all containing unknown

quantities aluminium phosphide. In total over 30 people across the UK claimed to have been exposed to aluminium phosphide dust or phosphine. No serious symptoms were reported but some exposed individuals developed respiratory irritation or skin rashes. Discussion: These cases highlight the potential risks of fumigants when safety procedures are not followed or staff are unfamiliar with these agents. Methyl bromide and phosphine are both potentially highly toxic agents and assessing the health risks from low-level exposures may cause difficulties.

141. THE CHRONIC TETRAETHYL LEAD POISONING OF THE FOUR-PERSON FAMILY-CASE REPORT

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Objective: Presentation of the chronic tetraethyl lead poisoning of the four person family in the place of settlement. Case report: A 15.5-year-old man was admitted to the regional Pediatric Ward because of changes of behavior, hallucinations, agitation. Nausea, vomiting, metallic taste and diarrhea were observed prior to the admission. In the case history, there were no data suggested of the toxic origin of the disorder. The cerebro-spinal fluid examination and CT of the brain were normal. Increased activities of CPK, GOT, GPT, and LDH in blood were found. Paranoid syndrome was diagnosed by psychiatric evaluation. The patients' mother presented similar signs in almost the same time. The laboratory tests of the blood taken from the patients' father and older brother revealed the increase activity of the same enzymes (CPK, GOT, GPT, LDH). All family members were admitted to the Department of Clinical Toxicology in Krakow because of suspicion of heavy metal poisoning. The toxicological laboratory test showed a toxic serum lead concentration in all patients: 440 ug/l—older brother, 490 ug/l— father, 508 ug/l—mother, and 635 ug/l—primary described patient. Because there were no characteristic changes for lead poisoning in the blood picture toxicological investigations were continued. As a result of these examinations presence of a diethyl lead in urine was confirmed. In the evaluation of the multiorgan damages connected with tetraethyl lead poisoning, we paid special attention to CSN dysfunctions, confirmed by neuropsychological examinations. The different kinds of arrhythmias indicated on cardiovascular system damage. Based on clinical presentation and laboratory investigations chronic tetraethyl lead poisoning was diagnosed. Conclusions: Coexistence of psychiatric disturbances and elevated activity of CPK, GOT, GTP, LDH should be suspected for lead compounds poisoning and should be followed by toxicological investigations of lead serum concentration and presence of the metabolites of tetraethyl lead in urine.

142. ENVIRONMENTAL EXPOSURE TO LEAD IN A POPULATION OF CHILDREN LIVING IN MONTERREY, MEXICO

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Objective: Monterrey is a city polluted by lead from industrial emissions. Consequently, there is a need to monitor lead exposure in vulnerable populations. In this study we evaluated the blood lead concentration (PbB) in children and its correlation with delta-aminolevulinic acid dehydratase (ALA-D), hemoglobin (Hb) and hematocrit (Ht) as biological indicators of lead exposure. Methods: A random sample of 400 children 1 month to 14 years old were selected among patients attending the pediatric unit of the University Hospital for a routine visit. Mothers were asked to fill out a questionnaire on demographic variables and potential sources of lead exposure. Blood samples were obtained from the children and blood lead levels were determined by atomic absorption spectrophotometry. Results: Blood lead level ranged from 1 to 33.6 μg/dl, with a mean of 6 μg/dl (SD 3.8), and 10.75% ($n = 43$) of the children had a blood lead level > 10 μg/dl; this group had a mean PbB of 14.4 μg/dl (SD 5.3) and the main determinant of blood lead level was the place of residency, since they were children living within 2 km radius of lead industries.The Hb values ranged from 12.3 to 18.5 g/dl (mean 12) and the Ht values ranged from 18 to 58% (mean 36%). A negative correlation between ALA-D and lead concentrations was found and no correlation were observed with Hb or Ht values. Conclusion: The results

emphasize the need for strict regulatory policies for lead control to protect vulnerable populations as well as the need for more extensive screening to estimate the magnitude of the problem.

143. MOTOR APHASIA IN LATE NEUROPSYCHIATRIC SYNDROME OF CARBON MONOXIDE POISONING

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Background: For three years our group has conducted a follow-up program for patients who have suffered from acute carbon monoxide poisoning (CO) and has prospectively evaluated 215 patients. Until now, no cases of motor aphasia as part of the late neuropsychiatric syndrome due to CO poisoning have been clearly reported. We wish to describe four cases of motor aphasia in our group of patients with late neuropsychiatric syndrome. Case reports: Four women between ages 42 and 55 years old were treated for acute CO poisoning. All suffered from dizziness and headache, three from nausea, and two briefly lost consciousnesses. Their carboxyhemoglobin levels oscillated between 19% and 35%, and they were treated with 100% normobaric oxygen. Ten days after discharge, the women underwent a routine checkup as part of the follow-up program. Questioned separately, each reported disorders of expressive language, anomia, decrease in fluency, verbal paraphasias and alterations in repetition. The disorders lasted between four and eight days. During the checkup, one of the patients was within the pathological range of the Spanish version of the Boston Diagnostic Aphasia Examination, but the test was normal seven days later. Using MRI, alterations in the left parietal cortex were observed in another patient. More detailed questioning revealed that for ten successive Saturdays they had played cards in a wine cellar heated by a defective wood burning heater. Each Saturday they suffered from intense headaches, and some from dizziness and/or nausea, but not one related the problems to possible CO inhalation. Discussion: Our report reveals transitory motor aphasia, as a manifestation of late neuropsychiatric syndrome, demonstrating the polymorphic character of this syndrome. It is also of note that the disorder simultaneously affected 4 women suffering from probable subacute exposure to CO for 10 consecutive Saturdays, the most intense being the last weekend. It is difficult to ascertain why the language of all the women was affected and the effect produced by the repeated exposure on said disorder. Conclusion: It is advisable to keep in mind late neuropsychiatric syndrome due to CO in the etiologic diagnosis of aphasia and to include tests which evaluate possible language disorders in the follow-up of patients who have suffered CO poisoning.

144. HEAVY METALS PROFILE OF CHILDREN FROM URBAN AND RURAL REGIONS IN THE UNITED ARAB EMIRATES

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Objective: Exposure to heavy metals has increased with industrialization and humans are subjected through different environmental sources. In oil-producing countries heavy metals are considered as major threat to the population. Metals such as cadmium, arsenic, and mercury impact various organs of the body and controlling their toxicity is crucial for individuals at risk. Previous studies utilized blood levels for monitoring metal toxicity. The current study was designed to investigate exposure to metals like cobalt, nickel, copper, arsenic, cadmium, and mercury using scalp hair. Methods: Hair samples were randomly collected from 42 children (aged 6–18 years) representing rural and urban areas of the United Arab Emirates. The rural regions were defined as at least 50 km away from factories or traffic sites. Immediately after cutting, hairs were stored in plastic bags and attached to a questionnaire with the relevant background information. Samples were dried, weighed, and sealed with polyethylene envelopes. Following the extraction procedures with nitric acid, ICP-MS instrument was utilized for metals determination. Results: The analytical instrument showed a high degree of sensitivity for measuring heavy metals. Furthermore, the study revealed significant differences between levels of some metals in hairs from rural and urban areas. Conclusion: Many areas could be contaminated with heavy metals due to industrial activities. Studies investigating metals contamination have identified continuous monitoring as a key factor in controlling toxicity. Measuring metal concentration in scalp hair could be a useful method for studying exposure and

Table 1. Metal content in scalp hair of children from rural (n = 21) and urban (n = 21) areas (mean ± SD).

Metals	Cobalt	Nickel	Copper	Arsenic	Cadmium	Mercury
Rural (μg/g)	0.04 ± 0.01	0.65 + 0.3	11.6 ± 5	0.16 ± 0.08	0.03 ± 0.01	0.18 ± 0.05
Urban (μg/g)	0.05 ± 0.02	3.94 ± 1.3	9.1 ± 2	1.3 ± 0.4	0.24 ± 0.07	1.35 ± 0.4
P value	NS	$P < 0.001$	NS	$P < 0.001$	$P < 0.001$	$P < 0.001$

assessing environmental pollution. Although the technique has the potential of being an effective tool for evaluating the extent of pollution and identifying potentially toxic elements, this cannot yet replace the standard procedures of measuring air, water and soil content. The introduction of controlling policies might reduce the potential risk for heavy metals intoxication particularly in oil producing countries. Such policies will also contribute positively to the overall reduction of environmental pollution. (This study was supported by a research grant from the United Arab Emirates University).

145. MCS IN GERMANY: PREVALENCE AND RELEVANCE OF SUBJECTIVE CHEMICAL SENSITIVITY

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Objective: Multiple chemical sensitivity (MCS) is defined as a dose-independent overreaction to small doses of widely used and generally non-toxic chemicals. Diagnosis of the contentious syndrome is often based on the subjective and unspecific feeling of sensitivity to chemicals. But the value of subjective chemical sensitivity as a diagnostic feature of MCS is debatable. We obtained information about the frequency of self-reported chemical sensitivity and the diagnosis MCS in Germany. We compared the prevalences to international data and comment on the appropriateness of subjective chemical sensitivity as a clinical and research criterion for MCS. Methods: We conducted a representative survey among 2032 adult Germans. Results: We found self-reported chemical sensitivity in 9% and sensitivity to odors in 24% of our representative sample. 48% believed that humans are now more sensitive to chemicals than in the past. 11% were familiar with the term "multiple chemical sensitivity or MCS." Physician-diagnosed MCS was reported by 0.5% of the general population—being consistent with about 300,000 patients with MCS in Germany. Conclusion: The prevalence of subjective sensitivity to chemicals is similar to rates reported from other countries. There is a relatively low awareness of the multiple chemical sensitivity-concept, and it seems to be diagnosed less frequently than in other countries. Due to the lack of specificity of subjective chemical sensitivity we suggest to derive conclusions about MCS with caution, but a clearly defined clinical syndrome with objective physical findings cannot be delineated so far. Congruent with former studies on noise sensitivity we feel that chemical sensitivity results from psychological rather than physiological mechanisms.

146. TRANSPORT ACCIDENTS WITH CHEMICALS IN AUSTRIA

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Objective: As a result of industrial development and globalization the transport volume of chemicals on Austria's transit roads and railways has been growing rapidly. Accordingly, the incidence of transport accidents has been become an increasing problem during the last decade. As in Germany, the chemical industry has developed an emergency response system (TUIS) in Austria and is equivalent to the ICE-System (International Chemical Environment) of CEFIC. Some 40 companies have made it their business to provide rapid, accurate information and advice to the emergency services, if necessary supported by practical assistance. The intended object is to prevent or help minimize any potential adverse effects on the public, property and the environment. In this emergency response system the Austrian Poison Information Centre (PIC) is integrated as an expert source for toxicological and ecotoxicological information since 1998. One

purpose of this study was to evaluate the number and type of interventions and the chemicals involved. The other was to examine the question how frequently the PIC had been consulted. Methods: The TUIS records from 1990 through 2000 have been analyzed as to the number and category of interventions which are differentiated into three response levels: (1) provision of information, (2) provision of advice at the incident scene, and (3) provision of practical assistance at the incident scene. In comparison with that the records of the PIC for the period from 1996 through 2002 have been examined as to accidents with chemical freight. Results: There was a total number of 227 interventions with an upward tendency from year to year, 63% classified as response level 1, 16% as level 2 and 21% as level 3. The respective chemicals involved were mostly corrosive or flammable fluids or gases and liquid fuels with varying toxicity. Contrarily, the evaluation of the records at the PIC did not reveal any consultation related to a transport accident. There were only a few cases of emergency exercises. Conclusion: Despite the increasing incidence of transport accidents on Austria's roads and railways the toxicological risk appears to be minimal. This is reflected by the fact that the PIC as an integrated member of the TUIS has not been contacted in cases of emergency until now. Accordingly, the main issue of safety in carrying chemical goods as a prerequisite to avoid toxic hazards is to provide experienced technical assistance in cases of emergency. On the European level, comparable emergency response systems are currently ready for action in 15 countries including some 800 member companies.

147. CHLORINE GAS INHALATION: A REVIEW OF 97 CASES

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Objective: To evaluate clinical data and outcome of chlorine gas inhalation in 97 cases indexed by a poison center. Methods: A prospective study undertaken by the Poison Centre of Strasbourg from January 2000 to September 2002, count 97 cases of chlorine gas inhalation. 26 patients were admitted to the hospital and were followed up by the Poison Centre three months later. Results: This case series involves 91 adults (average age: 36 years) and 6 children, 43% women and 57% men. 74% of the intoxications happened at home and 26% in industrial settings. The release of chlorine gas was caused by mixtures of sodium hypochlorite and acid scaling products in 68 cases and during handling of swimming pool chlorine tablets in 22 cases. Ninety-one patients had symptoms: irritative cough in 65 cases; cough and dyspnea in 24 cases. 26 patients were admitted to the hospital, 15 of these patients had a respiratory medical history (2 asthma, 3 chronic bronchitis, 2 allergy and 8 tobacco smoking). Twenty-one patients complained of dyspnea and 5 had expiratory wheezing. Chest X-rays were taken in 9 cases and an anormality was found in one case. Two patients were found to have hypoxemia with capillary pulse oxygenation ranging from 88% to 90%. Spirometry was done in 4 cases and showed an obstructive airway syndrome in one case. One patient had a positive metacholine test. Seven patients were treated with inhaled bonchodilatators, 4 with corticosteroids and 15 with bronchodilatators and corticosteroids. A 76-year-old woman developed acute respiratory distress requiring 24h of mechanical ventilatory support. The patients average period at the hospital was 24 hours. The follow-up by telephone, 3 months later, revealed that 2 patients complained of residual symptoms compatible with reactive airways dysfunction syndrome. Conclusion: Chlorine gas inhalation is a frequent household exposure. The most common symptom is irritative cough that resolves itself generally within a few hours. Significant morbidity can be observed in patients with pre-existing lung disease and chronic cigarette smoking.

148. CALLS TO THE FINNISH PIC FOR FAULTY DRUG ADMINISTRATIONS BY MEDICAL PROFESSIONALS

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Objective: To study the extent and type of faulty drug administrations leading to a call to the PIC. Methods: The 38087 calls received by the Finnish PIC in 2001 were analyzed. Data was retrieved from the call database for calls made by health-care professionals and concerning any type of faulty administration of a medicinal product. Results: Altogether 130 calls for faulty administrations were found, which was only 0.51% of all calls related to actual or suspected human poisonings, but 2.7% of the calls received from health-care professionals. The call was made by nursing staff in 61% of

the cases, and by a physician in 24%. The type of facility were the error was made was a nursing home in 65 (50%). A hospital/health center was the facility in 14 cases (10.8%). The call was made in <1 h after the administration in 63%, 1–4 h after in 15%. In 8% the dose had been given repeatedly. The median age of the patients who received the drug was 70.0 yrs, and 80% were adults. The drug was given orally in 76% of the cases. The types of error were wrong patient ($n = 53$; 40.8%), wrong drug ($n = 13$; 10%), wrong dose ($n = 13$; 10%), extra dose ($n = 14$; 10.8%), wrong route ($n = 6$; 4.6%). In children the most common error was wrong drug or dose, while in adults it was wrong patient. Altogether 23 (17.7%) patients received an overdose, 10 of them were children. Three of the children received a 10-fold overdose (newborn indomethacin i.v., newborn erythromycin i.v., 8 yr old chlorpromazine p.o.). Two adults received a 10-fold overdose (phosphenytoin i.v., oxycodone i.m.). A drug was falsely administered i.v. in 3 cases (fluconazole oral mixture, tetanus vaccine and enoxaparine i.v. instead of s.c.). Symptoms were reported at the time of call in 22 patients (17.8%). Conclusion: Elderly patients in nursing homes were the patients most often involved in calls related to faulty drug administration, however in calls regarding overdoses hospital patients were most often involved.

149. A QUALITY DEVELOPMENT PROGRAM: THE MILAN POISON CENTRE EXPERIENCE

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Objective: To start a quality development system at the Milan Poison Centre (PCC), aiming to meet the request of an external audit with accreditation in 2003, by the Regional Health System which financially supports the Centre. Methods: In September 2001 a working group was started with PCC staff members and external quality consultants to identify a development system program for the Centre. The current Italian legislation on "Criteria of quality and confidentiality for Poison Centres" and Scientific Societies' (EAPCCT, AAPCC) documents on quality were examined to identify national legal rules and international standards for PCCs. The Quality system named by "International Organisation for Standardisation" ISO 900: 2000 was introduced and adopted to develop the project. Results: In the first year of the program the Service of the Milan PCC was defined on the basis of its legal status and its history. Essential activities of the Centre were identified as 24 h information service, antidotes supply, toxicovigilance within the Regional and National Health System and 24 h medical assistance for all poisoned patients admitted to the Hospital where the Centre is located. The Centre users or customers were defined as general public, health professionals and public institutions. A Quality Manual has been prepared to describe the Center's organisation and the main procedures regarding the centre's activities. Conclusion: A quality development program was requested in Milan PCC, to certificate the center, according to the Regione Lombardia health policy. The plan is an ongoing process which involves all the staff members, and resulted to be a useful challenge for the Centre as a whole. The ISO quality system adopted has proved to be a useful tool: it helped define the Centre quality objectives and the procedures which are requested to maintain a regular quality control policy for the PCC. References: Certification and recertification of Regional Poison Centres and Poisons Center systems—American Association of Poison Control Centers AAPCC April 28, 1999—Washington, DC. EAPCCT Working Group on Quality and Accreditation of Poisons Centres, EAPCCT Congress Barcelona 2001. Gazzetta Ufficiale della Repubblica Italiana AllegatoII 23-11-2000. International organization for standardization, UNI Ente Nazionale Italiano di unificazione, Dicembre 2000.

150. TDI—A NETWORK OF INFORMATION AND CASE DOCUMENTATION IN GERMAN POISON CENTRES

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Objective: In recent years, all 10 poison centers (PC) serving different regions of Germany and the Federal Institute for Risk Assessment (BfR, formerly BgVV), Berlin, have intensified their cooperation. Among other aspects, the exchange of data on consumer product, delivered from industry either voluntarily according to the "EAPCCT format" (1) or on legal basis, has become an important part of PC work and quality management. The research project "TDI" (Toxikologischer Dokumentations—und Informationsverbund = Cooperation on Toxicological Case Documentation and Information),

funded and formally managed by the German Federal Ministry of Environment, Natural Protection and Nuclear Safety, was constituted 1999 to design, develop, and implement a computer network as a tool for reliable and easy-to-handle product data exchange and data retrieval. Methods: Based on experience from two technical projects of cooperation in the past experts from 7 German PCs formed 4 working groups to develop concepts on (a) use of computer technology for project's database development (b) industry—PC relations, including design of a product data acquisition program, (c) product categorisation and (d) procedures for cooperation and data exchange. Staff members and several external software companies have developed the project's software. The working groups have continuously controlled the project's developmental work and have organized software implementation and testing. Results: In summer 2002 all components of the TDI have been implemented and successfully tested in 7 PCs as well as in industry: in several industrial companies product data is entered into the system using the project's data acquisition program EMIL. Data files created by the EMIL software are sent to one selected project center (primary center, i.e., PC or BfR) using the well-defined ROSETTA data format. The primary center checks the data source and data quality by an automatic procedure and distributes data to all other project partners (secondary centers) using encrypted electronic data exchange. Finally, all centres integrate the evaluated product data records in their local relational TDI database (ORACLE) for retrieval within PCs' daily work. Conclusion: Product information delivered by industrial companies in a reliable data format is easily checked and quickly distributed to all German PC and the BfR using several technical tools developed in the TDI project. The project works as a peer-to-peer network without central steering institution and is therefore a model how an international data exchange could be realised in the future. Reference: (1) Exchange of information between European Poison Control Centres and Industry (AIS:FIFE:FEA). EAPCCT Newsletter April 1996, p. 3–13.

151. THE TOXICOLOGICAL IMPACT OF TWO PUBLIC HEALTH PROTECTION MEASURES IN IRELAND

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Objective: To investigate the toxicological impact of two public health protection initiatives introduced in Ireland. Background: The first public health measure examined was the initiative of using disinfectant liquids and mats at the entrances of farms and businesses during the Foot and Mouth disease (FMD) scare in early 2001. The second initiative was the distribution of stable iodine tablets as part of the National Emergency Plan for Nuclear accidents. Methods: For this study we examined the enquiries received by the National Poisons Information Centre (NPIC) in relation to both protection measures and their toxicological impact. Results: The chemicals used in the make up of FMD disinfectants are generally either strong acids or alkalis, some with a pH as low as 1.8. They were distributed in concentrated form and required dilution (sometimes 1000-fold) before use, usually to soak straw or mats at farmyard entrances. The NPIC received 24 enquiries in total about these products. Eight enquiries concerned the accidental ingestion of these agents in 5 patients, 3 were symptomatic. Symptoms reported included hematemesis, epigastric pain, coma and hypotension. 3 patients had dermal exposure. All were symptomatic with skin burns, discoloration and oedema reported. A further 3 patients suffered inhalation exposure. Again all patients reported symptoms, including respiratory tract irritation, syncope, dyspnoea and coughing. 2 children had ocular exposure, they complained of red, sore eyes. 6 enquiries did not involve patients, 3 from journalists and 3 from members of the public regarding safety procedures for these products. There has been 22 enquiries regarding ingestion of potassium iodate tablets in the 5 months to date. Ten cases were accidental. Six of these involved children, 3 related to adults (2 of whom had diminished mental ability) and 1 case involved a dog. 12 enquiries involved deliberate ingestion of this medication (two enquiries related to one patient). 7 were male, 4 female. 5 patients co-ingested other medication (paracetamol was a co-ingestant in 4 of these 5 cases). Treatment is generally recommended for more than 20 tablets have been ingested by an adult or 10 tablets by a child. 1 adult patient took 24 tablets. She remained asymptomatic and required no specific treatment. Conclusion: Both measures had an impact on the number of calls to the NPIC. The FMD disinfectants proved to have a far greater toxicological impact with nearly all patients developing symptoms.

152. TOXAPEL—FIRST HOTLINE FOR CHILDREN IN ROMANIA

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Objective: Poisoning in children under 1 year of age has received little attention due to its low frequency. TOXAPEL is the first emergency pediatric hotline for poisoning in Romania, created in 1999 and sponsored by the Humana Foundation—USA. With TOXAPEL, callers are expecting to receive information about first aid in poisoning till specialized help arrives. TOXAPEL is available 24 h a day. It can be called from every kind of phone: public, mobile or home posts and is manned by volunteers, nurses or physicians from the toxicology department. The database contains all the drugs available as accepted therapies in Romania, and details of toxic and non toxic substances used in home or industry; a total of almost 5000 items. Each item is linked to a first aid protocol. We present an evaluation of the phone calls received in the period 1999–2002 from an epidemiological study of acute poisonings in children whose parents gave enough information to receive advice on first aid in the first half hour after ingestion. Methods: Retrospective review of the cases of poisoning who contacted TOXAPEL in the November 1999 to November 2002. Results: Number of patients: 1725; Age: average 3 yrs. (range 1 month–18 yrs.). Toxic drugs responsive for the poisoning: Drugs (mostly benzodiazepines)—40%, Oil and derivates—8%, Ethyleneglycol—6%, Mushrooms—23%, Cleaning substances—9%, Formaldehyde—5%, Pesticides—5%, Non toxic substances—4%. Conclusion: TOXAPEL was a valuable help for parents and physicians; by giving first aid as soon as possible, the effect of poisoning may be reduced, the time in hospital is shorter, and the prognosis is potentially improved. References: Haddad, Shannon, Winchester. Clinical Management of Poisoning and Drug overdose, 3rd edition. Saunders 1998.

153. TREATMENT OF ACUTE INTOXICATIONS AT NATIONAL POISON CONTROL CENTRE IN BELGRADE

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Objective: National Poison Control Centre (NPCC) is the only institution for treatment of adult's acute poisonings in Belgrade and suburbs. Center includes 1. Clinic of Toxicology and Clinical Pharmacology with Intensive Care Unit; 2. Institute of Experimental Toxicology and Pharmacology with two subunits—Toxicology Information Department and Department of Experimental Toxicology and Pharmacology; 3. Mobile Toxicological—Chemical Squad. Methods: Analysis of acute poisoned patients treated at NPCC during year 2001. Results: Of the 2556 acute poisoned patients examined at the outpatient room, 780 (30.4%) were hospitalised. The remaining 1776 (69.6%) were discharged after examination and treatment in the outpatient room. Hospitalized patients were poisoned with drugs (495 or 63.5%), caustics (69 or 8.8%), pesticides (68 or 8.8%), and gases (39 or 5.0%), substances of abuse (34 or 4.4%), industrial poisons (33 or 4.4%) and other agents (42 or 5.4%). Of all hospitalized patients, 515 (66.0%) have been treated at Intensive Care Unit (ICU). Main reasons for admission at ICU were coma in 193 patients, delirium and agitation in 103, acute respiratory failure in 94, acute cardiocirculatory failure in 78, gastrointestinal bleeding in 28, acute respiratory distress syndrome in 10 and acute renal failure in 9. Some of those patients had disturbances of more than one vital function at the same time. Treatment included mechanical ventilation in 104 (13.3%), antidotes in 82 (10.5%), extracorporal detoxification in 15 (1.9%), cardiac pacing in 8 (1%) together with other symptomatic and supportive measures. Bronchopneumonia was the most frequent complication. Average duration of hospitalisation was 4.4 days. 44 patients died despite intensive therapy. Total fatality rate was 1.68% and hospital lethality rate was 5.51%. Conclusion: Drugs are the most frequent agents of acute poisonings in our population. The majority of acute poisoned patients could be successfully treated at the outpatient room. The majority of hospitalised patients required treatment at ICU.

154. REPORTING OF LAVAGE METHODOLOGY TO A REGIONAL POISON CENTER

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Background: In 2001, the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS) reported 498,524 cases of poisoning that were treated in health care facilities. Of those, there were 29,798 cases where gastric lavage was reported as a decontamination technique performed. Even though orogastric

lavage (OGL) is an accepted method of decontamination, some physicians are not familiar with it, and may actually perform nasogastric lavage (NGL). Since data collected by the poison centers (PC) are used for research purposes, we wanted to test the accuracy of these reports. Furthermore, inadequate decontamination may add to the morbidity and mortality in cases of poisoning. Methods: A prospective evaluation of a regional PC calls was done comprising the period from 6/7/02 to 11/12/02. A standardized survey instrument was used. If the caller reported gastric lavage, questions were asked regarding the methods used to perform the lavage. The questions included tube diameter, route of use (oral vs. nasal), and time from exposure. Data was collected for all cases, except when the caller refused to participate. Results: A total of 119 cases were collected, including 9 pediatric patients. One case was excluded from analysis due to inability to determine the lavage method used. In 103 cases, the oral route was used (87%). In the other 15 of cases, the nasal route was used for lavage (13%). Overall, 54 of the cases (46%) had a positive lavage. Of these, 93% were using the oral route and 7% using the nasal route. The lavage was performed ≤ 1 h in 55 cases (57%). In 13 cases, that information was undetermined. Conclusion: This study shows limitations in the reporting of gastric lavage to our regional PC in a number of cases. In 13% of the reported cases, gastric lavage did not meet the standard medical practice of OGL. In those cases, the patients did not receive the accepted and correct decontamination technique. Those cases would have been incorrectly reported to the AAPCC-TESS as OGL. The toxicology community uses this national data to evaluate trends in poisoning, effectiveness of treatment, and outcomes after poisoning. Interpretation of these data may fail to demonstrate a benefit of the intervention. Poison center personnel should incorporate education about proper decontamination techniques in their recommendations.

155. USE OF TOXICOLOGY ADMISSION TEMPLATE IN THE EMERGENCY DEPARTMENT

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Objective: Clinical information that is incomplete and difficult to access impedes the care of toxicology patients and increases the difficulty of toxicology research. Review of toxicology patient charts at our institution revealed omission of critical elements in history, physical examination, and management details.[1] Use of preformatted charts has been shown to improve documentation and care in toxicology.[2] To improve documentation and data collection in our institution a Toxicology Admission Template (TAT) was used for all toxicology admissions patients admitted from the emergency department (ED). Methods: We used a before and after method to determine the effectiveness of the form on documentation and ease of use. *Retrospective*: To assess the proportion of omitted pertinent documentation, 105 toxicology admissions prior to the introduction of the TAT were reviewed. *Prospective Data Collection*: The Toxicology Admission Template was used on all patients admitted to the ED for overdose or toxic exposure. Residents, physician assistants and ED attending staff dictated toxicology patient admission data using the TAT. Researchers and research assistants reviewed all dictated records on toxicology patients for completeness of documentation and clinical assessment. To assess improvement in documentation with the TAT we compared the amount of information collected from retrospective chart reviews of prehospital, ED nursing, and provider records to prospective use of the TAT in the ED either by completion of the form itself or using it as a dictation template. Results: 98 consecutive toxicology admissions utilized the TAT. Use of the TAT allowed collection of significantly more data—74% vs. 55% overall—and improved data collection in 5/8 categories (exposure history, past history, neurological examination, complete physical examination, and management/investigations). Prehospital information, vital signs, and general examination were not significantly improved with use of the TAT. Conclusion: Use of the TAT to dictate toxicology admissions would improve documentation of toxicology admissions from the ED and would be a useful tool for patient care and toxicology research. Incomplete use of the TATs was most likely secondary to time demands in the ED and would be improved by shortening the form. Widespread use of the TAT would be the first step in creation of a nationwide Toxicology Database containing pertinent information for toxicology research. References: 1. Harris CR. The utilization of medical intensive care unit for toxicology admissions. *Unpublished* 2000. 2. Buckley NA, White IM, Dawson AH, Reith DA. Preformatted admission charts for poisoning admission facilitate clinical assessment and research. *Ann Emerg Med* 1999; **34**:476–482.

156. ETHNIC DIFFERENCES IN THE HOME MANAGEMENT OF POISONINGS

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Objective: To evaluate differences in knowledge and awareness in the management of poisonings by ethnicity. Methods: Stratified random sample of residents in Dallas County, Texas. A random digit dial survey of 900 citizens was done. The respondents were asked the following: "If someone you know accidentally or intentionally swallows something that is poisonous, what are the first three things you would do?" There were four choices for response: calling 911 (the emergency services dispatch center in the USA); go to the Emergency Department (ED); induce vomiting; and call the poison center. The top three choices were recorded for every respondent. The data were stratified by ethnicity. Results: Hispanic respondents were one third as likely as Caucasians to call the Poison Center and half as likely as African Americans ($p < 0.00001$). Hispanics were also more than twice as likely to go to the ED than Caucasian or African American respondents ($p < 0.00001$). There were no differences in the proportion of who would induce vomiting or call 911, although the latter is by far the most popular countermeasure. See Table 1 for results.

Table 1.

Results (%):	Caucasian	African American	Hispanic
Call 911	68.0	69.7	62.7
Go to the ED	15.1	17.7	35.0
Induce vomiting	21.0	16.7	17.0
Call Poison Center	46.3	28.7	14.7

Conclusions: Poison centers collect regional data that is reported to a national surveillance system to study trends and impact of poison exposures across the United States. Our survey reflects the need for a major outreach and education to certain groups, especially Hispanics, in order for this national data to be accurate and representative of the general population. Disparities in health seeking behavior and education may also have implications for ED resource utilization. By increasing the outreach and increasing the likelihood of calls from these minority groups to the poison centers, the resources will be better utilized. Furthermore, ED visits may even be decreased by improving the efficacy of the health services across our community. More studies are needed to determine the reasons for this significant disparity in the mindset of utilization of poison centers.

157. TDI-PROJECT: A HARMONIZED CATEGORY-SYSTEM FOR PRODUCTS IN POISONS CENTRES (PC)

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Objective: Grouping systems are important tools for retrieval and processing of huge data volumes in PC. Since 1999, German PCs and the Federal Institute for Risk Assessment (BfR, formerly BgVV) have been working on the toxicological data and information-network (TDI-Project, funded and formally managed by the German Federal Ministry of Environment, Natural Protection and Nuclear Safety) in order to establish a standardized procedure for product data transfer from industry to PC/BfR. The creation of a uniform category-system for products and biological substances is one of the main tasks of this project. Methods: 1. Survey for importance and usage of grouping systems in PC/BfR. 2. Conception of the technical integration. 3. Creation of a hierarchically arranged category tree. Results: 1. Four important functions were identified: a) Grouping of new products within the case documentation. b) Epidemiological evaluations with regards to product groups for reports. c) Group specific analysis of cases of poisoning for the development of monographs. d) Retrieval of toxicological information for one product group, if specific product information is missing. 2. The category-system is hierarchically structured in nine levels and connected with the main index of the product names. The hierarchy of the categories is determined by a code with optionally 26 letters or 99 numbers (similar to ATC-Code). 3. The classification of the noxious substances is made according to its purpose (products), taxonomical (natural environment), its source, or its properties (civilization load/waste). Conclusion: The common use of a harmonized category-system facilitates the classification of the product information submitted by industry. For the future, it allows a uniform classification of cases of poisoning in Germany. The systems with about 10,000 different categories are currently being tested and built up. Internationally established systems were integrated

Table 1. Sample fragments of the category-system.

L1	L2	L3	L4	L5	L6	L7	L8	L9	Category-name
P									Products
P	E								Everyday essentials
P	E	C							Cosmetics
P	E	C	S						Skin cosmetics
P	E	C	S	01					Skin detergents
P	E	C	S	01	S				Soap-cosmetic
P	E	C	S	01	?				...
P	E	C	Z						Cosmetics—other/unknown
P	R								Remedies
P	R	D							Drugs (human)
P	R	D	?						... (following the ATC-Code)
N									Natural environment
N	F								Fungi
N	P								Plants
N	A								Animals
N	?								...
C									Civilization load/waste

(e.g., ATC-Code, IPCS/INTOX). The technical base has been created in a flexible mode and allows more international harmonizations in future times.

158. A TOXIC EVENT SURVEILLANCE SYSTEM IN THE EMERGENCY DEPARTMENT OF SPANISH HOSPITALS

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Objective: To maintain an updated profile of the toxic incidents caused by chemical products that reach the Emergency Departments of Spanish Hospitals, within the frame of a collaborative program developed by the Health Ministry and the section of Clinical Toxicology of the Spanish Association of Toxicology since 1999. Methods: Data are submitted by members of the staff of the emergency department of the participating hospitals. The clinical data for each patient include: sex, age, symptoms, treatment and outcome and product identification, exposure cause, location of exposure and exposure route. We present here the results of the first 3 years of the program. Results: 15 hospitals are participating and have reported a total of 1622 cases. Admission was required in 460 cases (28.36%). Mean age is 37.41 years. Males represent 52.30% and females 47.70%. Reasons for the exposures were domestic accidents in 1062 cases (65.47%), suicidal in 211 cases (13%), occupational 271 (16.70%), other 67 (4.13%) and unknown in 5 cases (0.30%). The main families of chemical compounds have been classified: toxic gases 549 cases (33.84%), caustics 507 cases (31.27%), solvents 136 cases (8.38%) and detergents 134 cases (8.26%), pesticides 194 (11.96%), metals 11 (0.67%), other 91 (5.61%). The most frequent individual agent is carbon monoxide (302 cases) followed by domestic bleach (236 cases). The route of exposure has been oral in 654 cases, inhalation in 648 cases, cutaneous in 95 cases and ocular in 272 cases, some of them associated. 1429 cases had some symptoms: neurologic 355, respiratory 360, digestive 501, cutaneous 71 and ocular 271, renal 4, cardiovascular 22. Treatment was necessary in 1361 cases: gastric decontamination in 162, cutaneous or ocular decontamination in 161, antidotes in 333, enhanced elimination in 18 and symptomatic measures in 967 cases. Mean stay in hospital has been around 24 hours. There have been 25 deaths, caused by methanol (4), paraquat and other pesticides (11), HCl (7) and CO (3). Most of the non-lethal cases have had a good outcome with a few minor sequelae. Conclusion: This program is useful to maintain an updated profile of poisoning by chemical products. The data show a homogeneity over the years that allows identification of the most dangerous compounds and families and contribute to the development of preventive strategies to avoid the most frequent or dangerous exposures.

159. QUALITY ASSURANCE OF ANTIDOTAL THERAPY—APPLICATION VERSUS ADVICE

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Objective: Antidotal therapy is a key aspect in the management of poisoning. This report describes an audit of the use of antidotes, carried out by the Poison Centre of Mainz, using the poisoning documentation system ADAM©. Methods: 141,284 cases referred to the PC, between 01/01/1995 and 06/30/2002 (7.5 years), were analyzed for any mention of the use of antidotes. A unique follow-up procedure allowed an assessment of the evolution and outcome of these cases. Results: There were 20,210 cases (14.3% of total) where antidotes were optionally advised, advised and/or used. In the documentation of these cases there were 23,273 references to 30 different antidotes (1.15 per case). Written follow-ups were available for 9,930 cases (49%). In 4,902 cases (3.5% of all cases) a total of 5,230 antidotes (1.07 per case) were actually given, with 2,116 given before and 3,114 given after the consultation. Assuming the same frequency of antidote usage in all cases then it can be estimated that antidotes were used a total of 8,471 times in 7,940 cases (5.6%). On average, antidotal therapy was given 1.3 times more often than recommended by the PC and antidotes were given 3.0 times more often after consultation than before. Conclusion: From PC data some antidotes are given more often than recommended (e.g., Flumazenil, Naloxone). This introduces both unnecessary costs and the risk of adverse effects for the patient (1). The audit of the use of antidotes is continuing and is expected to highlight further issues concerning their appropriate and inappropriate use. It also will provide information about the efficacy and complications of antidote therapies and will improve quality assurance measures. References: Krenzelok EP. New developments in the therapy of intoxications. *Toxicol Lett* 2002;**127**:299–305.

Table 1. Five most frequently used antidotes and estimated total usage of antidotes. (*)The estimated number of antidote therapies assuming frequency of usage is the same as in followed-up cases.

Antidote	Frequency antidotes advised/used	Before consult.	During consultation		After consultation		Total (before + after c.)		Quotients	
		Given	Optionally advised	Advised	Given	Given(*)	Given	Given(*)	Given(*) /advised	After(*) /before c.
Physostigmine	7107	160	6451	475	310	633	470	793	1.7	4.0
Flumazenil	4455	822	3152	319	244	498	1066	1320	4.1	0.6
Acetylcysteine	3811	268	302	3181	1432	2922	1700	3190	1.0	10.9
Biperiden	2452	71	2201	183	87	178	158	249	1.4	2.5
Naloxone	1058	245	738	87	71	145	316	390	4.5	0.6
Total top 5	18883	1566	12844	4245	2144	4376	3710	5942	1.4	3.8
Total 30	23273	2116	14395	6378	3114	6355	5230	8471	1.3	3.0

160. RETROSPECTIVE STUDY OF ACUTE POISONINGS ADMITTED TO A DANISH HOSPITAL IN 2001

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Objective: Epidemiology describing poisoned patients treated in the emergency ward at H:S Bispebjerg Hospital has not been published for many years. We wanted to describe this population mainly regarding substances ingested and pattern of gastric decontamination performed. Methods: A retrospective study of poisoned patients treated in the emergency department at H:S Bispebjerg Hospital, during 2001, as identified by a search performed by our IT department. All patients discharged with poisoning codes (ICD-10) were identified. All hospital case record forms of this search were pulled from the electronic system, anonymized, and analyzed. All forms were double-checked by the first author for discrepancies in scoring. Results: 225 cases were identified, 88 male (mean age 41.7, range 16–91) and 137 female

Table 1. Ingested substances divided into groups. Numbers are actual cases.

Ingestion	Paracetamol	ASA	NSAID	SSRI/TCA	Antipsychotics	Benzodiazepines	Opioids	Alcohol	Illicit drugs	Other
Single	38	10	3	2	6	23	11	12	4	17
Multiple	17	9	7	5	12	57	22	70	15	27

patients (mean age 40.5, range 13–90). 75.6% were intentional (suicide attempts), 24.4% were unintentional (medication errors or unintentional overdoses of illicit drugs). 126 patients had been poisoned by one substance. The most common drug ingested in this group was paracetamol (30%), followed by benzodiazepines (18%), and alcohol (12%). 99 cases were multiple ingestions (alcohol 71%, benzodiazepines 58%, opioids 22%, illicit drugs 15%). For more details, see Table 1. Of particular interest in the group labeled other drugs, were 6 atypical antidepressants, 5 phenobarbitals, 4 carbon monoxide exposures, and 12 antiepileptics. A total of 72% of patients could supply a history of intake. In only 13 cases was no history obtainable. Gastric decontamination should have been performed according to department guidelines in 156 cases, but was only done in 98 cases. Activated charcoal was given in 95, gastric lavage in 1 and a combination of the two in 2 cases. A total of 57% were discharged to the home without complications, 5% with minor complications and 38% were transferred to other departments, usually the psychiatric department. There were no fatalities. In 117 cases (52%) there were marked discrepancies between discharge codes and the actual poisonings identified by analyzing the case records. In 22 cases of paracetamol or benzodiazepine poisonings, these were coded as T36.9, antibiotics. Conclusion: Paracetamol, benzodiazepines and alcohol were the predominant substances ingested in cases of poisonings treated at our hospital. Activated charcoal was the dominant method of gastric decontamination. Several discrepancies in the coding of poisonings were found.

161. ESTIMATION OF THE RISK OF PATIENTS WITH ACUTE DIGOXIN-INTOXICATION

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Objective: There is an obvious correlation between the severity of digoxin-intoxication and the serum concentration of the drug after an equilibrium of distribution. This level can only be considered at least 6 h after ingestion. The aim of our study was to obtain clinical and laboratory parameters giving a good estimation of the prognosis of the intoxication. Patients and Methods: In a retrospective study data of 41 patients were analyzed who were treated at our department in the last 6 years. The following parameters were obtained: age, sex, underlying diseases, vomiting, heart rate on admission, blood pressure, serum potassium, serum digoxin (fluoroimmunpolarisation assay-Abbott TDx). Results: The patients were divided into two groups according to the Poison Severity Score: PSS 3, 16 cases (39%) and PSS 1 or 2, 25 cases (61%) with the mean values of serum digoxin concentration measured between 6–12 hours after ingestion 11.78 ng/ml (8.54–17.2) and 3.95 ng/ml (2.11–6.72), respectively. In 5 cases of the former group and in 10 cases of the latter we determined the serum digoxin concentration within 6 hours after ingestion. The mean values were 15.01 ng/ml (4.42–32.6) and 6.78 ng/ml (2.9–19.24), respectively. Among laboratory and clinical parameters three ones were selected the occurrence rate of which seemed to be most characteristic for severe cases: vomiting 14/14 (100%), bradycardia (HR $<$ 60/min) 14/16 (87.5%), hyperkalaemia (serum potassium $>$ 5.0 mmol/l) 10/16 (62.5%). The same

Table 1. The occurence rate of bradycardia, hyperkalaemia, vomiting in patients with digoxin-intoxication.

	Non-severe (n = 25)	Severe (n = 16)
3 symptoms	0	8
Any 2 symptoms	7	5
1 symptom	9	3
No symptom	9	0

values of the PSS 1–2 group were the followings: vomiting 14/25 (56%), bradycardia 5/21 (23.8%), hyperkalaemia 4/25 (16%). Conclusions: In accordance with other studies we have found that the serum digoxin concentration obtained between 6–12 hours after ingestion correlated well with the clinical course of intoxication, whereas the concentration determined within 6 hours cannot indicate the prognosis of the intoxication. The main message of our retrospective study is that the bradycardia, hyperkalaemia, vomiting are the most predictive symptoms in patients with acute digoxin intoxication. This simple but important observation helps us to introduce an adequate specific therapy with Digibind in severe cases.

162. FIVE-YEAR RETROSPECTIVE REVIEW OF TOXIC EFFECTS FROM METFORMIN EXPOSURE

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Background: The major risk associated with metformin is lactic acidosis. The incidence of lactic acidosis is not clear. Hypoglycemia is not expected to be a major concern after metformin exposure. This study assessed the demographics, toxic effects and clinical syndromes of metformin exposures reported to poison centers nationally. Method: The Toxic Exposure Surveillance database (TESS) of the American Association of Poison Control centers was searched for all metformin-only exposures for the 5-year period from January 1, 1996 through December 31, 2000. Results: There were 10,958,526 total poisoning exposures reported to TESS during the study period. 4072 cases met the study criteria, of which 2421 (59%) were females. 3074 were acute exposures (75%), 767 acute-on-chronic (19%), 200 chronic exposures (5%) and 31 chronicity was unknown (1%). Children ≤ 12 years old experienced few adverse outcomes and no deaths. There were 20 moderate effect outcomes (1.8%) and 2 major effect outcomes (0.2%) for the <6 years group and 4 moderate effect outcomes (2.3%) and no major effect outcomes in the 6 to 12 year group. In the adult population the

Table 1. Evaluation of clinical effects reported with metformin exposure grouped by occurrence and medical outcome.

Hypotension	6 (3%)	9 (28%)	6 (75%)	$P < 0.05$
Acidosis	36 (19%)	23 (72%)	8 (100%)	$P < 0.05$
↑ Anion gap	4 (2%)	7 (22%)	8 (100%)	$P < 0.05$
Hyperglycemia	10 (5%)	1 (3%)	7 (88%)	$P < 0.05$
Coma	1 (1%)	7 (22%)	5 (63%)	$P < 0.05$
↑ Creatinine	7 (4%)	8 (25%)	4 (50%)	$P < 0.05$
Vomiting	25 (13%)	4 (13%)	3 (38%)	N.S.
Respiratory arrest	0 (0%)	0 (0%)	7 (88%)	N.S.
Hypoglycemia	98 (52%)	13 (41%)	1 (13%)	N.S.
Confusion	15 (8%)	5 (16%)	0 (0%)	N.S.

adverse outcomes were distributed evenly across the age span, with a trend toward more serious outcomes in the elderly. There were 8 deaths (0.3%), 30 major effect cases (1.1%) and 153 moderate effect cases (5.5%). In all age groups acidosis was rare ($n = 67$, 1.6%). Hypoglycemia is more common than previously reported. ($n = 112$, 2.8%). Clinical effects associated with a major outcome or death were hyperglycemia, acidosis, elevated anion gap, elevated creatinine, hypotension and coma (Table 1). Conclusion: Severe adverse events after exposure to metformin are not common, occurring in approximately 1% of cases. This is agreement with previous reports.

163. DIPYRONE OVERDOSE

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Background: Dipyrone is a pyrazolone derivative used as analgesic and antipyretic. Agranulocytosis, dipyrone's most serious and potentially fatal adverse effect, has led to its withdrawal in many countries. However, agranulocytosis is

subject to geographical variability with risk ratio ranging from 0.8–23.7. In several countries dipyrone is widely used in adults, children and even as an OTC preparation. Information on the effects of dipyrone overdose is scanty. Objective: To determine the demographic and clinical characteristics of dipyrone overdose. Methods: Retrospective poison center chart review of acute exposure to dipyrone over a 3-year period, descriptive analysis, Mann–Whitney test where relevant. Results: 234 records were retrieved and the following distribution was found: 67.9% and 27.1% of calls were made by physicians and the general public, respectively; 58.4% and 34.6% involved females and males, respectively; 59% and 41% were unintentional exposures and suicide attempts, respectively; 88% of exposures occurred at home and 92.6% involved the oral route. Median age was 17 y (4m–83y), median amount 5 g (250 mg–45 g) and time to consultation 2 h (5 min–48 h). Toxic events (49) occurred in 39 (16%) patients, 57% of them were gastrointestinal, all mild. Time to consultation was significantly longer in symptomatic patients (4 h vs. 1.5 h, respectively, $p = 0.001$) and in children (8 h vs. 3.5 h in adults). Suicides ingested significantly larger amounts (8 g vs. 3.7 g, respectively, $p = 0.001$), as did patients with G-I symptomatology (7.5 g vs. 5 g in asymptomatics, $p = 0.001$). No agranulocytosis was reported. Discussion: Dipyrone overdose is associated with mild, mainly gastrointestinal, toxicity that was noted at a median dose of 7.5 g. Early G-I decontaminaton may have prevented toxicity. Time of presentation of overdosed symptomatic patients corresponds to the known peak therapeutic response. The suggested treatment includes G-I decontamination (if < 1 h) and supportive measures.

164. COX-2 INHIBITORS: A REVIEW OF TOXICITY

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Objective: At therapeutic doses Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may have serious side-effects such as gastro-intestinal bleeding. Cox-2 inhibitors such as meloxicam, rofecoxib and celecoxib selectively inhibit cyclo-oxygenase 2 with little or no inhibition of cox-1, resulting in anti-inflammatory and analgesic action while minimizing the risk of gastro intestinal (GI) adverse events. Most NSAIDs, such as ibuprofen, have a good safety profile in overdose, although mefenamic acid and phenylbutazone related drugs are notable exceptions. As cox-2 inhibitors are relatively new, very little is known about the action of these drugs in overdose, although the expectation is of a similar toxicity profile to ibuprofen and other NSAIDs. The aim here is to review available data and case notes, to establish the anticipated effects of Cox-2 inhibitors in overdose. Methods: All cases of Cox-2 inhibitor ingestion (adult and paediatric) reported to NPIS (London) from 1999 onwards were reviewed and followed up by postal questionnaire. The data collected has been reviewed to determine a toxicity profile for Cox-2 inhibitors in overdose. A literature search was also undertaken. Results: Between 1994 and 2001 advice was requested from NPIS (London) regarding a total of 539 cases of overdose with meloxicam, rofecoxib, etodolac, or celecoxib. Most cases involved meloxicam or rofecoxib (296 and 136 cases respectively). Of the 352 cases reviewed between 1999 and 2001, none had significant effects directly attributable to this type of NSAID. In multiple agent overdoses nausea and vomiting were the only GI symptoms noted. In cases where a cox-2 inhibitor had been taken alone, patients were asymptomatic. Single overdoses of up to 49 tablets (rofecoxib), 28 tablets (meloxicam), and 28 tablets (celecoxib) were reported. Where undertaken, no biochemical or renal abnormalities were observed. A Medline search of the literature revealed only one account of overdose involving a Cox-2 inhibitor (etodolac).[1] An increase in prothrombin time (of no clinical significance) was noted although the patient remained clinically asymptomatic. No fatalities have been reported as a result of cox-2 inhibitor overdose. Conclusion: Cox-2 inhibitors have no unexpected effects in overdose, and appear to be well-tolerated. GI effects such as nausea and vomiting may occur, as with other NSAIDs such as Ibuprofen, but there have been no reports of renal complications or GI bleeds occurring *de novo*. References: Boldy DAR, Hale KA, Vale JA. Etodolac Overdose. *Hum Toxicol* 1988; **7**:203–204.

165. ARE ACUTE POISONINGS ALWAYS DUE TO OVERDOSE?—A SYSTEMATIC REVIEW OF CASES ADMITTED IN A TOXICOLOGICAL INTENSIVE CARE UNIT

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Objectives: Acute poisoning represents a major cause of admission in emergency departments and intensive care units (ICU), especially among young patients. In recent years, an increasing number of poisonings have been reported to be consecutive to multidrug ingestion. Therefore, close relationships between the patient symptoms and the supposed ingested toxicants are becoming more difficult. The objectives of our study were to describe the poisoned patients admitted to an ICU and to evaluate the importance of drug overdose in the mechanism of poisoning. Methods: We prospectively collected data of all poisoned patients admitted in our toxicological ICU, regarding the supposed ingested toxicants, the clinical features, the toxicological analysis, the prescribed treatments and antidotes. Patients were classified according to the type of intoxication (intentional versus accidental) and to the nature of the intoxicants (e.g., psychotropic or cardiotropic drugs). Overdose was defined as blood concentration in a toxic range of at least one toxicant. When poisoning involved toxicants with measurable blood concentrations, we calculated, the percentage of symptomatic poisoned patients who had negative or non-toxic concentrations (defining the non-overdose condition). Results: Over a 5-month-period, 174/386 patients (45%) were admitted in our ICU for an acute intoxication, with 44/174 patients (25%) referred from the Emergency Department. The majority of poisonings (171 cases) resulted from an intentional ingestion (153 suicidal attempts and 18 addictive uses), whereas only 3 cases were consecutive to an accidental ingestion. Intoxication mainly involved psychotropic drugs (86%). 14% of the patients presented a cardiovascular toxicity risk (hypotension or membrane stabilizing effect). 20/174 patients (11%) developed aspiration pneumonia, 5/174 severe toxic-related cardiac failure and 7/174 (4%) died. 88/174 patients (51%) received antidotal treatments, including flumazenil (20 patients), 8.4% bicarbonate (13 patients), N-Acetylcysteine (10 patients), activated charcoal (9 patients), naloxone (7 patients), glucagon (6 patients), vasoactive drugs (5 patients) and fomepizole (5 patients). In 20/174 patients (11%), symptoms requiring ICU admission were not completely explained by significant ingested toxicants or toxic blood concentrations. However, we could not eliminate that insensitivity of the semi-quantitative blood tests may be responsible for failure to detect overdose in some cases, like benzodiazepines. Conclusion: Poisonings are responsible for severe morbidity and increased mortality in ICU. There are a significant group of patients whose symptoms cannot be explained alone by toxic doses or blood concentrations of the poisons. In these cases, one may thus hypothesize that drug–drug interactions are the responsible mechanisms of toxicity.

166. RESULTS OF PARACETAMOL AND SALICYLATE ASSAYS IN UNITED KINGDOM HOSPITALS

Dale C, Henry JA. *Academic Department of Accident and Emergency Medicine, Imperial College London, St Mary's Hospital, London, UK.*

Objective: Paracetamol overdose is a common presentation in Accident and Emergency Departments in the United Kingdom and is a significant cause of morbidity and mortality. It accounts for 48% of hospital admissions for poisoning in the UK (1) and is associated with 500 deaths per annum (2). Due to the prevalence of their use and the fact that an overdose with paracetamol or aspirin can be initially asymptomatic it is common practice for clinicians to check drug levels when presenting with a drug overdose or is unconscious with unknown cause. Because clinicians have a low threshold to perform these tests we carried out a survey to see what proportion of paracetamol and salicylate assays were negative or <10 mg/l and <50 mg/l respectively. Methods: Multicenter Research Ethics Committee approval was obtained. Biochemistry departments within the United Kingdom were randomly contacted by telephone or e-mail. Data was collected on the number of paracetamol and salicylate levels taken over a period of one year (01/01/01–31/12/01) and how many were negative.
Results:

Number of hospitals responding: 23

Number of paracetamol tests per hospital: 7–3277; median 853

Number of salicylate tests per hospital: 3–2881; median 869

% Negative paracetamol: 68.1% (range 52–85.7; C.I. 64.2–72.0)

% Negative salicylate: 85.8% (range 59.6–100; C.I. 81.3–90.4)

Three hospitals were unable to give a full calendar year; figures were adjusted to one year's data. Conclusions: A large proportion of paracetamol and salicylate levels were negative, explicable by the need to rule out the presence of these drugs because of the potential consequences of a missed overdose. P.I. Dargan et al. (3) concluded that there is potential to miss a significant paracetamol overdose in the unconscious patient and therefore checking for the presence of paracetamol is clinically justifiable as it is potentially fatal yet treatable. With the recent development of a near patient test for the presence of paracetamol and salicylate in blood which has the potential to rule in or rule out these two drugs it would be possible to avoid a laboratory test in 68% of patients. References: (1) Hawton K et al.; Paracetamol self-poisoning—characteristics, prevention and harm reduction. *Br J Psychiatry* 1996;**168**:43–48. (2) Paracetamol related deaths in England & Wales 1993–1997. *Health Statistics Quarterly*, Autumn 2000. (3) Dargan PI et al.; Measuring plasma paracetamol concentrations in all patients with drug overdose or altered consciousness: Does it change outcome? *Emerg Med J* 2001;**18**:178–182.

167. VALIDATION OF A POINT OF CARE TEST FOR THE PRESENCE OF PARACETAMOL AND SALICYLATE IN BLOOD

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Objective: To find out the sensitivity and specificity of a point of care test (PoCT) for the presence of paracetamol and salicylate in blood. What are the potential time savings when using this PoCT? Methods: Ethics Committee approval was obtained for a multicenter trial to take place in St Mary's and Charing Cross, London; Wexham Park, Slough; Prince Charles, Merthyr Tydfil. Any patient presenting to AED with a clinical indication for paracetamol and salicylate levels was included and a blood sample 4 hours post-ingestion was analyzed using the near-patient test (SureStep™, Euromed, London—http://www.euromed.ltd.uk) and the remainder sent for laboratory analysis. Results and times were documented.

Results:

N = 312 (186F:123M) Average age: 34.1 (range 1–86 years)

Time from ingestion to presentation:	Mean 266.2 mins	(C.I. 220.3–312.0)
Time in department:	Mean 385.7 mins	(C.I. 351.3–420.1)
Time difference between PoCT and lab result:	Mean 119.2 mins	(C.I. 109.5–129.0)

Using a cut-off of 25 mg/l for paracetamol

Sensitivity = 110/112 = 98% Specificity = 144/200 = 72%.
NPV = 144/146 = 0.99 PPV = 110/166 = 0.66

Using a cut-off of 100 mg/l for salicylate

Sensitivity = 22/24 = 92% Specificity = 264/284 = 93%
NPV = 264/266 = 0.99 PPV = 22/42 = 0.52

Discussion: The two patients recorded as negative for paracetamol with the PoCT and yet above 25 mg/l on the laboratory test were at 28 and 56 mg/l. The two recorded as negative for salicylate were at 110 and 113 mg/l. Observer error is possible with these tests. The design of the test with the line becoming visible when there is NO drug present may confuse people who have not been trained and who are familiar with pregnancy tests. Training is crucial to avoid this. Conclusion: Screening for paracetamol and salicylate in the overdosed or unconscious patient is clinically justifiable and will be until there is a dramatic change in trends. This test is quick and simple to use, and can rule out a paracetamol overdose with a sensitivity of 98% and NPV of 0.99. The time saving of almost 2 h, as well as improving patient satisfaction, reduces departmental workload and stress. The cost of these tests may be similar to traditional laboratory tests, but it is believed that in many cases they may result in a reduction in overall costs.[1] Reference: 1. Hobbs FDR et al. *Health Technology Assessment* 1997;**1**:No 5.

168. HUMAN CLOTIAPINE POISONING

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Objectives: Clotiapine is an antipsychotic drug, and poisoning with this agent has increased in Switzerland over the last decade, data about human overdose is scarce. The aim of our study was to investigate the acute toxicity of oral clotiapine overdose with regard to dose-dependent severity, critical doses for moderate and severe symptoms, and influence of age and early decontamination on clinical outcome. Methods: We retrospectively analyzed all feedback reports from physicians on patients with clotiapine poisoning between January 1971 and December 2001. Only cases with clotiapine monointoxication containing sufficient information regarding ingested dose and severity of symptoms were included. Severity was assessed according to the Poisoning Severity Score (Persson H et al. *J Toxicol Clin Toxicol* 1998;**36**:205–13). Statistical analysis was done with logistic regression. Results: Eighty-six patients were included in the study, 26 female, 59 male, 1 unknown. The median age was 29.5 years (range 1.5 to 66). 9 patients were children (< 16 years old). The mean ingested dose was 0.95 g (median 0.8 g, range 0.02 to 4.8 g). Circumstances of poisoning were accidental in 9, and intentional in 76 cases (1 undetermined). Early decontamination (within 1 hour of ingestion) was performed in 19 cases (22%). Minor, moderate, and severe symptoms were observed in 53 (69%), 21 (27%), and 1 (1%) adults and in 4 (44%), 4 (44%), and 1 (11%) children respectively. One patient remained asymptomatic, no fatalities occurred. Minor symptoms included, somnolence (n = 57), mild extrapyramidal signs incl. dysarthria (n = 15), tachycardia (> 140 bpm) (n = 10). Moderate symptoms included coma (n = 13), moderate extrapyramidal signs (n = 3), agitation (n = 3), arterial hypotension (systol). (BP < 80 mmHg) (n = 3), and respiratory insufficiency (n = 2). The 2 severe cases exhibited deep coma (GCS < 7). Miosis was recorded in 15, mydriasis in only 3 cases. An anticholinergic syndrome (2 peripheral anticholinergic symptoms) was present in only 1 patient. The correlation between higher severity (asymptomatic or mild vs. moderate or severe) and increasing dose was statistically significant ($p = 0.005$), and children had a more severe outcome ($p = 0.003$); an influence of early decontamination on severity was found in the high dose group only ($p < 0.05$, chi square test).

Table 1.

Dose group	Number of patients with asymptomatic/mild symptoms	Moderate/severe symptoms
< 0.5 g (n = 30)	22 (73%)	8 (27%)
0.5–1.0 g (n = 30)	23 (77%)	7 (23%)
1.0–1.5 g (n = 12)	9 (75%)	3 (25%)
> 1.5 g (n = 14)	6 (43%)	8 (57%)

Conclusions: Clotiapine leads to toxic symptoms in a dose-dependent manner, with doses above 1.5 g leading to a higher proportion of moderate or severe outcomes. Children are more susceptible to clotiapine toxicity than adults. Early decontamination has a significant effect on outcome in doses > 1.5 g only. Most frequent symptoms are CNS-depression and extrapyramidal symptoms, whereas anticholinergic signs are rare.

169. INCIDENCE OF BUTTON BATTERY INGESTION IN WALES AND THE SOUTH WEST OF ENGLAND

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Objective: To analyze the incidence of button battery ingestion in Wales and the South West of England between 1997 and 2001. Methods: Call records of button battery ingestion made to the NPIS (Cardiff Centre) were retrieved to evaluate the pattern of exposure. Data analyzed included the age of the patient and reason why ingestion was thought to have occurred. Results: Over the five-year period studied, 370 calls were received by the NPIS (Cardiff Centre) concerning button battery ingestion. This accounted for 0.2% of all calls received during the time of this study. Of these calls, 43 were repeat inquires about patients. During 1997, 48 inquires were made regarding button battery ingestion. Eighty-four calls were received during 1998, 78 calls in 1999, 76 calls in 2000 and 84 during 2001. The ages of patients involved ranged between 1 to 94 years with 48% of all calls received involving a child aged between 1 to 5 years of age. One year

old children were involved most commonly (14%). Accidental ingestion of a button battery accounted for 338 of the calls received, 27 calls were recorded as intentional ingestion of a button battery and 5 were recorded as intentional attempted suicide with a button battery. Conclusion: The number of appliances which require button batteries, has increased, resulting in an increase in the number and type of button battery now available. Children up to the age of 5 years appear to be at the greatest risk of ingesting one of these batteries. Due to the size of these batteries, the majority traverse the gastrointestinal tract uneventfully. Problems arise if the battery becomes lodged in the intestinal tract or leaks. In these instances a button battery can cause electrical burns, chemical burns and chemical toxicity. For older batteries, a single mercury cell can contain enough mercury to prove fatal if ingested by a child; a chilling thought as 48% of calls received involved a patient under the age of six years.

170. POISONS ADMISSIONS IN EDINBURGH: PREDICTORS OF READMISSION ACCORDING TO DRUG TAKEN AT FIRST ADMISSION

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Objective: To describe, using discharge data from a single hospital, predictors of readmission with acute poisoning, according to drug taken at first admission. Methods: A database containing information on all discharges from, and deaths in, the Royal Infirmary of Edinburgh with a diagnosis of poisoning or toxicity in any of six diagnostic fields from 1981 to 2000 was used. Diagnoses were classified according to ICD 9 codes until March 1996, whilst ICD 10 codes were used thereafter. Data were "linked," so that records relating to individual patients could be identified. For different drugs taken at first admission Cox proportional hazards regression was used to evaluate prognostic factors for readmission, with followup censored at either death or the end of 2000. Results: There were 6641 first admissions with paracetamol in any of the six fields. In a multiple regression analysis adjusted for year of admission, age ($P < 0.001$) and deprivation category ($P < 0.001$) both significantly predicted readmission, whereas sex did not. Readmission rates were relatively constant in those aged less than 35 years but were greater in older patients. Estimates (95% confidence limits) for percent readmission rates after one year were 14.4 (13.4–15.4) in patients under 35 and 17.6 (16.2–19.0) in those over 35. For deprivation, the figures were 14.6 (14.3–15.8) in categories 1–4 (affluent) and 19.9 (18.0–21.8) in categories 5–7 (deprived). Predictors of readmission following poisoning with other drugs taken at first admission were: Benzodiazpines ($n = 4059$)—increased age, male sex, greater deprivation and more recent first admission (all $P < 0.001$); antidepressants ($n = 3223$)—increased age, male sex and more recent first admission (all $P < 0.001$); non-steroidal anti-inflammatory drugs ($n = 2063$)—increased age ($P < 0.001$) and more recent first admission ($P < 0.05$); salicylates ($n = 1652$)—increased age ($P < 0.001$); opiates ($n = 1353$)—increased age and more recent first admission (both $P < 0.05$), and greater deprivation ($P < 0.01$); antipsychotics ($n = 839$)—increased age ($P < 0.001$); antiepileptics ($n = 714$)—increased age ($P < 0.01$) and greater deprivation ($P < 0.05$). Conclusion: Linked admission data are valuable in determining factors that predict readmission in acute poisoning. The results may help in planning future strategies to reduce readmissions.

171. ACUTE METHOTREXATE OVERDOSE: A CASE REPORT AND DEVELOPMENT OF MANAGEMENT GUIDELINES

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Background: There are few reports of adult deliberate acute methotrexate overdose in the peer-review literature. Leucovorin rescue may be required but toxicological texts differ widely in their recommendations. Following an index case, we reviewed consultations by our center, plus the toxicology and oncology literature, and developed new methotrexate management guidelines for our center. The objective of this report is to present the index case, and discuss management guidelines. Case report: A 42-year old female presented 6 h after ingesting 500 mg of her own methotrexate tablets (10 mg/kg, 320 mg/m^2). Activated charcoal (50 g) was administered and 15 mg of leucovorin was given orally every 6 h until 30 h after the ingestion. Serum methotrexate levels at 6, 12, 30 and 54 h after the ingestion were 0.96, 0.17,

0.01, and 0.02 mcmol/L, respectively. All levels fell below the treatment line of the methotrexate-leucovorin nomogram. A full blood count performed at one week was normal. Conclusions: Current oncology practice is to withhold leucovorin following acute intravenous dosing unless greater than 400 mg/m^2 is administered. In such cases leucovorin is given at 24 h after the methotrexate dose. Large oral doses of methotrexate are poorly absorbed. This case generates the hypothesis that leucovorin may be withheld in adult patients who take an acute overdose of less than or equal to 500 mg of methotrexate, provided activated charcoal is administered, renal function is normal, and a level is performed within the first 24 h. Prospective studies are required.

172. QUINIDINE-LIKE EFFECTS FROM QUETIAPINE OVERDOSE WITH DOCUMENTED SERUM LEVELS

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Objective: Quetiapine is a newer atypical antipsychotic believed to have a better safety profile than previous antipsychotic agents do. It is a dibenzothiazepine derivative similar to clozapine with increased serotonergic activity compared to dopaminergic effects. It also has very little antimuscarinic and alpha-1-antagonist receptor activity and no reported sodium channel blocking activity. Common reported effects after overdoses include CNS depression, tachycardia and hypotension. We present the first reported case of QRS widening after quetiapine overdose correlated to a specific serum quetiapine level. Case report: A 29-year-old male presented approximately 1 h after ingesting nearly 8,000 mg of quetiapine and an unknown amount ethanol. Upon arrival he was obtunded without protective respiratory reflexes and required orotracheal intubation. Orogastric lavage was performed and activated charcoal was given. Initial vital signs revealed a pulse of 170 bpm, and a blood pressure of 135/78 mm Hg. Initial chemistries were normal. Liver function tests were slightly elevated with AST of 203 IU/ml and ALT of 139 IU/ml. Urine drug screen was negative for common drugs of abuse and tricyclic antidepressants. Serum ethanol was 238 mg/dl. All other labs were within normal limits. The QRS from the initial electrocardiogram was 138 ms. He received one ampoule of sodium bicarbonate (50 mEq) IV push and was started on a bicarbonate drip, three ampoules of $NaHCO_3$ in 1 L of D5W infused at 200 cc/hr. Follow up EKG taken 15 minutes after sodium bicarbonate bolus showed QRS of 92 ms. The patient developed aspiration pneumonia requiring mechanical ventilation for two additional days and IV antibiotics. No further QRS widening was reported after the bicarbonate drip was discontinued. Quetiapine levels drawn upon admission were 7100 Ng/mL. He was discharged to a psychiatry facility 6 days after admission without any neurologic deficit. Conclusion: Occurrences of QRS prolongation with quetiapine are rare with only one previous case series reporting a non-quantified increase in QRS duration. This case illustrates a confirmed QRS prolongation with quetiapine overdose, related to a specific serum quetiapine level, which corrected upon administration of sodium bicarbonate. This patient did not have prescriptions for any other medications and there is no indication that a confounding factor may have contributed to the cardiotoxicity observed. Electrocardiographic changes from quetiapine have infrequently been reported in the literature, but may be mediated by antichoninergic or quinidine-like mechanisms similar to cardiotoxicity caused by traditional antipsychotics. Health care providers should be aware of the possible risk of QRS prolongation associated with quetiapine.

173. GERIATRIC OVERDOSE OF 1,4-BUTANEDIOL MASQUERADING AS SYNCOPE AND SEIZURE

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Objective: Gamma-hydroxybutyric acid (GHB) was used as an anesthetic agent in the United States after its discovery in the 1950s. Although no longer used for this purpose, the drug is approved for the treatment of narcolepsy. Youths in the "club scene" abuse GHB for its euphoric effects. Recently, the use of its pro-drugs gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) has increased as a result of wider availability. These agents, found commonly in solvents and cleaning products, are converted to GHB in vivo. Adverse events associated with the use of these drugs include respiratory suppression, seizure-like activity or myoclonic jerks, coma, and death. Altered mental status and respiratory

suppression in young club-goers should raise suspicion for the use of GHB, GBL, or 1,4-BD. However, failure to consider GHB intoxication in other populations, including geriatric patients, may result in missed diagnosis. Case report: We recently encountered a 63-year-old male patient who had witnessed syncope followed by a generalized tonic-clonic seizure. This occurred minutes after ingesting a small amount of "Chimney Magic," a cleaning product containing a GHB precursor drug. His urine GHB level, determined by GC–MS, was 439 μg/ml. He required mechanical ventilation due to respiratory depression. His electrocardiogram was normal and an electroencephalogram showed diffuse brain wave slowing. The patient recovered uneventfully after a 24 h period. This case represents the oldest patient reported to have used recreational GHB or one of its precursors. Conclusion: Clinicians should be aware that GHB abuse is not restricted to youths. The wide availability of GBL and 1,4-BD makes abuse of these drugs likely to continue. In addition, their use may spread beyond the "club scene" to include larger numbers of older adults. This case illustrates the need to maintain a high index of suspicion for "club drug" use in a wider patient age range. References: Mason PE, Kerns WP. Gamma hydroxybutyric acid (GHB) intoxication. *Acad Emerg Med* 2002;**9**:730–9. Dyer JE. Gamma-hydroxybutyrate: a health-food product producing coma and seizure-like activity. *Am J Emerg Med* 1991;**9**:321–4. Zvosec DL et al. Adverse events, including death, associated with the use of 1,4-butatendiol. *N Engl J Med* 2001;**344**:87–94.

174. SEVERE AMLODIPINE OVERDOSE: RELATIONSHIP BETWEEN TOXICOKINETICS AND TOXICODYNAMICS

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Objective: Amlodipine is a dihydropyridine calcium channel antagonist with predominant arteriolar dilator effect. We describe a case of intentional ingestion of amlodipine, in which the relationship between toxicokinetics, described as time course of drug concentrations, and toxicodynamics, defined as quantitative effect of amlodipine on the blood pressure (BP), was investigated. Case report: A 46-year-old, 45 kg woman with a history of hypertension and depression ingested 560 mg amlodipine and 50 mg bromazepam in a suicide attempt. On arrival at the hospital, she was awake and oriented with a BP of 85/50 mm Hg and a heart rate of 100 bpm approximately 3 h after ingestion. Electrocardiogram showed mild signs of slowed intraventricular conduction. She was treated with dopamine 8 to 16 μg/kg/min, dobutamine 8 μg/kg/min, oxygen, massive vascular filling according to the value of central venous pressure, gastric lavage and activated charcoal 50 g. Three hours later, BP decreased to 70/40 mm Hg. Twelve hours after ingestion, hypotension (75/45 mm Hg) did not respond to glucagon (100 μg/kg followed by 200 μg/kg/h), that was stopped 3 h later. Oliguria was treated with high doses of furosemide and volume loading. In the following hours, hemodynamic status slowly improved. The woman required three days of vasopressor therapy to achieve and maintain hemodynamic stability. On day 4, electrocardiogram and echocardiogram were normal (ejection fraction of 65%). She had a good recovery. Amlodipine and bromazepam analysis were respectively performed by high-performance liquid chromatography and gas chromatography. Blood samples were taken at 3.5, 6, 12, 24, 30, 38, 48, 72, 96, 108, 120, 158, 182, 264, 456 hours postingestion. Bromazepam serum peak level was 740 ng/mL (normal 80–170 ng/mL), at 12 h after ingestion. No signs related to bromazepam overdose were observed. The highest amlodipine serum concentration (415 ng/mL, therapeutic 5–15 ng/mL) was found at 6 h postingestion. In the following hours, a two-phase exponential decay was calculated according to the equation: $y(ng/mL) = 401e^{-0.098\times(hours)} + 259e^{-0.004\times(hours)}$. The time for amlodipine concentration to return to a therapeutic level was 264 hours (15 ng/mL). During the clinical course, the relationship between the values of mean BP and the corresponding amlodipine concentrations was described by the equation: $y(mm\,Hg) = 93.4 - 0.108 \times (ng/mL)$. There was a good correlation between toxicodynamics and toxicokinetics: $r = 0.90$, $p < 0.0001$. Conclusion: This case shows that intensive symptomatic treatment is effective in counteracting the cardiovascular failure related to a dose of amlodipine as high as 12.4 mg/kg. This case also shows that improvement of BP appeared to be related to the reduction of circulating amlodipine concentration.

175. BIDIRECTIONAL-WIDE COMPLEX TACHYCARDIA AFTER CITALOPRAM OVERDOSE

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Objective: The serotonin-specific reuptake inhibitor citalopram has been associated with cardiac conduction abnormalities and seizure activity in overdose. We report an unusual case of bidirectional-wide complex tachycardia after deliberate citalopram ingestion. Case report: An otherwise healthy 22-year-old 68 kg female presented to a community emergency department an unknown time after ingestion of citalopram 1200 mg. Prior to her arrival, she experienced a self-limited generalized tonic-clonic (GTC) seizure. A second self-limited GTC seizure occurred shortly after arrival. At presentation, vital signs included heart rate 155 beats per minute (bpm), blood pressure 157/77 mm Hg. Mental status was reported as awake and oriented. Initial ECG demonstrated a wide complex tachycardia with left bundle branch block (LBBB) morphology, ventricular rate 154 bpm, QRS interval 134 msec, QTc 515 msec. P waves could not be readily discerned. ABG demonstrated severe acidemia, with pH of 6.97. She received single-dose activated charcoal and gastric lavage. Two ampules of sodium bicarbonate (50 mEq) were provided, and a sodium bicarbonate infusion initiated. Despite this therapy, a second ECG obtained 45 minutes later demonstrated persistent tachycardia (152 bpm), persistent QRS prolongation (126 msec; LBBB appearance), and persistent QTc prolongation (541 msec). Repeat ABG demonstrated improved acidemia, with pH 7.34, pCO_2 44. A rapid, antibody-based drug screen was negative, and electrolytes were within normal limits. By 2 h after presentation, she had developed a bidirectional-wide complex tachycardia, with a heart rate of 99 bpm, QRS duration 125 msec, and QTc 475 msec. The patient was subsequently transferred to a tertiary care medical intensive care unit. Upon arrival in the MICU, approximately 5 h after initial presentation, she was noted to be in normal sinus rhythm (84 bpm), with resolution of QRS interval prolongation (84 msec). The patient remained somnolent and oriented only to person for approximately 24 h. Conclusion: This patient developed significant interventricular conduction delays with an LBBB morphology after citalopram ingestion, as previously described. However, the abnormalities were not responsive to sodium bicarbonate and were associated with an apparent paucity of atrial P waves. This is the first report of a bidirectional-wide complex tachycardia associated with citalopram ingestion. Although the cardiac irritability resolved within hours and the patient never developed evidence of hemodynamic compromise, such profound cardiac disturbances have the potential to degenerate into malignant rhythms.

176. A DOCUMENTED BUPROPION BEZOAR IN THE EMERGENCY DEPARTMENT

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Background: The formation of a bezoar is a rare but potentially serious complication in both normal medication use and overdose situations. Bupropion is a commonly prescribed antidepressant that is available in immediate release (IR) and sustained release (SR) preparations. Bupropion inhibits dopamine and norepinephrine reuptake. Sinus tachycardia, lethargy, tremors, and seizures are common manifestations of toxicity. Bezoar formation has not been reported. We describe a patient who vomited a 15–20 pill mass of bupropion SR seven hours after ingestion. Case report: A healthy 18 y/o female was brought to the ED after taking approximately 30 tablets of Wellbutrin SR (4.5 g) over several minutes in an apparent suicide attempt. She arrived with a normal neurologic exam and vital signs (BP 138/84 HR 100 RR 16 T 37.0). Initial laboratory values included: APAP < 1.0 mcg/dl, ASA < 1.0 mg/dl, normal anion gap, CBC, and chemistries. Urine drug screen was positive for marijuana. The patient received 50 g of activated charcoal 1 h after ingestion. She became restless and mildly agitated over the next 4 h. Five hours after ingestion she had a 90-second tonic clonic seizure. The patient received 2 mg of IV lorazepam and returned to normal mental status within 20 minutes. Seven hours after the ingestion the patient vomited, producing a 15–20 pill bezoar in a small volume of gastric fluid. The patient was admitted for 23 h observation and psychiatric evaluation. She was asymptomatic during the rest of the hospital stay. Conclusions: This case demonstrates the risk of bezoar formation after acute ingestion of bupropion SR tablets. Formation of a medication bezoar places the patient at risk for serious morbidity and mortality, including delayed toxicity and intestinal obstruction.

177. SOME EPIDEMIOLOGICAL DATA OF VENOMOUS AND NONVENOMOUS ANIMAL ACCIDENTS OF UNICAMP POISON CENTER, 1994–2001. CAMPINAS CITY, S. PAULO STATE (BRAZIL)

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Background: Epidemiological data concerning the incidence of venomous bites and stings, in Brazil, are collected by the National Databank of Major Causes of Morbidity (SINAN), National Information System on Poisoning (SINITOX),

Table 1. Experience of the Unicamp Poison Center with venomous and nonvenomous animal accidents.

Animals	Total	Deaths
Scorpions	1568	1
Spiders	1455	—
Venomous snakes	266	1
Nonvenomous snakes	355	—
Lepidoptera	596	—
Hymenoptera	770	3
Ticks	96	—
Millipedes	7	—
Fish	6	—
Coelenterata	5	—
Unknown	562	1
Total	5686	6

Hospital Information System of the Unified Health System (SIH-SUS), and Mortality Information System (SIM), which have specific characteristics and different demands. As envenoming caused by venomous bites and stings represents an important part of the work of Unicamp Poison Center (UPC). From Jan 1984 to Dec 2001 the UPC was consulted about 55531 cases; 12005 (21.6%) of them were accidents with venomous animals, about 667/year. According to SINITOX, which collects data from 31 Brazilian Poison Centers, in the year 2000, 16157 (22.20%) out of 72786 cases attended, were victims of venomous animals. Since 1983 the UPC has been the reference service for poisonous animals in Campinas region, S. Paulo State. Objectives: To present some epidemiological data of venomous and nonvenomous animal accidents of UPC from 1994 to 2001. Methods: A retrospective review of data on venomous and nonvenomous animal consults with the UPC from Jan 1994 to Dec 2001. Results: From Jan 1994 to Dec 2001 the UPC were consulted about 28675 cases, of which 5686 were accidents with venomous animals—(19.83%). 64.8% were attended in the University Hospital and 33.2% were telephone calls, 64.1%—adults, 35.9% children. Six of the patients died. Three died at the University Hospital, while the other three deaths occurred at different medical services (phone calls).
The scorpion species was not identified in 848 out of 1568 cases; 495 involved Tityus bahiensis; 220, Tityus serrulatus, and 5, other species of Tityus. The spider species was not identified in 616 out of 1455 cases; 589 involved Phoneutria; 136, Loxosceles; 71, Lycosa, and 43, others. The venomous snake species was not identified in 56 out of 266 cases; 141 involved Bothrops; 51, Crotalus; 9, Opisthoglyphas, and 9, Micrurus. 428 out of 770 cases with Hymenoptera involved Bees; 226, Wasps; 52, Ants, and 64, others. Eight out of 596 cases with Lepidoptera were with Lonomia. Conclusion: Nearly 20% of the cases attended at the UPC involve accidents with venomous animals.

178. DIAGNOSTIC VALUE OF URINARY AMANITIN ANALYSIS IN MUSHROOM POISONING: A PILOT STUDY

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Background: Amatoxin-containing species are responsible for the most severe cases of mushroom poisoning, with a related mortality of 6–18%. Therefore, this poisoning must be ruled out in all patients presenting gastroenteric symptoms after wild mushroom ingestion. Although urinary amanitin analysis has long been available, there is a lack of knowledge about the usefulness of this test for the early diagnosis in the ED. Objective: To determine sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of urinary amanitin analysis in cases of suspected mushroom poisoning. Methods: All cases of wild mushroom ingestion with subsequent gastrointestinal symptoms presenting in the ED in the period August 1–31, 2002 were analyzed. Definitive diagnosis, based on history, symptoms at presentation, overall clinical course and laboratory results, was considered the gold standard. Urine samples were collected between 5.5 and 92 h (mean 20.7 ± 20.2) after mushroom ingestion. Amanitin

measurements were performed with Bühlmann Amanitin ELISA Kit (Bühlmann Laboratories, Allschwil, CH). The method has a functional least detectable dose of 1.5 ng/ml; a cut-off value is not clearly established. Results: Sixty-one patients were included in the study. Definitive diagnosis of amatoxin-containing mushroom poisoning was made in 10 cases (16.4%). SENS and SPEC of initial diagnostic assessment made by a trained toxicologist were 100% and 61% respectively. Diagnostic performance of urinary amanitin analysis is showed in the Table.

Urinary amanitin levels		SENS	SPEC	PPV	NPV
≥ 1.5 ng/ml	All patients	70%	82%	44%	93%
	Urine collected within 36 hours	100%	89%	58%	100%
≥ 5.0 ng/ml	All patients	60%	100%	100%	93%
	Urine collected within 36 hours	100%	100%	100%	100%
≥ 10.0 ng/ml	All patients	50%	100%	100%	91%
	Urine collected within 36 hours	83%	100%	100%	98%

In most cases, amanitin levels between 1.5 and 10.0 ng/mL required individualized evaluation, based on history and clinical findings in both the patient and companions who had eaten the same food. False negative values were observed because of delayed sample collection. Discussion: Urinary amanitin analysis may significantly contribute to the management of suspected mushroom poisoning. The arbitrary cut-off of 5 ng/ml seems to discriminate well between amatoxin poisoning cases and other diseases. However, these results need to be validated in a prospective study to be used in the clinical practice. At present, especially for patients presenting late after mushroom ingestion, the best diagnostic performance can be obtained with the combined use of clinical assessment (more sensitive) and urinary amanitin analysis (more specific).

179. TRANSAMINASE LEVELS IN AMANITA PHALLOIDES POISONING

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Objectives: The main toxicological effect after ingestion of Amanita mushrooms is toxic hepatitis. A number of serum enzymes have been used to distinguish hepatocellular injury and transaminases have proved a useful biological marker. We have examined the relationship between increase of different transaminases in blood and the severity of poisoning. Methods: We retrospectively evaluated medical histories of 12 patients with phalloid poisoning treated at the Clinic of Toxicology and Urgent Internal Medicine in the last year. We compared the De Ritis index (AST to ALT ratio) in patients divided in two groups: 4 pts who died (33.3%) compared to 8 pts (66.6%) who survived. Results: Increased levels of transaminases were detected in all pts usually after the second day. The highest value was detected at days 4–6. In the group that died the average value of AST was 4456 ± 534 (2260–6328) and of ALT 3578 ± 1054 (1870–6388). Their ratio was generally higher than 1.0 (1.41 ± 0.28; 0.96–1.61). In the second group the average value of AST was 271.5 ± 110 (67–661), and ALT was 1235.37 ± 212 (63–4641), and their ratio was below 1.0, (0.32 ± 0.0085; 0.14–0.46). Our results show that the first site of toxic effect is the cytosol of the hepatocyte, but in pts with fatal hepatic injury the release of mitochondrial AST is higher than cytosolic ALT and DeRitis index is above 1.0. The highest values of transaminase were in the most severely poisoned patients. Conclusion: The aminotransferases are important biological markers. In this ongoing study, these preliminary results suggest there is a prognostic value in monitoring transaminases and measuring their ratio.

180. TOXIC MEGACOLON IN THE COURSE OF SEVERE AMANITA PHALLOIDES INTOXICATION

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Objective: Intoxications with amatoxin-containing mushrooms like Amanita-, Lepiota- and Galerina-species occur frequently between June and October with a maximum in August and September. Beside the well-known complications such as hepatic failure, encephalopathy and multiorgan failure, involvement of other organs like bone marrow, pancreas, kidney and gastrointestinal tract (except for the initial cholera-like gastroenteritis) are not well documented in the literature. In addition to supportive intensive care therapy early antidotal treatment with silibinin or penicillin G can prevent sometimes life-threatening fulminant hepatic- and multiorgan failure which lead to death. If liver transplantation is possible, several techniques enable bridging the patient until a suitable transplant is available. Uncommon complications like toxic megacolon require an empirical approach. Case series: A 72-year-old male patient consumed a mushroom meal containing amanita phalloides, which he had confused with agaricus campestris. Approximately 6 h later, a typical gastrointestinal syndrome emerged with copious loss of fluids. Antidotal treatment with penicillin G was initiated followed by a continuous silibinin infusion before the patient was transferred to our toxicological department. Laboratory findings showed a severe hepatic damage, elevation of serum creatinine and a serious disturbance in the coagulation system. Although clinical condition and laboratory findings nearly fulfilled transplantation criteria, hepatic injury resolved during intensive care therapy. Intractable diarrhea and dilatation of the intestine on X-ray met criteria of toxic megacolon. Other possible reasons, like antibiotic-associated pseudo membranous colitis, were excluded. In addition to therapy with antibiotics, systemic and topical steroids, the patient needed decompression therapy by a catheter, which was placed by colonoscopy. Colonic mucosa showed severe ulcerative damage with high regeneration activity. Thirty days after a serious amanita poisoning complicated by development of toxic megacolon, the patient resolved without sequelae and was discharged. Conclusion: In the treatment of amatoxin poisoning addition to supportive intensive care therapy, one has to keep in mind other infrequent and poorly described complications like ulcerative colitis and toxic megacolon, the gut being a further "target organ" of eukaryotic cell-damage due to amatoxin-induced inhibition of RNA-polymerase II. In severe cases multiple endoscopic interventions may be required, despite serious complications like colonic perforation or perpetuation of inflammation. Early interdisciplinary discussion between toxicologists, surgeons and gastroenterologists is helpful in deciding optimum therapy. Therefore, early transfer of these patients in specialised centres is recommended.

181. ACUTE POISONINGS WITH BREYNIA OFFICINALIS—AN OUTBREAK OF HEPATOTOXICITY

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Background: In combination with other traditional Chinese medicines, Breynia officinalis, a species of Euphorbiaceae, has long been used to treat contusions, heart failure, venereal diseases, growth retardation, and conjunctivitis. Breynia officinalis, regarded as a poison, was mistaken for Securinega suffruticosa and used in dealing with the problem of muscle soreness, lumbago and as a tonic in this outbreak. Case series: Nineteen patients, 11 males and 8 females with an average age of 49.2 ± 9.1 years old, consumed about 130 ml (30–900 ml) of Breynia officinalis. Fourteen cases developed diarrhea, 10 experienced nausea and chilly sensations, 9 had sensations of abdominal fullness, and 7 suffered from vomiting. The results of abnormal liver function tests indicated that the observed peak median levels were alanine aminotransferase 647 (89 ~ 9,440) U/L, aspartate aminotransferase 314 (47 ~ 7,756) U/L, alkaline phosphatase 251 (224 ~ 278) U/L, and gamma glutamyl transpeptidase 106 (84 ~ 313) U/L. The median time corresponding to the observed median peak levels showed alanine aminotransferase 3 (2 ~ 12) days, aspartate aminotransferase 2 (1 ~ 12) days, alkaline phosphatase 5 (5 ~ 5) days, and gamma glutamyl transpeptidase 12 (2 ~ 14) days respectively. With supportive treatment, majority of abnormalities of aspartate aminotransferase and alanine aminotransferase (14 cases out of 19 cases) subsided within six months. Conclusions: Consumption of Breynia officinalis Hemsley resulted mainly in gastrointestinal signs and symptoms associated with hepatotoxicity. Marked jaundice did not develop. Hepatocellular liver injury rather than cholestatic liver injury and dose related effects were observed.

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182. PLANT AND HERB EXPOSURES IN SPAIN

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Introduction: Plants can be used not only ornamentally at home and in the garden, but also, as medicinal drugs, drug of abuse, insecticides, as food, dietary supplements, and in magic rituals. Intoxication by plant toxins can therefore occur in many different scenarios. The purpose of this study is to examine the plant and herb exposures in our country. Methods: From January 1991 to May 2002 all plant and herb exposures (excluding pharmaceutical preparations) documented by our Service were recorded. Gender, age, etiology, exposure route, place of intoxication, clinical features and severity at the time of consultation, and the type of plant or herb (for plants involved in 10 or more inquiries) were registered. Results: A total of 1590 consults about plant or herb exposures were recorded during the study period. Fifty-six percent of patients were male. Adults accounted for 23.6% of cases and children for 75.7%; 59.3% were less than 24 years old. Unintentional exposures were 90.4% (of these 30.2% because of dose confusion), abuse 3%, suicidal attempts 1.8%, occupational 0.8%. There were two chronic cases, one homicide, and in 3.6% the plant was unknown. Ingestion was the route more usually involved (84.8% of cases), followed by mucous membrane contact (11.5%), dermal contact (2.1%), subcutaneous (0.3%), inhalation (0.2%), and multiple routes (1%). Fifty-six percent of consults came from members of the general public. The exposures occurred at home in 51.3% of cases, followed by countryside (21.1%), street (1.2%), workplace (0.5%), and unknown (26.2%). 37% of cases were symptomatic. The clinical manifestations of symptomatic patients were: gastrointestinal (41.9%), mucous membrane irritation (38.5%), neurological (25.5%), and cardiovascular (6.1%). Moderate to severe manifestations occurred in 30.2% of cases. The plants most frequently implicated in decreasing order were: *Dieffenbachia* spp (10%), *Colocasia* spp (7.2%), *Euphorbia* spp (5.2%), *Nerium oleander* (3.9%), *Scindatus pictus* (3.8%), *Datura stramonium* (3.5%), *Ficus* spp (3.2%), *Ricinus communis* (3%), *Ilex aquifolium* (2.7%), *Solanum* spp (2.4%), *Viscum album* (2.2%), *Acacia* (2%), *Aesculus hippocastanum*, *Iris germanica*, *Taxus baccata*, *Arum* spp, *Daphne* spp, *Cactus*, *Illicium verum*, *Prunus* spp, *Clivia miniata*, *Dracaena fragans*, *Narcissus* spp, *Hedera helix*, *Eucalyptus globulus*, *Calla palustris*, *Capsicum* spp, *Asparagus* spp. Conclusions: In our study children are the more affected population. Errors in dosage are common among consumers of herbal remedies. The vast majority of exposures were by plants containing insoluble calcium oxalate crystals, followed by plants and herbs which have systematically active toxins.

183. ACUTE LIVER AND KIDNEY INJURY AFTER ABUSE OF SENNA ALKALOIDS

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Background: We present a case of acute liver, and probably also kidney, injury following chronic abuse of senna alkaloids. Case report: A 51-year-old woman was admitted with weakness and jaundice. Clinical examination showed hypotension, tachycardia, jaundice, without hepatosplenomegaly and encephalopathy. According to the relatives, the patient chronically ingested vitamins (including vitamin A), with additional daily use for more than 3 years of infusions of senna alkaloids for constipation. Laboratory data were as follows: ASAT 6640 IU/L (2–41), ALAT 9140 IU/L (2–45), γGT 160 IU/L (11–50), alkaline phosphatase 354 IU/L (28–94), bilirubin 6.3 mg/dL (0.3–1.2), ammonia 290 μg/dL (<100), glucose 40 mg/dL, INR 5,27 (1–1.3) and factor V 19% (70–110), urea 63 mg/dL (15–50) and creatinine 3.2 mg/dL (0.8–1.4). A severe metabolic acidosis was also noted with high lactate levels. Common causes (viral, toxic, autoimmune,. . .) of acute liver failure were ruled out by laboratory investigations. Hepatic encephalopathy progressed from day 2 (GCS 6/15, grade IV according to the EEG) and the patient required respiratory and cardiocirculatory support. The possibility of a liver transplantation was even discussed. At the same time, she developed a proximal renal tubulopathy manifested by a persistent acidosis metabolic, hypokalaemia, hypophosphatemia, tubular proteinuria, phosphaturia, aminoaciduria, glycosuria, and increased excretion of β_2-microglobulin (344210 μg/g creatinine [<300]) and retinol binding protein (4700 μg/g creatinine [<300]). This tubulopathy was associated with a moderate glomerulopathy and nephrogenic diabetes (diuresis >7000 ml/day, serum osmolality 312 mOsm/kg H_2O, urine osmolality 165 mOsm/kg H_2O, natremia 148 mmol/L). Biological signs of liver and kidney dysfunction gradually improved over one month. Discussion: Senna alkaloids derive from *Cassia senna* leaf and fruit and are administered for

constipation and ingested as infusion. These alkaloids are split in the intestine by intestinal bacteria to rhein anthron, a similar structure as danthron, a well-known hepatotoxic laxative. Senna is a potent laxative that should not be used on a daily basis. The hepatotoxicity of the senna alkaloids, probably by a toxic damage (pericentric necrosis is also observed with paracetamol, in the absence of eosinophilia), is occasionally reported in the literature in vitro and in vivo. In contrast, there is almost no data in the literature concerning the possibility of nephrotoxicity.[1] Conclusion: An acute hepatocellular liver injury can be induced by products marketed as dietary supplements or herbal remedies. Chronic use of senna alkaloids may cause life-threatening liver and perhaps kidney injury. Reference: [1]Adam SE, Al-Yahya MA, Al-Farhan AH. Combined toxicity of Cassia senna and Citrullus colocynthis in rats. *Vet Hum Toxicol* 2001;**43**:70–2.

184. DESCRIPTION OF THE 2002 SEASON OF MUSHROOM POISONINGS IN THE POISON CENTRE OF MARSEILLES

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Objective: Mushroom poisonings are observed every year during a short period (one or two months) which usually begins at the summer end. As mushrooms have an important role in the French cuisine, the first cases of intoxication happen as soon as the September rains induce the fungi development. Every 4 years, a special prospective study is performed in the "Toxicovigilance" unit of the Poison Centre of Marseilles in order to evaluate the importance of mushroom poisonings in South Eastern France. Case series: The 2002 mushroom season was unusually long because the rain began to fall the first week of August and the cold winter wind was not present until the middle of November (study period 01/08/02 to 15/11/02). 116 observations of gastrointestinal syndrome concerning 195 patients were collected (average delay of 3 hours between ingestion and symptoms, vomiting for 75% of the patients, abdominal pain 30%, diarrhea 27%. Main implicated species: *Boletus satanas* and *Clitocybe olearia*). The second frequent kind was the Muscarine syndrome with 27 observations and 34 patients (shorter delay for the onset of symptoms, with an average value of 1H30. Main symptoms: perspiration for 94% of the patients, vomiting 53%, aqueous diarrhea 50%, hypersalivation 24%, myosis 18%, bradycardia 12%. Main implicated genus *Inocybe*). The other syndromes were less frequent, but more severe: 2 cases of Psilocybin syndrome with the death of a 17 years old patient who ingested a specimen of *Copelandia cyanescens* and who jumped through the window thinking he was able to fly; 2 cases of Phalloides syndrome including one collective poisoning with 4 adults who presented severe hepatic cytolysis after ingestion of unidentified *Amanita* species; 4 cases of behavior disturbances during Pantherina syndromes; 1 case of renal insufficiency during a Proxima syndrome after ingestion of *Amanita proxima*. For several observations, the clinical features did not correspond to classical descriptions, and the responsible species was not identified: 3 cases of Myalgias with creatine kinase blood level elevation, 3 cases of severe and initial hematemesis 3 hours after a mushroom meal, and 3 cases of elevated fever without infectious origin during a gastrointestinal syndrome. Conclusion: Mushroom poisonings are frequent in the fall and represent an important part of the French Poison Centre activity during the short concerned period. Once again the origin of the poisonings was the ignorance of the population: the patients were not able to identify what they ate and were really irresponsible.

185. CARDIOVASCULAR DISORDERS INDUCED BY ACONITUM SPECIES

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Objective: The Aconitum genus of plants is considered highly toxic. Aconitine has been described as the "queen mother of poisons" of the ancient world. While the toxicology of the diterpene and norditerpene alkaloids isolated from various species of Aconitum is relatively well-known, human poisonings seem to be rare and only very few have been published. We report a case of Aconitum poisoning we recently observed. Case report: A 31-year-old male with a history of bipolar affective disorder ingested 60 blue flowers of Aconitum species, probably Aconitum cammarum, which is a hybrid plant of Aconitum napellus (Monkshood). On admission to hospital 5 hours after ingestion he had tremors, nausea, vomiting, and a cold periphery. BP varied between 90/40–110/70 mmHg. Ethanol level was 150 mg/l (3.26 mmol/l). Blood

glucose and oxygen saturation were normal. An ECG showed bigeminy, right bundle branch block (RBBB), and his pulse was irregular (50–130). Activated charcoal was administered for gastric decontamination. I.v. fluid fill-up was not enough to treat early stage hypotension (MAP 60 mmHg), but the BP normalized after dopamine-infusion was started. The patient felt weak and tired, but had no disturbed consciousness. Within 24 h the ECG returned to normal and the patient recovered uneventfully. Conclusion: The toxicity of any particular plant of Aconitum species varies depending on the amount of toxic alkaloids. Even small amounts of this plant can be fatal if ingested. In this case a quite massive dose induced potentially dangerous transient cardiovascular disturbances which resolved uneventfully within 24 h. References: 1. Lewis R. *Lewis' dictionary of toxicology 1998.* 2. Imazio M, Belli R, Pomari F et al. Malignant ventricular arrhythmias due to Aconitum napellus seeds. *Circulation* 2000;**102**:2907. 3. Tai YT, But PP, Young K et al. Cardiotoxicity after accidental herb-induced aconite poisoning. *Lancet* 1992;**340**:1254–1256. 4. Alanko P, Huusko J, Kahila P. *Tammen suuri puutarhakirja [Tammi's book of gardening]* 1998.

186. SALVIA DIVINORUM, A NEW ABUSE POTENTIAL PLANT

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Objective: The aim of this study is to alert European clinical toxicologists to a brand-new use of *Salvia divinorum* as an hallucinogenic substance. Method: OFDT (Observatoire Français des Drogues et des Toxicomanies) evaluated different products used for recreational abuse during feasts and parties: the SINTES program (Système National d'Identification des Toxiques Et Substances). The products are bought by the SINTES organization directly from the users during the parties with the French law authorities' agreement. Two toxicological laboratories in France analyze the collected samples, including the toxicological laboratory of the Poison Centre of Marseilles. Report: During summer 2002, specimens of *Salvia divinorum* used as a recreational drug during rave parties were collected in southern France. The plant was sold as vegetal powder or dried leaves at the price of five euros per gram. *Salvia divinorum* (Labiateae) is an hallucinogenic mint used for divination in the Mexican state of Oaxaca, by the Mazatic people. The main active compound is salvinorin A, also called Divinorum A, which is a diterpene. Its activity and potency are similar to mescaline. *Salvia divinorum* can be considered as a plant with abuse potential. Dried leaves and vegetal extract are smoked in the same way as marijuana. The hallucinogenic activity begins 1 minute after use and is effective for 30 minutes. Conclusion: This phenomenon may increase in France and Europe because Salvinorin A is not listed as a narcotic substance. Only Australia, in June 2002, listed *Salvia divinorum* and Salvinorin A among illicit drugs. Reference: *Salvia divinorum*: a hallucinogenic mint which might become a new recreational drug in Switzerland. Giroud C, Felber F, Augsburger M, Horisberger B, Rivier L, Mangin P. *Forensic Sci Int* 2000;**112**:143–50.

187. EXOTIC SNAKE ENVENOMATION (ESE) BY *TRIMERESURUS ALBOLABRIS*

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Objective: The keeping of exotic reptiles as pets in the U.S. is a growing hobby, in part related to a large Internet community around their sale. Physicians should be well-versed in the initial management and stabilization of exotic snake envenomation (ESE) and about specific management resources. We describe a patient with ESE reported to our PCC. Case report: A 38-year-old ambulatory male presented 60 minutes following ESE proximal to the ankle by white-lipped, green-tree pit viper. Early paresthesias and minimal bleeding from bite site were reported. Pain and swelling quickly progressed to involve the foot. Complaints suggestive of systemic toxicity were absent. There was no prior history of envenomation or exposure to antivenom. PE revealed: BP, 113/63 mm Hg; pulse, 72 beats/min; RR, 16 breaths/min; and T, 99.7°F. Three puncture wounds (0.5 × 0.2 cm) near the right lateral malleolus, were surrounded by a 4 cm area of central pallor, with a 10 cm diameter area of dark discoloration. Passive stretch of the toes was not painful. Pulses and capillary refill were intact. Laboratory results were: WBC 10.7, Hgb 16.2, Plt 183, INR 0.9, PT 10.6, PTT 21, and fibrinogen 301. Treatment included narcotic analgesics and empiric antibiotics. Since the patient was a member of a private antivenom bank that arranged delivery, five vials of Green Pit Viper Antivenom became available. These were given 12 h post-envenomation for progressive swelling involving the entire extremity. Diphenhydramine and

hydrocortisone were administered empirically. Despite antivenom use, ecchymoses and swelling continued to progress, but there was no evidence of systemic coagulopathy or hypotension. The patient was ambulatory with a cane at discharge on hospital day 4. The patient's locale had an ordinance against the keeping of dangerous animals, and 37 venomous snakes representing 17 species were confiscated from his house. Conclusion: This is the first US report of ESE by *Trimeresurus albolabris*. Clinical features were reminiscent of envenomation resulting from other pit vipers. As has been previously reported with this species, antivenom did not appear to halt progression of local toxicity in this case. While this occurrence was geographically unexpected, venomous reptiles are increasingly being held in private collections far from their native environments. Since collectors can rarely afford to maintain diverse antivenom supplies, private societies are forming that offer members access to such exotic antivenoms. The physician needs to have a sound diagnostic and therapeutic approach to an unknown ESE. Furthermore, enhanced awareness that PCCs can provide access to specialized identification resources, information on antivenom location, and treatment guidelines is needed.

188. MANAGING AN OUTBREAK OF BOTULISM: A CASE REPORT

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Background: Botulism is a neurotoxic disease caused by the toxin produced by *Clostridium botulinum*. We report an outbreak of foodborne botulism involving eight individuals and our experience during the initial management of these cases. Case report: A healthy 7-year-old boy presented to his physician with one day of vomiting and generalized fatigue. He was diagnosed with a viral syndrome, but he returned the next day with double vision, difficulty moving his tongue, slurred speech, dysphagia, weakness, and ataxia. Significant physical examination findings included bilateral ptosis, diplopia, and tongue weakness. The same day, five of the patient's family members presented with similar symptoms. All involved family members had ingested canned chili 3 days before. The patients were referred to two tertiary care facilities with a presumptive diagnosis of botulism. The Department of Health and CDC were contacted, and a supply of botulinum antitoxin was immediately flown in and administered to the patients. Over the next five days, two additional patients were diagnosed with botulism linked to the same source. Six patients required intubation for respiratory failure. The length of intubation ranged from 19–54 days, and the length of hospital stay ranged from 5 to 72 days. No patients died. Conclusions: Effective treatment of foodborne botulism requires immediate recognition and treatment with antitoxin. Rapid teaching of health care personnel must occur in cases of unusual diseases. This includes teaching of nurses and ancillary personnel. Even small outbreaks, such as this one, can overwhelm hospital resources. ED physicians should familiarize themselves with whom to contact and where a supply of botulinum antitoxin is stored in order to expedite its administration.

189. A RARE COMPLICATION OF SNAKE BITE—ACUTE PANCREATITIS

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Objective: The only venom known to produce pancreatitis is from the scorpions Tityus trinitatis and Tityus serrulatus, found in South America. Case report: An old Chinese man had no previous history of abdominal or other diseases. Following a bite to the left lower leg from the Vipera russelli formosensis he developed nausea, epigastric pain, and drowsiness. Ecchymosis and bloody vesicles developed over the left leg initially and, at that time, he also had a coagulopathy (Active Partial Thromboplatin Time >120 sec). The epigastric pain persisted but no rebounding pain was noted. High levels of amylase and lipase were also noted (amylase: 320 IU/L, lipase: 291 IU/L). Abdominal CT scan revealed pancreatitis with hemoperitoneum. Rhabdomyolysis, acute renal failure and upper GI bleeding ensued. After the use of 4 vials of antivenom for Russell's viper, the coagulopathy improved within 24 h, but the acute renal failure and epigastric pain persisted. Serum lipase level rose to 1150 IU/L on the third day. However, after no oral alimentation for 3 days, the epigastric pain also improved by the fourth day. Serum amylase and lipase eventually returned to normal. By discharge, there was no recurrence of abdominal pain or further biochemical evidence of pancreatitis. Conclusion: The mainstay for treatment for poisonous bites is IV administration of the appropriate antivenom to neutralize the effects of

the venom. Vipera russelli formosensis antivenom is capable of preventing hemorrhage. However, the antivenom of Vipera russelli did not alter the course of severe pancreatitis. To the best of our knowledge, this is the first case report of pancreatitis following a snake bite treated with antivenom.

190. SEVERE BONE MARROW DEPRESSION INDUCED BY AN ANTI-CANCER HERB "CANTHARANTHUS ROSEUS"

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Introduction: The beneficial properties of *Cantharanthus roseus*, a species of myrtle, have been described in medicinal folklore in various part of the world. It contains indole alkaloids, especially vinblastine and vincristine. These alkaloids are cell-cycle specific agents and block cells in mitosis. Although the potential for poisoning exists, actual accidental human poisonings have not been reported. Case report: We report a 67-year-old woman with hepatitis C related liver cirrhosis and hepatoma who developed severe bone marrow depression after taking Cantharanthus roseus as an alternative anticancer treatment. She presented with nausea, vomiting, diarrhea, oral ulcer and marked weakness about one week after taking 5-day course of Cantharanthus roseus. Bone marrow smear and biopsy showed severe hypoplastic, near aplastic bone marrow, with only a few lymphocytes, plasma cells and degenerative megakaryocyte. The effect on the hematopoietic cells was impressive. Before herb therapy, her leucocyte cell count was 6,400/cumm, platelet count was 105,000/cumm and hemoglobin was 11.0 g/dL, respectively. Eight days after beginning the herb, her leucocyte cell count dropped to 100/cumm, platelet count 24,000/cumm and hemoglobin 8.8 g/dL, respectively. During hospitalization, she was also noted to have pancytopenia, severe gastrointestinal disturbances, bacteremia, urinary tract infection, and impaired renal and liver function. She received intensive care with broad-spectrum antibiotics, granulocyte colony-stimulating factor (filgrastim) injection, repeated blood transfusions and albumin supplement. She recovered gradually and was discharged after 48 days hospitalization. Conclusions: Cantharanthus roseus, a famous anticancer herb, is potentially toxic to the bone. The active ingredients, vinblastine and vincristine, are well known clinical agents for treatment of several cancers, but not hepatoma. Misuse of anti-cancer herb without clinical guidance is dangerous.

191. AN OVERVIEW OF PLANT AND FUNGAL POISONINGS IN THE UK, AND SOME INTERESTING CASES

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Objective: To determine which plants and fungi are actually involved in poisoning cases, and the clinical effects that they cause, if any. Methods: Specific questionnaires were faxed to treatment centers reporting plant and fungal poisoning cases to the National Poisons Information Service between February 1996 and December 1999. The questionnaire asked what the plant or fungus had been identified as and what method of identification had been used. It requested the treatment centers to send any plant or fungal material, and the completed questionnaire, to the Royal Botanic Gardens, Kew. The NPIS was informed when plant or fungal material was received and a follow-up questionnaire was then sent to the treatment centre to obtain further case details. The plant or fungus was accurately identified by a botanist or mycologist at Kew. The questionnaire answers, verified identification, and case details were entered into a bespoke database. Results: 453 plant and fungal specimens were received by Kew, relating to 425 cases. Only 5 specimens could not be identified to genus or species. The three most commonly ingested plant genera were *Solanum*, *Arum* and *Cotoneaster*. Kew received only two specimens of *Atropa belladonna*, but it was named in 13 cases. At the treatment centres 46% of plant specimens were identified correctly, 26% of identifications were incorrect, and 28% of plants were not identified. For fungi, only 12% of identifications were correct, 31% were incorrect and 57% of fungi were not identified. *Panaeolina foenisecii* was by far the most commonly eaten fungus, with *Marasmius oreades* and various *Agaricus* species the next most common. By comparison, *Psilocybe semilanceata* was the name most frequently given

by the treatment centres. The 425 cases for which material was received involved 458 individual patients. Follow-up was obtained for 295 (64%) patients. Clinical effects were reported for 139 (30%) patients, the most common being vomiting (47 cases), nausea (29), buccal irritation (22), abdominal pain (20), tachycardia (17), swelling (13) and diarrhea (12). Conclusions: In many previous reports some question remains over the true identity of the plant material involved. In this series we are confident that this doubt has been removed. Treatment centres were better at identifying plants than fungi. There was a tendency for misidentifications to assume a species of greater toxicity than that actually involved. Several interesting cases emerged involving various potentially toxic plants and fungi including: *Atropa belladonna*, *Delphinium* sp., *Euphorbia* spp., *Aconitum napellus*, *Lepista* spp., *Solanum nigrum* and *Oenanthe crocata*.

192. COAGULATION DYSFUNCTION IN VIPERA ASPIS ENVENOMATION: DO WE NEED MORE DATA TO ENCOURAGE ANTIVENOM TREATMENT?

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Objective: To discuss the reluctance of some emergency physicians to administer antivenom when coagulation dysfunction occurs in vipera aspis envenomation. To report about two cases of *Vipera aspis* envenomation managed by emergency physicians without the Poison Center's advice. Background: In the management of venomous snake bites, coagulation disturbances are widely accepted as a definitive indication to antivenom administration. Nevertheless, these may range from moderate alterations with no symptoms to severe ones with life-threatening manifestations (cerebral hemorrhage). In addition, purified Fab antivenom is not always available and the risk of allergic reactions to equine antivenom could strongly influence the therapeutic strategy. Case reports: First case: a 73-year-old man was admitted to the ED 2 hours after a vipera bite complaining only of nausea and visual disturbances. After 4 hours abdominal pain, vomiting, local signs of envenomation and hypotension occurred. Laboratory assessment revealed a D-dimer value of 912 ng/ml. Treatment with equine Viper Antivenom Serum was initiated. The patient was hospitalized in a General Medicine Department for 3 days. The coagulation profile showed alterations (D-dimer 5832 ng/ml; INR 1.11; PT 80.8%) that improved on the third day. The patient was discharged in good condition. Second case: a 63-year-old was admitted to ED for suspected snake bite. Her right leg showed only one fang mark; no other signs and symptoms were present. Five hours later the patient became disorientated, agitated, dyspnoeic. Local signs of envenomation appeared. Disseminated Intravascular Coagulation (DIC) occurred with severe fibrinolysis (D-dimer 19500 ng/ml, platelets 8000/mm^3). Rectal haemorrhage, haematuria, hypotension and somnolence were also present. The treatment included plasma transfusions and antibiotics. After 3 days the patient improved and moved to a Medicine Department in good condition apart from palpebral ptosis and visual disturbances that lasted one week. Conclusions: The first patient was given Antivenom serum 4 hours after a Viper bite because of coagulation disturbances. The clinical course was rapid with hospital discharge in 3 days. The second patient was not given Antivenom serum despite a severe clinical course. The envenomation syndrome required Intensive Care treatment with hospital discharge after 9 days. When coagulation disturbances appear after a vipera bite, anti-venom treatment should be initiated, especially if other systemic signs and symptoms are present. Although the equine antivenom serum carries a risk of rare serious adverse effects as anaphylactic shock, it provides reduction of mortality, morbidity and hospitalization time. The availability of specific Viper FAB Fragments reduces the risk of allergic reactions and encourages emergency physicians to establish antivenom therapy. References: 1. Bogdan GM, Dart RC. Recurrence of coagulopathy following north American pit Viper envenomation. *Toxicon* 1998;**36**:1260. 2. Persson H. Envenoming by European vipers antivenom treatment—influence on morbidity. *Przegl Lek* 2001;**58**:223–5. Review. 3. Obianim F, Belotte F. [Management of a viper bite]. *Soins* 2001 Nov; (660):55–6.

193. A FATAL CASE OF MONKSHOOD POISONING

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Background: Monkshood is a member of the buttercup family, and while it is rare in the wild, there are many cultivated forms and it is often used in herbal and homeopathic medicine. It was cultivated in the Middle Ages as a liniment, potent

painkiller and hunters' poison. Monkshood is sometimes referred to as the most poisonous plant in Europe with the main toxins being diterpene alkaloids. There is no specific antidote. Many cases of poisoning have been reported, either through intentional ingestion, or accidental poisoning where the roots of the plant have been eaten in mistake for horseradish. A fatal case has also been reported in a 20-month-old child who ingested the flowers from a garden and another case report details a botanist who suffered tingling and palpitations after dissecting Monkshood. Case report: A 20-year-old male was admitted to hospital following an intentional ingestion of Monkshood (Aconitum napellus). After suffering abdominal pain and vomiting at home, an ambulance was called. Although fully conscious when paramedics arrived, his level of consciousness decreased en-route to the hospital, with a Glasgow Coma Scale of 12 on arrival. The patient suffered a cardiac arrest shortly after arrival and despite nearly an hour of resuscitation, he could not be revived and was declared dead approximately 1–5 h after the ambulance was called. The NPIS (Cardiff Centre) was contacted initially for information on treatment of the patient. Subsequent enquiries to the Poisons Centre included requests for advice on potential effects to the ambulance crew who were contaminated with vomit, effects on staff that treated the patient in hospital, and on what protective equipment was required by police when removing remaining plant material from the patients home. These enquiries were relevant as Monkshood may cause toxicity via skin contact. Later the same evening, the hospital admitted four family members for observation as a precaution. Neither these, nor the ambulance staff developed any symptoms. The following evening the hospital enquired if it were possible for a relative to view the body and have a lock of his hair to keep. Subsequent reports indicated that a family member was a homeopath who grew Monkshood at home for medical purposes. Information on the uses and toxicity of Monkshood was available and the patient was thought to be aware that it was potentially highly toxic. He had made and eaten soup out of plant material, the remains of which were found by the police following his death. Post-mortem results were revealed acutely congested lungs, consistent with aconite poisoning.

194. INCIDENCE OF MAGIC MUSHROOM POISONING IN SOUTH WALES

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Objective: To analyze the epidemiology of psilocybin (magic mushroom) poisoning in Wales and the South West of England between 1997 and 2001 as reported to the NPIS (Cardiff Centre). Methods: Computer records were reviewed and analyzed retrospectively to evaluate the annual patterns of exposure. Data analyzed was for patient age, sex, intent (i.e., accidental or deliberate), and clinical symptoms. Results: There were a total of 223 calls about 'magic mushrooms' made to the NPIS (Cardiff) in the 5 years studied. This is less than 1% of the total calls received during that period. However it accounts for 47% of the total number of calls involving fungi. The total number of calls concerning magic mushrooms dropped significantly from 70 in 1997 to 39 in 1998 and has remained static around 40 per year since then. The autumn months of September (67), October (87), and November (15) involved the greatest number of calls. This correlates with the known growing season. Of the total number of psilocybin enquiries, 166 cases (74%) were as a result of deliberate ingestion (abuse/drug dependence, intentional, intentional abuse and intentional suicide). The mean age of these groups was 17.9 years. There were 34 cases (15%) of accidental exposure (one of these involving ingestion by a dog). The mean age in this group of accidental exposures was 10.7 years, with a range of one to 25 years. A total of 15 cases (7%) were about accidental misuse and in 8 cases the circumstance was recorded as either not applicable or unknown. Analysis of cases involving magic mushrooms alone, showed dilated pupils and hallucinations to be the commonest effects although many also experienced nausea, vomiting, hyperventilation, sweating and tachycardia, while a few patients displayed aggression. All patients were believed to have survived the acute phase of poisoning regardless of the quantity ingested, however it should be noted that very few cases were actively followed up. Conclusion: Ingestion of magic mushrooms is uncommon in Wales and the South West of England and severe poisoning is rare.

195. TREATMENT OF MODERATE TO SEVERE PARAQUAT POISONING WITH DEXAMETHASONE/CYCLOPHOSPHAMIDE COMBINATION: A CASE SERIES FROM THE TOXICOLOGY CONSULTATION SERVICE AT SIRIRAJ HOSPITAL, BANGKOK, THAILAND

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Table 1. Description of cases of paraquat poisoning consulted to the Toxicology service.

Patient	Age (years)	Amount of ingestion (gram)	Onset of treatment (hours)	Renal failure	Hepatitis	Pulmonary toxicity	Survival at one month follow up
1	21	5	48	Yes	Yes	No	Yes
2	2	0.7	120	No	No	No	Yes
3	28	5	36	Yes	Yes	No	Yes
4	29	10	30	Yes	Yes	No	Yes

Objective: Description of four patients who survive moderate to severe paraquat poisonings with the combination of cyclophosphamide/dexamethasone regimen. Methods: There were 4 patients consulted to the Toxicology service at Siriraj Hospital, Bangkok, Thailand with the history of significant paraquat poisoning. Severity of poisoning was judged by the history of ingestion of 1 gram total or 20 mg/kg. All 4 patients received treatments with a 14-day-regimen consisting of: 1. Enteral administration a single dose of 150 g. of 15% Fuller's earth solution. 2. Cyclophosphamide 5 mg/kg/day divided to every 8 hours administered intravenously. 3. Dexamethasone 10 mg or 0.2 mg/kg IV every 8 hours. 4. Vitamin C (500 mg/amp) 6 gm/day IV. All patients were monitored for the occurrence of renal failure, hepatitis, and pulmonary fibrosis in the hospital until the end of the treatment, then re-examined one month after discharge from the hospital. Results: From November 2001 to October 2002, there have been 4 cases (Table 1) of significant paraquat poisoning presented to Siriraj Hospital. All of the patients presented later than 24 hours after the ingestion. All of the patients, except for the 2-year-old child, developed acute renal failure and mild hepatitis. No pulmonary toxicity were observed in this group and all patients survived the poisoning. Conclusion: From previous reports, moderate to severe paraquat poisonings were associated with a mortality rate of approximately 57% and the main cause of death was pulmonary toxicity. The use of immunosuppressive agents known for its ability to treat inflammatory lung disease such as cyclophosphamide and dexamethasone presents a viable alternative to an otherwise serious and untreatable poisoning. References: 1. Addo E, Poon-King T. Leucocyte suppression in treatment of 72 patients with paraquat poisoning. *Lancet* 1986;**1**:1117–20. 2. Lin JL et al. A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat-poisoned patients. *Am J Respir Crit Care Med* 1999;**159**:357–60.

196. AUDITORY NEUROTOXICITY AFTER MSMA (MONOSODIUM METHANARSENATE) HIGH-DOSE ORAL INTAKE

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Objective: Organic arsenic compounds have been considered of low toxicity compared to inorganic arsenic compounds such as pentavalent and trivalent salts. A recent literature review shows a remarkable lack of toxicological studies or clinical cases of organic arsenic compound intoxication. We report a case of MSMA (monosodium methanarsenate) intoxication leading to severe auditory neurological sequel. Case report: A 36-year-old, previously healthy male, was seen at ED 2 hours after having ingested, in a suicide attempt, around 250 mL of a MSMA 480 g/L preparation, commercialized as an herbicide. Before presenting to the ED, the patient had been submitted to a gastric lavage with 2 L of 0.9% saline. He was awake, oriented, drowsy, blood pressure 120/70 mm Hg, in sinus rhythm, and had vomited four times during the first hour of observation. Oral LD50 of MSMA for rats is 1105 mg/kg. The dose ingested by the patient, empirically calculated, surpassed by 600 mg/kg the oral LD50 for rats (he supposedly ingested around 1714 mg/kg). Urine was tested for arsenic, using the Reinsch redox reaction test, with a strong positive reaction in 10 minutes. AAS-HG analysis of the same sample, performed afterward, showed a concentration of 96,600 μg/L (a total of 263,000 μg of arsenic in 24 h). When the Reinsch test result was known, chelation therapy with dimercaprol was started, with 800 mg IM every 4 h during the first 2 days, followed by 800 mg every 6 hours for 1 day, and 400 mg every 6 hours thereafter, completing 28 uninterrupted days of chelation. No signs of hypovolemic shock, renal or hepatic failure were seen during treatment. After 5 days of treatment, the patient started complaining of rapid and progressive deafness. Audiometric test

then showed a bilateral neurosensorial pattern of deafness with symmetrically losses of 110 to 120 dB in both ears, compromising conductive and bone conduction, affecting all tested frequencies. Brainstem auditory evoked potentials (BERA test) were totally absent bilaterally, after maximum stimulation (105 dB NA), confirming severe cochlear lesion of both ears, compatible with arsenic neurotoxicity (although a possible adverse effect of dimercaprol). Conclusion: Despite the classification of MSMA as a substance of low toxicity due to its high oral LD50, herbicides preparations are marketed in very high concentrations, increasing the risk of clinical intoxication and neurologic sequelae, by inadvertent or voluntary ingestion of relatively small amounts, demonstrating the need for more restrictive regulation of these commercial formulations.

197. SPANISH POISON CONTROL CENTRE SURVEY OF HERBICIDE OCCUPATIONAL EXPOSURES

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Objective: Farming is the occupational activity in which work-related exposures to chemicals occur most frequently according to the Spanish Poison Control Centre (SPCC) data. Herbicides accounted for 23% of agricultural exposures second only to insecticides. The objective of this work is to analyze the epidemiology of herbicide exposures in the occupational environment. Methods: Descriptive analysis of SPCC data of occupational exposures to herbicides between 1991 and 2002. Results: The SPCC recorded 711 consults due to occupational exposures to herbicides. This represented 47.1% of all herbicide poisonings. Other exposures were household accidents (22.7%), suicidal attempts (15.9%) and accidents such as food contamination (14.3%). All occupational exposures were acute except four cases of chronic poisoning. There was a predominance of males (male:female ratio 22:1). Mean age of the patients: 43 years (range 15–84 years). Herbicide was the only product involved in 86.6% of occasions. The main groups of active ingredients were: glyphosate 34%; bipyridyliums 29.1%; chlorophenoxyacid derivates 9%, triazines (simazine, atrazine, terbutryn, etc.) 7%; amide-acetanilides (pendimethalin, alachlor, propachlor) 6%; substituted ureas (diuron, linuron, etc.) 4.5%. During the 12-year period there were an increasing number of glyphosate poisoning and a progressive decline of paraquat exposures (the latter increased again in 2002). Most cases occurred in the area of the Mediterranean, the region with more intensive agriculture and green-houses. Forty-nine percent of the exposures were by inhalation, 21% dermal contact, 13% inhalation and dermal, 4% by eye contact and the rest involved other or several routes of exposure. There were three fatalities during the study period: acute pulmonary edema by inhalation of ethofumesate, aplastic anemia by chronic respiratory exposure with dichlorophenoxy acetic compounds and multiorganic failure after ingestion of paraquat. Conclusions: Modern techniques in agriculture in Spain account for the high possibility of occupational

Table 1. Clinical features in the main routes of exposure (data in %).

		Glyphosate	Bipyridyliums	Chlorinated phenoxyacids	Others	Total
Dermal exposure (n = 138)	*Asymptomatic*	7.9	9.5	0	5.9	23.3%
	Erythema	16.1	13.9	0	3.7	33.7%
	2–3 grade burns	0.7	18.2	0	0	18.9%
	Mild systemic	6.6	6.6	4.4	4.4	22%
	Severe systemic	0	1.4	0.7	0	2.1%
	Total	31.3%	49.6%	5.1%	14%	100%
Respiratory exposure (n = 280)	*Asymptomatic*	4.7	2.6	1.3	4.7	13.3
	Upper airways	4.4	3.3	0.4	0.7	8.8
	Lower airways	5.9	5.6	0.7	2	14.2
	CNS	10.7	5.6	3.3	9.3	28.9
	Digestive	6.9	1.5	1.9	4.9	15.2
	Other	8.3	3.3	2.3	5.7	19.6
	Total	40.9%	21.9%	9.9%	27.3%	100%

exposure to chemicals. Preventative efforts need to focus on protection measures at a job that can result in severe intoxication, especially in countries with a vast horticultural and farming activity.

198. PATTERN OF ACUTE PESTICIDE POISONINGS IN TAIWAN

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Objective: Although pesticide poisoning is fairly common in Taiwan, there are limited data regarding its pattern of exposures and clinical outcomes. To better understand the pattern of acute pesticide poisonings and the demographic characteristics that may be associated with poisoning-related fatality, we conducted a retrospective analysis of all pesticide poisonings reported to a poison control center. Methods: All telephone inquiries concerning pesticide exposures from July 1985 through December 2001 were identified from the database of the Poison Control Center located at the VGH-Taipei. After excluding 34 non-human exposures and 1,764 inquiries with non-toxic or chronic exposures, and general inadequate information, 11,269 patients remained. The computerized records of these patients, including their age; gender; time, intent, route and substance of exposure; presence of concurrently exposed toxins; clinical severity; and use of antidotes were included in the analysis. Pattern of poisonings was presented by descriptive statistics, while logistical regression models were used to evaluate the potential predictors of poisoning-related death. Results: During the study period, male (63.9%) outnumbered female patients (36.1%) in pesticide poisonings, and most poisonings occurred among adults (43.3 ± 18.9 years). Most exposures involved a suicide attempt (7,511 patients, 66.7%), an oral exposure (8,930 patients, 79.2%) and an insecticide (5,217 patients, 46.3%). Herbicides (3,833 patients, 34.0%), fungicides (765 patients, 6.8%) and pesticides other than the above noted pesticides (1,454 patients, 12.9%) were responsible for the remaining exposures. There were a total of 1,638 fatalities (14.5%). Many pesticides, especially paraquat (825 patients), and organophosphates (344 patients) were associated with a high mortality rate. Using patients with pyrethrin and pyrethroid poisoning as the reference and adjusting for other demographic variables, the highest risk of death was found among patients with paraquat poisoning (OR 101.7, 95% CI 71.7, 144.2), followed by various insecticide exposures (OR 19.7 for mixed insecticides, 95% CI 12.1, 32.2; OR 7.0 for organophosphates, 95% CI 5.0, 9.9; OR 6.7 for carbamates, 95% CI 4.4, 10.2). Increased age, suicide attempt, exposure via routes other than skin or respiratory tract, concurrent exposure with other pesticides, and exposure at earlier calendar time were also associated with a higher risk of fatality. Conclusion: Pesticide poisoning remains a serious problem in Taiwan. Although the mortality rate has somewhat decreased over the last decade, pesticide poisoning is still associated with many fatalities, especially among patients who attempted suicide and patients with paraquat exposures. More efforts, such as legislative control of the availability of pesticides and further innovation in therapeutic measures, are required to reduce the serious impacts of pesticide poisonings.

199. UNCOMMON PRESENTATION OF HEMOLYTIC ANEMIA IN PARAQUAT INTOXICATION. TWO CASE REPORTS

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Objectives: Paraquat is the most toxic dipyridilium herbicide and has caused numerous human fatalities. Poisoning with paraquat can induce serious damage to many organs, especially the lungs, the kidneys, or the liver, and is associated with a high mortality rate. We present two cases with severe paraquat intoxication, and observe the severe jaundice and uncommon hemolytic anemia after gastrointestinal symptoms, respiratory distress and oliguric renal failure. Case report: The first patient was a 27-year-old male, who intentionally drank about 50 mL of 24% paraquat mixed with the same amount of wine and was transferred to our ER for management several hours after ingestion. Severe vomiting and diarrhea, and rapid renal function deterioration were present. Uncommonly, jaundice and pallor face were observed on Admission Day 4. Hemolytic anemia was found. Glucose-6-phosphate dehydrogenase (G6PD) deficiency was identified unexpectedly. The second case was another 27-year-old male heroin abuser, who injected about 5 mL of 24% paraquat intravenously in a suicide attempt and was brought to our ER about 5 h after exposure. Rapid renal function deterioration

and acute pancreatitis were present. Progressive jaundice, pale conjunctivae and shortness of breath occurred since Admission Day 3. Hemolytic anemia was also observed and blood transfusion with packed red blood cell was performed. Conclusion: It is well known that paraquat produces circulatory failure, with multisystem organ failure and respiratory failure. The mechanism of paraquat toxicity has been attributed to the production of superoxide, resulting from redox cycling of paraquat in microsomes. In addition, paraquat could cause hemolysis in individuals deficient in G6PD because it poses an oxidant threat to red blood cells.

200. DELAYED ONSET OF TOXICITY WITH UNKNOWN PESTICIDE INGESTION

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Objective: Ingestions of unknown toxins in children can be problematic if there is a potential for delayed toxicity. Pesticides are often kept in unlabeled bottles, and the contents are unknown. Case reports: (Case 1). An 18-month-old girl was brought to the hospital one evening after ingesting an unknown pesticide that was stored in a window washing solution bottle. The product had been given to her family in an unlabeled bottle by an exterminator's employee to be used as a roach killer. She was asymptomatic, physical examination was normal, and she was admitted to the hospital for overnight observation. The next morning she was playful and examination was normal. She ate lunch and was ready for discharge when drooling developed. Examination was positive for motor weakness. She was transferred to a referral hospital PICU where pinpoint pupils, drooling, and motor weakness were noted. She was unable to hold her head up. Treatment with atropine and pralidoxime were administered, and all symptoms resolved. Plasma cholinesterease was 0.1 U/mL (normal range 17 to 25 U/mL). Red blood cell cholinesterase was 2.3 U/mL (normal range 5.7 to 9.0 U/mL). (Case 2). A 2-year-old boy presented after drinking bug spray the night before from an unlabeled container. Although the ingestion was not witnessed, the product was seen on his clothes and face. He was asymptomatic throughout the evening and slept throughout the night. The next morning he woke with tremors and not acting like himself. In the emergency department, physical examination revealed a heart rate of 160/minute, 3 mm reactive pupils, dry mouth, clear chest, with tremors and jerking movements of the extremities. When the toxicologist arrived, pupils were pinpoint. After intravenous hydration, salivation and drooling were noted. There were generalized tremors but oxygen saturation remained 98%. Muscle strength was judged normal. He was admitted to the PICU and treated with atropine and pralidoxime. Symptoms resolved, and he was discharged on the third day of hospitalization. Plasma cholinesterase was 0.1 Units (normal 17 to 25 U/mL). Conclusion: The first child was asymptomatic for 18 h after ingesting an insecticide from an unlabeled container before developing signs of cholinesterase inhibition. Treatment with atropine and pralidoxime was successful, and laboratory confirmation of cholinesterase inhibition was obtained. In the second case, signs typical of organochlorine insecticide ingestion were observed at 12 h, and then signs and symptoms of cholinesterase inhibition developed at about 18 h, with laboratory confirmation. A mixed ingestion was possible. These two cases suggest prolonged observation may be prudent after unknown pesticide ingestions.

201. TELEPHONE SURVEY OF ACUTE PESTICIDE POISONINGS LEADING TO A CALL TO THE FINNISH POISON INFORMATION CENTRE

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Objective: The aim of the study was to get more specific information on acute pesticide poisonings in Finland and to characterize the circumstances leading to an acute pesticide exposure. Methods: All calls related to a true or suspected human acute pesticide poisoning to the FPIC between 15.5.–31.7.2002 were eligible for the study. At the end of the call the caller was informed about the study and asked to participate. Information recorded from the call and contact details of the subject were sent to the Kuopio Regional Institute of Occupational Heath performing the survey. The subjects were contacted by telephone within one week of the original call and a structured interview was made by one physician. Results: FPIC received 252 calls concerning pesticide poisoning during the study period. In 123 cases no interview could be made due to missing consent (either refusal or failure of the FPIC to ask). 26 cases were excluded (interview not possible, no pesticide exposure etc.). One hundred and one exposures were included in the study. Children were involved

in 54 cases. Most commonly a child sprayed an insect repellent on the skin, in the eyes or the mouth or tasted an ant bite. 11 Children had mild or moderate symptoms and only in 2 the symptoms were considered to be related to the pesticide exposure. None of those children who tasted an ant bite had any symptoms. Adults had 33 non-occupational exposures, most commonly with herbicides and insecticides splashed on in the eyes or on the skin or clothes. Clinical symptoms were reported by 22 of adults exposed. Over 50% of adults with symptoms visited a physician, but none had symptoms considered related to the pesticide. 14 adult exposures were occupational, most commonly skin exposures, 13 had symptoms, and 3 of them had symptoms considered related to the pesticide exposure. In adult accidental exposures, instructions on protective clothing were not always followed. In over 50% of non-occupational and in 36% of occupational exposures protective clothing was not used at all. Conclusions: Pesticide exposures of children and adult non-occupational exposures were mild or moderate. In occupational exposures symptoms were more severe. Education on correct pesticide storage and working practices both to the public and the workers has to be continued.

202. ACUTE ORGANOPHOSPHORUS AND CARBAMATE INSECTICIDE POISONING IN SWITZERLAND

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Objectives: Poisoning with insecticides containing organophosphorus (OP) and carbamate (CB) cholinesterase inhibitors has not recently been analyzed in Switzerland. The aim of our study was to investigate human OP and CB poisoning with regard to severity, symptoms, products and active ingredients, in order to identify particularly hazardous products. Methods: We retrospectively analyzed all calls to the STIC dealing with exposures to OP or CB insecticides between 1966 and 2001. The products were identified using the poison center and the Swiss Federal Office of Public Health product register databases. For analysis of severe and fatal cases only monointoxications with medical followup reports containing sufficient information were included. For severity grading the Poisoning Severity Score was used, and causality was assessed according to a standardized protocol. For symptom comparison a matched random sample of four mild cases was drawn for each severe or fatal case. Results: In 35 years 6076 symptomatic human and veterinary exposures were recorded. Until 1985, the proportion of OP and CB exposures increased from 1.0% to 1.8% of total reported exposures and then gradually decreased to $<1.0\%$ since 1999. OP were most frequently involved ($n = 4601$), CB and combinations of the two less frequently ($n = 724$ and 751 resp.). Of the 5152 human cases, 5086 showed no severe symptoms, 40 had severe symptoms, and 26 a fatal outcome. 430 products were involved containing 61 different active ingredients. The proportion of severe or fatal poisoning was 2% for diazinon (total $n = 1391$), dimethoate ($n = 165$), malathion ($n = 128$), dichlorvos/propoxur ($n = 96$), whereas it was 5% for carbosulfan (5%, $n = 43$), fonofos (17%, $n = 30$), thionazin (10%, $n = 31$), mevinphos (5%, $n = 197$), and parathion (14%, $n = 118$). 71% of the severe or fatal cases occurred with liquid products although only 36% of all products are liquid. Circumstances and symptoms of the reported cases are listed in the table below:

	Oral route	Circumstances			Symptoms					
		Suicide	Occupational	Accidental	Cholinergic	Respiratory	Cardiovasc.	Neurologic	Muscular	Gastrointest.
Mild/ moderate ($n = 264$)	38%	10%	19%	61%	39%	14%	10%	34%	9%	63%
Severe/ fatal ($n = 66$)	89%	73%	6%	17%	83%	65%	65%	83%	45%	63%

Conclusions: Approximately 1% of toxic exposures reported to our poison centre are related to OP/CB insecticides, 1% of which have a severe or fatal outcome. Liquid products account for the majority of severe and fatal cases, most of which are suicidal with oral route of exposure. Substances in WHO Class Ia and Ib show a higher proportion of severe and fatal cases than those in Class II and III. *Supported by the Swiss Federal Office of Public Health*

203. POISONING BY AN ILLEGALLY IMPORTED CHINESE RODENTICIDE CONTAINING TETRAMETHYLENEDISULFOTETRAMINE

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Objective: To describe a case and subsequent laboratory investigation of an unintentional pediatric exposure to an imported Chinese rodenticide that contains tetramethylenedisulfotetramine. Case report: A previously healthy 15-month-old girl was found by her parents playing with a white rodenticide powder they had brought from China. Fifteen minutes later, the child developed generalized seizures and was brought to an Emergency Department (ED). Her initial fingerstick blood glucose was 108 mg/dL. The child was intubated for status epilepticus in the ED. Despite aggressive therapy with lorazepam, phenobarbital and pyridoxine, she had 4 h of intermittent generalized seizure activity. She was finally extubated on the third hospital day, but appeared to have absence seizures and cortical blindness. Continuous electroencephalogram monitoring, performed weeks later, revealed severe diffuse cerebral dysfunction with multiple epileptogenic foci. The child remains developmentally delayed and is on valproic acid therapy for seizure control. Translation of the Chinese package labeling did not clarify its contents. Initial investigation via the Internet of the manufacturer suggested that the ingredients could be: sodium monofluoroacetate, fluoroacetamide, tetramine, and strychnine. After acquiring two similar rodenticide baits from the family, laboratory investigations were negative for: sodium monofluoroacetate, fluoroacetamide, bromethalin, strychnine, 1,3-difluoro-2-propanol and carbamate insecticides. Tetramine is not the name of a specific compound but rather a general chemical name for a group of compounds that are derived from hexamethylenetetramine. This complicated the laboratory investigation until "tetramine" was implicated in a tragic intentional mass food poisoning in China, in which a rodenticide called Dushuqiang was responsible for 42 deaths. This refocused our investigation and tetramethylenedisulfotetramine was finally confirmed by gas chromatography-mass spectrometry in this rodenticide product. The rodenticide baits were then quantified against a tetramethylenedisulfotetramine standard that was synthesized in our laboratory. The tetramethylenedisulfotetramine concentration was 6.4% w/w in one rodenticide packet and 13.8% w/w in the other. Tetramethylenedisulfotetramine is grouped with other "cage convulsants," such as picrotoxin, since they have a similar intercalating cyclical molecular structure and cause seizures through noncompetitive GABA antagonism. The oral LD50 in humans is estimated to be as low as 100 μg/kg. Conclusion: Tetramethylenedisulfotetramine is an extremely potent poison. Our patient has severe diffuse cerebral dysfunction likely secondary to prolonged seizure activity after exposure to tetramethylenedisulfotetramine.

204. FIVE YEARS TOXICOVIGILANCE OF ACUTE POISONINGS BY AGRICULTURAL PESTICIDES IN ITALY

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Objective: Milan PCC receives annually approximately 64% of the total requests for toxicological advice reported to the National Health Institute from all the active PCC in Italy; the evaluation of data regarding pesticide poisonings is one of the most important toxicovigilance parts of our activities. Methods: In the years 1996–2000 the PCC in Milan received a total of 254,199 calls, for 14,707 of which advice relating to pesticides (approximately 5.78% of the total) was provided. When the uses of the pesticides involved was examined, 8387 cases (57.25%) were related to domestic or civil use, while 6320 cases (42.75%) were to agriculture (agricultural pesticides or AP), to protect plants from parasites and infestants. Results: Among calls related to AP, 5,285 calls (83.62%) were for suspected acute poisoning, while 1,035 (16.38%) were for general information only. In the group of suspected poisonings 4,856 (93.30%) were human cases, while only 349 cases (6.70%) were related animals. Calls related to AP came especially in late spring and early summer. The frequency of AP poisoning was greater among males (3669 cases, 75.55%) which parallels the composition of the agricultural working population in Italy. The highest risk (3372 cases, 69.45%) was for adults between 20 and 69 years, corresponding to the active age for agricultural workers. However we noted 538 (11.07%) cases of suspected poisoning in children between 0–4 years. This finding suggests that in agricultural areas, improper methods of storage of products used in fields may frequently be observed. In fact, 2463 cases (50.73%) happened in domestic surroundings, while 1994

cases (41.06%) were in the workplace. The main route of intoxication was inhalation (2372 cases, 48.85%), followed by ingestion (1606 cases, 33.07%) and skin exposure (878 cases, 18.08%). 2308 of cases (47.53%) were accidental-generic, and 2002 cases (41.23%) accidental-occupational. Five hundred and twelve cases (10.54%) were attempted suicides and 34 cases (0.70%) resulted from malicious or criminal activity. For cases of professional exposure to AP, only 6% of farmers used personal protective equipment correctly. For every case of suspected poisoning, we evaluated the correlation between route of exposure, the absorbed dose, reported symptomatology, latency of appearance, laboratory findings, and the features of the potential agent involved. Conclusion: Correct information about the risks related to exposure to pesticides is of primary importance in preventing poisoning. The steps necessary to obtain a license for purchase of pesticides is an opportunity to provide users with correct information on AP products.

205. UPDATE IN EPIDEMIOLOGY OF DELIBERATE SELF-POISONING WITH PARACETAMOL

von Mach MA, Stürer A, Lauterbach M, Kaes J, Weilemann LS. *Department of Clinical Toxicology and Poison Center, University of Mainz, Germany.*

Objective: Paracetamol is frequently used in deliberate self-poisoning resulting is a potential risk to patients due to its dose-dependent hepatotoxicity (Vale, 1995; Schiødt, 1997). In the present study cases of intoxication referred to our Poison Center were analyzed to illustrate recent trends. Methods: 38065 cases were registered during the study period from 01.01.1995 to 31.5.2002, of which 4021 had paracetamol intoxication. These were analyzed with respect to the ingested dose, concomitant substances, the degree of observed symptoms and the length of hospitalization. Results: The use of paracetamol in deliberate self-poisoning continuously increased during the study period from 8.9% in the year 1995 to 12.0% in 2001. Paracetamol was mainly used by female patients (ratio female:male = 2.8) and patients in the age group 10 and 29 years (Fig. 1). 88.6% of inquiries occurred within the first 12 h after ingestion (Fig. 2). Concomitant ingestions were most frequently non-steroidal antirheumatics and ethanol (Fig. 3). Paracetamol caused severe intoxication and death less frequently than other poisonings and the degree of symptoms tended to be dose-dependent. In 73.7% of cases the length of hospital stay did not exceed 3 days (Fig. 4). Conclusion: We have shown the increasing importance of paracetamol in deliberate self-poisoning, particularly in female and younger patients. The dose of paracetamol (Turvill, 2000) and the time interval before therapy are crucial determinants of prognosis (Wallace, 2002). With early antidote therapy (Buckley, 1999) hospitalization is usually short. The risk of complications often relates to

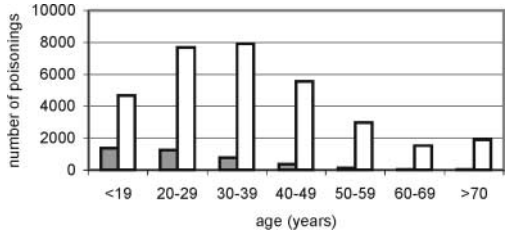

Figure 1. Poisonings with paracetamol (grey) in different age groups as compared to the remaining poisonings (white).

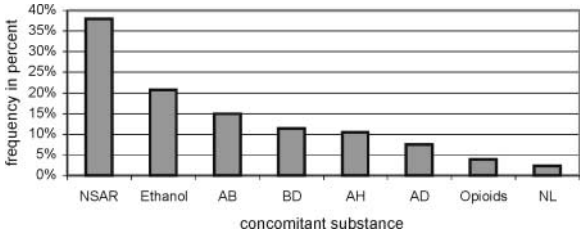

Figure 2. Concomitant substances in paracetamol poisonings (antibiotics-AB, benzodiazepines-BD, antihistaminics-AH, antidepressants-AD, neuroleptics-NL).

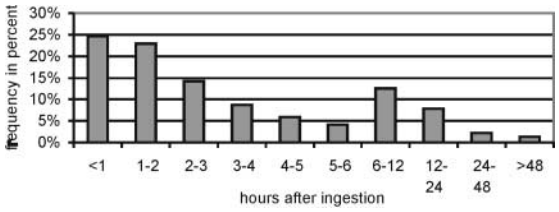

Figure 3. Hours after ingestion prior to contacting the poison center in paracetamol poisonings.

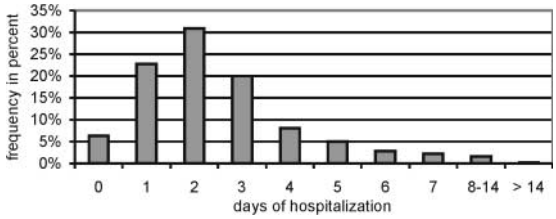

Figure 4. Days of hospitalization after paracetamol poisoning.

concomitant ingestions, making a careful history important. References: Buckley NA, Whyte IM, O'Connell DL et al. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999;**37**:759–767. Schiødt FV, Rochling FA, Casey DL et al. Acetaminophen toxicity in an urban county hospital. *N Engl J Med* 1997;**337**:1112–1117. Turvill JL, Burroughs AK, Moore KP. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. *Lancet* 2000;**355**:2048–2049. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995;**346**:547–552. Wallace CI, Dargan PI, Jones AL. Paracetamol overdose: an evidence based flowchart to guide management. *Emerg Med J* 2002;**19**:202–205.

206. INTOXICATION WITH ANTIDEPRESSANTS REPORTED TO THE SLOVAK TOXICOLOGICAL INFORMATION CENTRE IN THE YEARS 1996–2001

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Objective: Overdoses of antidepressants are potentially very serious and are increasing in frequency. To obtain more information about this problem, we undertook a retrospective study. Methods: We extracted all calls to our center involving data on antidepressant exposure and analyzed information on sex, age, ingested substances, intent of exposure and poisons severity grade. Results: During this 6 year period the Slovak Toxicological Information Centre recieved a total number of 244 calls (11.2% of all cases) concerning antidepressant overdose, with an increasing number each year. Antidepressant exposures in females (64%) were more frequent than those involving males (36%). Suicidal intoxications (63%) were more prevalent than accidental intoxications. The majority of intoxicated patients were adults (63%), most of them were from age group 19–30 years. Children represented 26% of all overdosed patients. The majority of these were teenagers with personal problems. The other large group were children from 0–5 years. Tricyclic antidepressants represented 52% of all cases (78% cases in children) versus 24% SSRIs. The poisonings were graded according to the Poisoning Severity Score. We reported one lethal intoxication caused by the combination of moclobemide, benzodiazepines and alcohol. Severe symptoms such as coma, seizures, severe dysrhythmias and respiratory depression requiring mechanical ventilation occurred in 29% of all exposures. Thirty-seven percent of patients developed no, or only mild, symptoms. Conclusion: Intoxications with antidepressants, especially by TCA are frequently referred to the Slovak TIC. Despite the known severity of TCA overdose, these drugs are still widely prescribed in Slovakia, probably because of their low price.

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207. TOXIC SURVEILLANCE: EXPERIENCE OF COLLABORATION BETWEEN THE POISON CONTROL CENTRE AND THE HEALTH AUTHORITIES

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Objective: One of the principal tasks of a Poison Control Centre (PCC) is the evaluation and control of risks from the exposure to chemical substances. In order to achieve this, good communication with the authorities is essential. The objective of this study is to evaluate our experience within a national toxic surveillance system. Methods: Description of cases of toxic surveillance at three levels of action. Results: Level 1: Direct contact with those responsible for product marketing: Twenty-three cases in adults of confusion of toilet bowl cleaners for toothpaste were detected during the years 2000 and 2001. The measure undertaken was to contact the company. At once the product was voluntary withdrawn and the design of the container was changed. Level 2: Contact with the national health authorities: A) An increasing number of exposures to drain cleaners containing sulphuric acid were detected in 1995–1996 in adults at home; 62% of cases had moderate or severe outcome. The marketing of these products was limited to professionals. B) There was an alarming number of unintentional ingestions of alkaline professional dishwashers from 1995 to 1997 due to a confusion with mineral water (181 patients). In 1999 the companies were obliged by the national authorities to add a dye to the product. Level 3: Regulation at a European level. A) From 1991 to 2000 there were 132 calls of exposure to floor polishers containing hexafluorosilicate. 77.3% were household accidents and the outcome was moderate or severe in 82%, with 7 deaths. The classification of hazard was changed at a European level and the marketing and the concentration of the active ingredient was limited in Spanish household products. B) From March to November 2001 advise was requested about 20 children with neurological symptoms after the ingestion of star anise. The label of the bags did not contain information about doses and indications. Afterwards a contamination of *Illicium verum* with *Illicium anisatum*, a neurotoxic herb species, was confirmed. At a European level, the import of *I. verum* from non-EC countries was regulated, and identification labels were changed inside the Spanish market. Conclusion: PCC can detect sentinel events and hazards. Contacts with the health authorities can result in effective risk control measures. Collaboration with the Ministry of Health through the Surveillance, Inspection and Control of Chemical Products National Network created in 1997 has produced good results.

208. ANTIDEPRESSANTS IN DELIBERATE SELF-POISONING FROM 1995 TO 2001

von Mach MA, Stürer A, Weilemann LS. *Department of Clinical Toxicology and Poison Center, University of Mainz, Germany.*

Objective: Antidepressant drugs are frequently used in deliberate self-poisoning (Whooley, 2000) resulting in a major risk for the patients due to their cardiac and central-nervous toxicity (Winokur, 1992; Montgomery, 1997; Personne, 1997). In the present study the cases of intoxications consulting our Poison Center were analyzed to illustrate recent trends in self-poisoning with antidepressants. Methods: During the study period from 1995 to 2001 35394 inquiries concerning deliberate self-poisoning were registered in our Poison Center. The substance used, age and gender of the patient, as well as the degree of the observed symptoms were documented. Antidepressant drugs were grouped as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and other antidepressants (AD). Results: The use of antidepressants in deliberate self-poisoning increased during the study period from 17.3 to 22.9% of all inquiries, and SSRIs and other antidepressants being observed more frequently than TCAs (Fig. 1). Antidepressant drugs were mainly used by female patients (ratio female:male = 2.4) and in the age group between 35 and 54 years (26.2% of deliberate self-poisonings in this age group). Antidepressant drugs caused severe intoxication and death more frequently than other poisons, with TCA showing a higher rate of complications than SSRI and other antidepressants (Fig. 1). Conclusion: In recent years, antidepressant drugs have been of increasing importance in deliberate self-poisoning, particularly in female and middle-aged patients. Due to the changing prescribing patterns larger numbers of intoxications with non-TCA antidepressants were observed. This may result in a reduced rate of complications following antidepressant poisoning (Glassman, 1998). Nevertheless, more severe symptoms were present in the three groups of antidepressants in comparison to the other drug overdoses, demonstrating the need for hospitalization and monitoring of intoxications with antidepressants. References: Glassman AH. Cardiovascular effects of antidepressant drugs: updated.

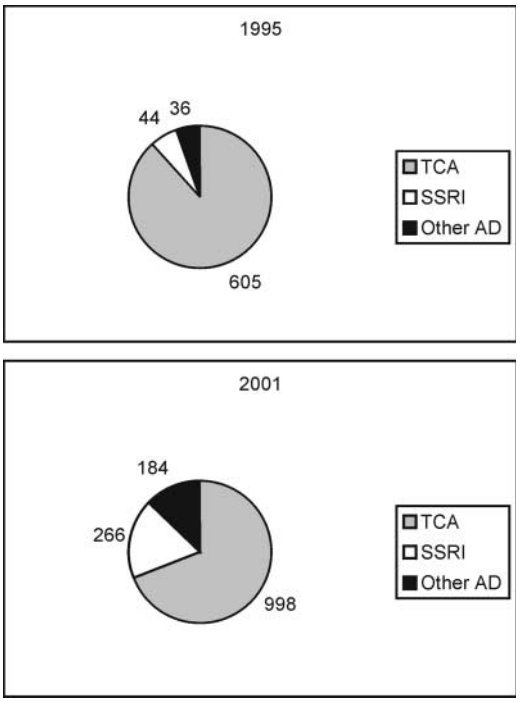

Figure 1. Changing patterns of deliberate self-poisoning with antidepressants 1995 and 2001—tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and other antidepressants (AD).

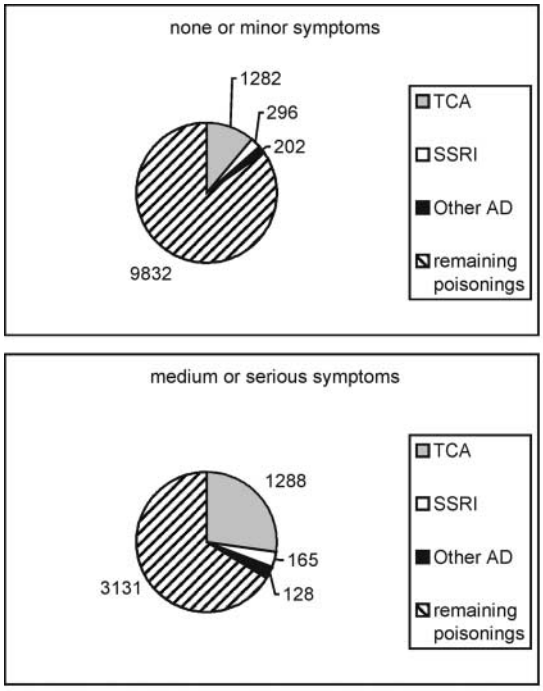

Figure 2. Degree of symptoms caused by deliberate self-poisoning with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI) and other antidepressants (AD).

J Clin Psychiatr 1998;**59**:13–18. Montgomery SA. Suicide and antidepressants. *Ann N Y Acad Sci* 1997;**836**:329–338. Personne M, Persson H, Sjoberg E. Citalopram toxicity. *Lancet* 1997;**350**:518–519. Whooley MA, Simon GE. Managing depression in medical outpatients. *N Engl J Med* 2000;**343**:1942–1950. Winokur G, Black DW. Suicide—what can be done? *N Engl J Med* 1992;**327**:490–491.

209. HIGH CORRESPONDENCE BETWEEN FEMALE AND MALE PATIENTS CONCERNING SEASONAL AND CIRCADIAN RHYTHMS IN DELIBERATE SELF-POISONING

von Mach MA, Weilemann I, Weilemann LS. *Department of Clinical Toxicology and Poison Center, University of Mainz, Germany.*

Objective: Deliberate self-poisoning has been shown to be an increasing problem in recent years (Whooley, 2000). In previous studies of a seasonality of suicide, peaks have often been found in the number of suicides in the spring and early summer and in the morning hours in both northern and southern hemispheres (Altamura, 1999). The purpose of the present study was to compare the month-related and time-related distribution of female and male patients with suicidal and parasuicidal intoxications consulting our Poison Center. Methods: During the study period from 1995 to 2002 (until September) 38260 inquiries concerning deliberate self-poisoning were registered in our Poison Center. The gender of the patient as well as the time of ingestion were documented using ADAM-Dok- and analyzed using ADAM-Aus-software. The correlation coefficient (R) was calculated using Pearson's correlation. Results: The frequency of deliberate self-poisoning showed for female as well as for male patients highest values in spring and summer and decreasing numbers in autumn ($r = 0.86$; Fig. 1). Analyzing the patterns of times of ingestion revealed corresponding rhythms between female and male patients with a minimum in the early morning, a continuous increase from midday and a maximum in the late

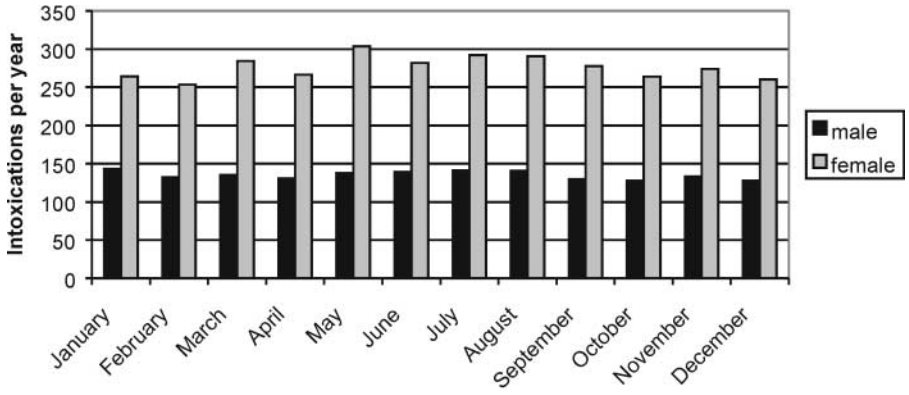

Figure 1.

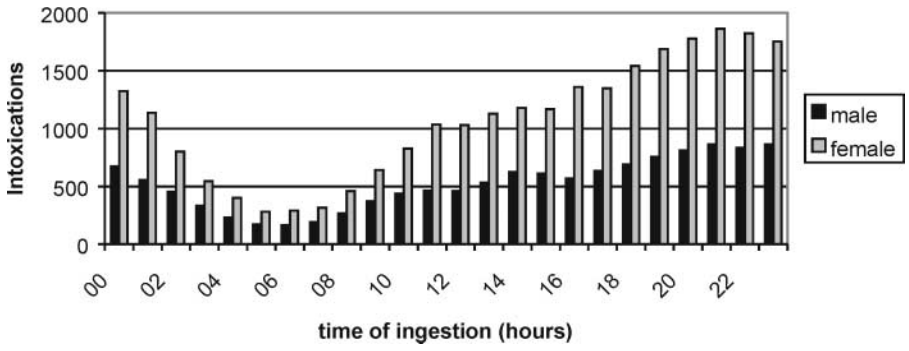

Figure 2.

evening hours (r = 0.99; Fig. 2). Conclusion: (i) As previously has been demonstrated for suicides (Altamura, 1999) in the present investigation, seasonal as well as circadian rhythms could be demonstrated in suicidal and parasuicidal deliberate self-poisoning. (ii) In accordance to studies concerning suicides highest frequencies were observed in spring and summer, while for suicides a peak in the morning hours has been described as compared to a maximum of poisonings in the late evening hours in the present study. (iii) Female and male deliberate self-poisoning behavior seems similar with respect to time of day and time of year. References: Altamura C, VanGastel A, Pioli R, Mannu P, Maes M. Seasonal and circadian rhythms in suicide in Cagliary, Italy. *J Affect Disord* 1999;**53**:77–85. Whooley MA, Simon GE. Managing depression in medical outpatients. *N Engl J Med* 2000;**343**:1942–1950.

210. ACUTE POISONINGS IN POLAND DURING THE PERIOD 1997–1998

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Objective: in Poland, since 1968, Toxicological Centers (T.C.) have sent data on treated patients to the National Poison Information Centre (N.P.I.C.). In 1996, after consultations with the state expert for clinical toxicology and with the heads of all Polish toxicological centres, N.P.I.C. decided to collect and analyze data on patients treated at T.C. and those treated at other health care units but where a toxicological centre specialist was consulted. Methods: Data from 10 toxicological centres for 1997–1998 were analyzed for this study. The collected data refer to patients hospitalized at T.C. and patients treated at other health care units where T.C. specialists were consulted. Results: Table shows number of poisonings in 1997–1998:

Toxicological centre in:	1997		1998	
	No. of poisonings	No. of poisoning exposures	No. of poisonings	No. of poisoning exposures
GDANSK	125	279	179	500
CRACOW	3,472	1,186	3,477	1,464
LUBLIN	1,152	288	1,188	382
LODZ	1,603	1,629	1,752	1,632
POZNAN	1,092	573	1,101	810
RZESZOW	378	—	349	—
SOSNOWIEC	260	4,302	316	4,258
TARNOW	200	154	215	155
WARSAW	221	2,798	288	2,437
WROCLAW	1,174	299	1,077	260
Total	9,677	11,508	9,942	11,898

The analysis shows that drugs constituted the most frequent cause of the poisonings (over 45%), in particular sleep-inducing, sedative, and psychotropic drugs. Poisonings by alcohols accounted for 17.6% of the total, gases 5.6%, pesticides 4.1%, street-drugs 4.1%, and organic solvents 3.8%. Suicidal poisonings constituted over 35% of total poisonings, accidental 24%, poisonings resulting from street-drugs and alcohol abuse over 23%, chemical emergency or fire 1%, while occupational poisonings constituted only 0.9% of total poisonings. In 1997–1998, the highest numbers of deaths were recorded after ingestion of drugs (61), ethylene glycol (24), methanol or ethanol (29, including 11 after ingestion of methanol), pesticides (8). Conclusion: It is the first time in Poland that the data for both patients treated at the toxicological centres and those treated at other hospitals with consultation with toxicological centers' specialists have been analysed together. As more than 50% of acutely-poisoned patients were treated in 1997–1998 at hospitals other than those of the toxicological centres, the results of the analysis presented in this work seem to reflect the true state better than those which would be based on data from the toxicological centres alone. Results of this analysis enable observation of the trends in poisoning with various chemicals.

211. ACUTE INTOXICATION IN THE ELDERLY: A 3-YEAR RETROSPECTIVE EPIDEMIOLOGICAL STUDY IN A GENERAL HOSPITAL

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Objective: Acute intoxication in the elderly represents a significant health issue; adverse drug events are more common and mortality rate from intoxication is higher in older patients (≥65 years) (1,2). Multiple drug therapy, comorbidity and age-related alterations in pharmacokinetics and pharmacodynamics contribute to increase the risk and worsen the outcome. A 2-phase (retrospective and prospective) epidemiological study and toxicokinetic analysis of poisoned elderly patients admitted to our hospital was planned as a part of a multicenter program on the "frail elderly" (PROMTO); the aim was to obtain local epidemiological data in order to support targeted preventive and therapeutic interventions. The final results of the retrospective phase are presented. Methods: We analyzed 3 years data (1998 to 2000) for admissions to our hospital (reference population: 968,723) of patients ≥65 years old with acute intoxication; hospital discharge diagnosis (ICD-9-CM codes from 960.0 to 989.9) and clinical records have been used to retrieve the eligible patients. Data was collected on a specially designed report form. Results: Of the 39,065 patients ≥65 years old hospitalized during the 3-year study period, 54 were admitted with a diagnosis of intoxication (12.6% of the 428 overall poisoned patients admitted; 46/100,000/year admissions). Seven cases were excluded from analysis (medical records not available). Of the 47 evaluable patients, 29 (62%) were female, while 37 (79%) were ≥70 years old. Drug intoxication accounted for 70% of cases, accordingly to European Poison Centers reports. Forty patients (85%) were exposed to a single agent; in almost all patients (96%) the way of exposure was ingestion and the exposure was unintentional (77%). In most patients (62%) exposure was chronic or acute on chronic. Almost all patients (96%) had symptoms and underwent symptomatic/supportive care; In 6 patients intensive care was required. Hospitalization time was greater than 4 days in 72% of cases (mean 10 days, median 9 days). Three fatalities occurred; 2 suicides (hydrochloric acid ingestions) and 1 lethal adverse drug reaction (phenformin-induced lactic acidosis). Conclusion: Despite limitations of this study (timing and small sample size), our data on acute intoxication in the elderly are in agreement with other literature. These data are relevant because unintentional poisonings are avoidable. Attention to the problem may result in preventative strategies. References: 1. Litovitz TL, Klein-Swartz W, White S et al. 2000 Annual report of AAPCC toxic exposure surveillance system. *Am J Emerg Med* 2001;**19**:337–395. 2. Rothschild JM, Bates DW, Leap LL. Preventable medical injuries in older patients. *Arch Int Med* 2000;**160**:2717–2728.

212. EPIDEMIOLOGY OF ACUTE POISONING IN CHILDREN IN SOUTH ROMANIA

Ulmeanu CE, Girnita VG, Petran EM, Conicescu S. *Toxicology Department, Children Emergency Hospital "Grigore Alexandrescu", Bucharest, Romania.*

Objective: Data relating to poisoning in most developing countries is often patchy, with most published information on poisoning being from developed countries. This is particulary true for poisoning in children who are normally the victims of accidental exposure. In view of this, we describe the toxiepidemiology of poisoning admitted to the Toxicology Department in Children Emergency Hospital "Grigore Alexandrescu" Bucharest, that is admitting all poisoning cases in children in South Romania. Also the most severe cases from other regions in Romania are transferred to the Toxicology Department for special investigations and treatment. Methods: A retrospective review of all cases of poisoning admitted to the Toxicology Department was conducted for the period January 2000–December 2001. All cases of poisoning occurring in children under 18 years were selected and analyzed. Results: There was a total of 1844 cases of paediatric poisoning admitted to the Toxicology Department—902 cases in 2000 and 942 cases in 2001. There were 683 cases of deliberate poisoning—321 cases in 2000 and 362 cases in 2001, and 1161 cases of accidental poisoning—581 cases in 2000 and 580 cases in 2001. The main groups of agents responsible for poisoning admissions are shown in the Table 1. Drugs accounted the most admissions, followed by caustics, pesticides, and petroleum products.There were 10 cases of death—3 cases in 2000 and 7 cases in 2001. Conclusion: The fact that drugs accounted for the highest number of hospital admissions in this study points to a need for toxicovigilance and public education programs aimed at raising awareness of the proper storage and distribution of pharmaceuticals. Further investigations will help identify whether interventions in

Table 1. Poisoning admissions per toxic group.

	Cases admitted in 2000 (% total cases)	Cases admitted in 2001 (% total cases)
Drugs	439 (48.6)	492 (52.2)
Benzodiazepines	144 (16.0)	162 (17.2)
Distonocalm	108 (12.0)	122 (13.0)
Tricyclic antidepressants	81 (9.0)	86 (9.2)
Barbiturates	61 (6.66)	75 (7.8)
Acetaminofen	45 (5.0)	47 (5.01)
Caustics	171 (19.0)	173 (19.0)
Alcohol	117 (13.0)	113 (12.0)
Pesticides	50 (6.05)	41 (4.41)
Petroleum products	53 (5.9)	39 (4.2)
Mushrooms	38 (3.85)	37 (4.0)
Abuse drugs	34 (3.54)	47 (4.98)

this area could reduce poisoning incidence. References: Ford, Delaney, Lung, Erickson. Clinical Toxicology, Saunders 2001.

213. A NEW BOX OF 4-AMINOPYRIDINE: CASE REPORT

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Introduction: 4-aminopyridine (4-AP), a potassium channel blocking agent that enhances the release of acetylcholine presynaptically, increasing the force of muscle contraction is used in the treatment of symptomatic multiple sclerosis[1]. A number of intoxications have been reported with effects ranging from choreoathetoid-type movements to generalized convulsions, cardiac conduction problems, hypertension and respiratory arrest. Ingestion of 0.6 mg/kg will produce toxic signs and symptoms which may require hospitalization. Ingestion of 60 mg in one patient led to a tonic clonic seizure and respiratory arrest[2,3]. Case report: A 41-year old woman, known with possible multiple sclerosis, was treated with 4-aminopyridine (4-AP), at a dose of 10 mg tid magisterially prepared. On the day of admission she had just started a new box of 4-AP. One hour after ingestion of one tablet of 4-AP she developed the following symptoms: shivering, vomiting, with a cold feeling and anxiousness. She was acting slowly and could hardly speak although she was alert and oriented to person, place, and time. On arrival in the hospital her Glasgow coma scale was 15/15. The blood pressure was 112/40 mm Hg, the heart rate 80/minute and oxygen saturation 97%. Her temperature was 34.9°C. She was anxious, hyperexcitable with tremors and dysarthria. Physical examination of heart, lung, and abdomen showed no abnormalities. ECG revealed non-specific repolarisation abnormalities while the laboratory results indicated a metabolic acidosis with respiratory compensation (pH 7.34; pCO_2 29 mm Hg; pO_2 142 mm Hg; bicarbonate 16 mmol/l) and a lactate of 4.8 mmol/l (normal values 1.0–2.4 mmol/l). Since intoxication with 4-AP was suggested and there is no antidote only active charcoal was administered and she was monitored in the intensive care unit. Analysis of the tablets confirmed the intoxication: the dose of one tablet was accidentally 200 mg instead of 10 mg, due to a written dosage mistake on the prescription. There were no further complications or new symptoms and she was discharged the next day. Conclusion: Despite intoxication with 200 mg 4-AP orally, leading only to mild metabolic lactate acidosis, hypothermia and mild neurological complaints, our patient recovered rapidly without any permanent complication. References: 1) Solari A, Uitdehaag B et al. Aminopyridines for symptomatic treatment in multiple sclerosis. *Cochrane Database Syst Rev* 2001;**4**:CD001330. 2) Ellenhorn MJ S, Schonwald G, Ordog J, Wasserberger. *Ellenhorn's medical toxicology: diagnosis and treatment of human poisoning*. 2nd ed. 1997. 957–958. 3) Stork CM, Hoffman RS. Characterization of 4-aminopyridine in overdose. *J Toxicol Clin Toxicol* 1994;**32**:583–7.

214. THE MYTH OF THE FATES CHALLENGED: FIVE TIMES POISONED AND STILL THE THREAD OF LIFE COULDN'T BE CUT

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Introduction: In Greek mythology our destiny lies in the hands of the Fates. There are three Fates. Clotho, who spins the thread of life. Lachesis, who chooses the lot in life and measures off how long it is to be. Atropos, she who cannot be turned, who at death with her shears cuts the thread of life. Atropine (Atropos) is only used as an oral drug for special psychiatric indications. Atropine as a cause of severe anticholinergic poisoning therefore is rare. We describe a case of an 82-year-old woman with repetitive severe anticholinergic poisoning where the toxidrome was only recognized at the third presentation and the cause of poisoning after the fifth presentation. Case report: An 82-year-old woman was admitted in October 2001 for reasons of dizziness and transient dysarthria. During hospitalisation an episode of "convulsions" of arms and legs, dysarthria, stupor, itching and plethora developed and was diagnosed as a transient ischemic attack. A myxoma in the left atrium was found and designated as embolic focus. The myxoma was removed surgically. One day after discharge the patient was readmitted with fever, stupor, dysarthria, and restless legs. Vital signs were pulse 110/min, blood pressure 200/80 mmHg, respiration 30/min, and temperature 38°C. Dilated pupils, extreme restlessness, itching and plethora of the face were noticed. Differential diagnosis included: postoperative sepsis, encephalitis and epilepsy. She required sedation with propofol. All investigations (labs, brain imaging, EEG, cerebrospinal fluid analysis, tox screen) were normal and the patient recovered completely by the next morning. After two weeks of hospitalisation without new signs she was discharged with a diagnosis of "transient ischemic attack." The next day she was admitted with the same clinical signs. Now the toxidrome pentad: "hot as a hare," "blind as a bat," "dry as a bone," "red as a beet," and "mad as a wet hen" was recognized and a diagnosis of anticholinergic poisoning was made although neostigmine 2 mg iv had no effect on her symptoms or signs. She recovered after 12 h. Despite repetitive questioning and toxicological screening for medication with anticholinergic properties (apart from atropine) no cause could be found. After another two admissions the family finally remembered an old prescription for headache containing caffeine 100 mg and atropine 0.01 mg pro tablet. Toxicological analysis of these recently renewed tablets showed 10 mg atropine pro tablet. There was a 1000 fold concentration mistake made by a pharmacist. Conclusion: This case report shows the high cost and morbidity due to not recognizing a toxidrome and the effect of withholding drug intake information by patient and family.

215. HEROIC THERAPIES IN VERY DANGEROUS POISONS

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Background: Trioxide of arsenic is one of the most toxic forms of arsenic. Death is believed to occur if the ingested amount is over 2 mg/Kg (200–300 mg). Case report: A 43-year-old male attempted suicide by drinking 54 g of arsenic trioxide. On arrival he was pale and diaphoretic. He was initially treated with gastric lavage and charcoal. Two hours later he developed vomiting, diarrhea, thirst, pharyngeal constriction, and paresthesias in the legs. Initial laboratory results were normal. The arsenic level in urine was 67.500 μg/L (normal $<$ 50 μg/L) and 132 μg/L (normal $<$ 5 μg/L) in blood. Aggressive hydration was undertaken and 5 mg/kg of dimercaprol (BAL) was administered every 6 h. An abdominal X-ray was taken, which revealed a large radiopaque mass in the gastric antrum. Laparotomy was performed with temporary mechanical closure (clamp) of the pylorus. Following this procedure, an attempt was made to remove the arsenic by means of gastric lavage consisting of 22 L of 0.45% saline. An intraoperative fluoroscopy showed abundant radiopaque material. Endoscopic removal was attempted without success because the arsenic had strongly adhered to the gastric mucosa. Manual removal of the arsenic was finally accomplished by gastrostomy. Following surgery, the patient was stable and asymptomatic for 2 days. On the fourth day, the patient became severely agitated and disoriented, and the level of arsenic in blood rose to 160 μg/L. Another abdominal X-ray was taken and arsenic radiopaque remains were observed in the ascending colon near the ileocecal valve. They were easily extracted by means of colonoscopy. The following day the patient was agitated and developed intense tremor, myoclonus and profound delirium and intubation

was required. He continued to be treated with BAL for 12 days, and later with oral D-penicillamine. On day 29 he was extubated and severe polyneuropathy affecting his arms and legs was observed. On day 55 the patient, displaying Mee's lines on his fingernails and toenails, was discharged from the hospital. Discussion: Conventional therapy of massive arsenic poisoning includes supportive measures and administration of chelators (BAL and others), and its mortality rate is very high. This case represents the first acute arsenic poisoning treated surgically and endoscopically. It is also the first case in which the patient survived after ingesting 54 g. (200 times the lethal dose). Conclusions: Surgery and endoscopy are very exceptional techniques for the treatment of poisoning. Nevertheless, when radiographic evidence demonstrates a failure of standard gastrointestinal decontamination methods, these techniques could be considered.

216. REGIONAL PAIN SYNDROME AND DELAYED NEUROTOXICITY FROM INTRAVENOUS DIPHENHYDRAMINE EXTRAVASATION

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Objective: The current body of literature describes the toxicity from diphenhydramine overdose as adverse anticholinergic effects, seizures, and cardiac conduction delays. We describe a case of delayed anticholinergic delirium followed by peripheral neuropathy and crippling reflux sympathetic dystrophy (regional pain syndrome type I) from intravenous diphenhydramine extravasation. Case report: A 39-year-old white female presented to the emergency department with 3 days of nausea and vomiting felt to be secondary to a viral syndrome. Initial therapy included 2 L of normal saline and 25 mg intravenous promethazine. Initial CBC, electrolytes, and drug screen were all within normal limits. Soon after receiving intravenous promethazine the patient developed restlessness, agitation, and a strong desire to remain moving (akathesia). Diphenhydramine, 50 mg, was administered, and the patient developed increasing agitation due to spasm of the neck and shoulder. Over the next 3 hours the patient received 800 mg of diphenhydramine until she was sedated. Inadvertently approximately 500 mg of the drug were administered subcutaneously and extravasated into the patient's soft tissues of her left arm. The patient also received 2 mg of lorazepam intravenously. After several hours of observation the patient was given 0.8 mg of flumazenil and discharged with a diagnosis of acute gastroenteritis and severe dystonic reaction. Several hours later, while at home, she became increasingly agitated, thirsty, and hot and returned to the emergency department. She was then noted to be confused and hallucinating. Intravenous saline and a small dose of diazepam were successful in controlling her symptoms and she was discharged the next day. At this time it was noted that her left hand was swollen and tender from the infiltrated IV she had received the night before. Cool compresses were applied and the patient was referred to an orthopedic hand specialist. Over the next several months the patient continued to have severe hypesthesias, erythema, and burning pain on the dorsal ulnar aspect of the left hand. Range of motion was limited to 40 degrees of flexion and extension and radiographic studies were negative. The diagnosis of Reflex Sympathetic Dystrophy (Chronic Regional Pain Syndrome Type I) was made. Despite physical therapy, stellate ganglion blocks, biofeedback, oral medications (gabapentin, ibuprofen) and consultation with a chronic pain specialist the patient has remained persistently symptomatic 2 years after her initial hospitalization. Conclusions: A combination of direct mechanical trauma from the pressure of the intravenous extravasation injury, as well as chemical injury from diphenhydramine (a known sodium channel blocker) and its preservative benzethonium chloride (a cationic detergent) are felt to be responsible for this patient's chronic injury.

217. SEIZURES AFTER ACUTE BUFLOMEDIL POISONING WITH FALSE POSITIVE PHENCYCLIDINE URINARY SPOT TEST

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Introduction: Buflomedil is a vasodilator widely used in Europe in the treatment of peripheral vascular disease. Buflomedil intoxications show clinical features of convulsions, coma, drowsiness, agitation, tachycardia, vomiting, and, less frequently, pulmonary edema, ventricular fibrillation or asystole with a possible lethal outcome. Case report: A 35-year-old woman with mitral valve stenosis and regurgitation, was found at home unconscious with tonic-clonic seizures. At hospital the patient was treated with diazepam and mechanical ventilation. Sinus tachycardia and hypotension

(80/50 mmHg) were present with mild metabolic and respiratory acidosis. Initial neurological evaluation showed an apparent left-side hemiplegia but cranial CT and lumbar puncture were normal. On the hypothesis of toxic cause a gastric lavage was performed followed by charcoal and cathartic administration. Toxicological analysis were negative for carbon monoxide, tricyclic antidepressants, barbiturates and ethanol, while urine test for drugs of abuse (solid-phase chromatographic monoclonal immunoessay, Syva RapidTest of Syva Company Dade Behring Inc.) was, surprisingly, positive for phencyclidine (a very rare drug in Italy). HPLC performed on REMEDi HS (Bio-Rad Laboratories Inc.) for confirmation, indicated the presence of buflomedil instead. Plasma concentrations were 3.87 mcg/ml (9th hour) and 1.30 mcg/ml (21st hour); the calculated concentration peak was about 6.4 mcg/ml with an elimination half-life of 8 h. Five hours after admission the patient was extubated, and discharged completely recovered 24 h later. The patient confirmed intentional buflomedil overdose. No indication of a cross-reaction between buflomedil and phencyclidine has been reported previously by the urinary spot test producer. Conclusions: Buflomedil intoxication should be suspected in patients with seizures due to toxic cause and more specific analytical methods should be always used for confirmation of drug abuse because antibody cross-reactions can produce false-positive urinary results.

218. UNEXPLAINED HEMOLYSIS IN YOUNG SUBJECTS: LOOK FOR POPPER USE AND G6PD DEFICIENCY

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Background: Poppers is the popular name for various alkyl nitrites widely used as quick-acting drugs for recreational purposes and to improve sexual performance. They are sold in small ampoules and consumed by inhaling the vapors. Young people are more likely to abuse poppers because they are cheap and readily available in discotheques, pubs, and sex shops. Poppers side effects, overlooked by most users, may be severe and represent a cause of Emergency Department (ED) referral. Case report: A 17-year-old man went to the ED because of severe weakness which had began a few days before. A blood test ordered the day before by the general practitioner revealed a state of hemolytic anemia (RBC $3.12 \times 10^6/\mu L$; Hb 9.2 g/dL; Ht 30.4%; total bilirubin 3.95 mg/dL; indirect bilirubin 3.15 mg/dL). Clinical examination showed pallor and scleral jaundice. Past medical history was uncontributory. The patient mentioned popper use during a school trip five days before. Blood tests run on the arrival to the ED confirmed the presence of hemolytic anemia (RBC $2.62 \times 10^6/\mu L$; Hb 7.8 g/dL; Ht 25.3%; total bilirubin 1.43 mg/dL; LDH 567 UI/L; aptoglobin 21.04 mg/dL) with normal methemoglobin levels (0.3%). The patient was then admitted to the medical ward to assess the cause of the anemia. Two days later, hemoglobin was stable (8 g/dL) and bilirubin got back to normal values (0.87 mg/dL); both a slight rise in LDH levels and a reduction in aptoglobin values still persisted. History of popper inhalation together with the presence of hemolysis suggested to investigate for a glucose-6-phosphate dehydrogenase deficiency (G6PD). Erythrocitary G6PD activity resulted 18 $mU/10^9$ RBC (normal values: 130–210 $mU/10^9$ RBC). No reduction of erythrocitary pyruvate kinase and RBC osmotic resistance was found. Definitive diagnosis of hemolytic anemia caused by amyl nitrite inhalation in a patient with previously undiagnosed G6PD deficiency was made. Discussion: Poppers users are generally affected by mild side effects such as headache, nausea, and tachycardia. However, the growing poppers popularity makes more likely their use by subjects with increased individual susceptibility to toxic effects. In patients with G6PD deficiency, nitrites oxidizing action may produce severe hemolysis, even after the use of one single ampoule. When cyanosis is transient and mild, signs and symptoms of anemia may represent the only cause of presentation to the ED some days after popper inhalation. Both popper use and G6PD deficiency should be considered in young subjects with unexplained hemolytic anemia.

219. METHAMPHETAMINE ABUSE DURING PREGNANCY AND ITS HEALTH IMPACT ON NEONATES BORN AT SIRIRAJ HOSPITAL, BANGKOK, THAILAND

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Objective: The purpose of this study is to ascertain impact of methamphetamine during pregnancy on the overall health of newborns at Siriraj Hospital, Bangkok, Thailand. Method: Birth records of somatic growth parameters and neonatal

withdrawal symptoms of 47 out of 57 infants born to methamphetamine-abusing women during January 2001 to December 2001 are compared to 49 newborns whose mothers do not use methamphetamine during pregnancy. The data on somatic growth and withdrawal symptoms are analyzed using multiple logistic regression and standard chi square test, respectively. Also, home visitation records of these children are reviewed. Results: Infants of methamphetamine-abusing mothers are found to have significantly smaller gestational age-adjusted head circumference (correlation coefficient $= -1.458$, $p < 0.001$) and birth weight (correlation coefficient $= -217.9$, $p \leq 0.001$) measurements. They also have more symptoms of agitation (5/47), vomiting (11/47), and tachypnea (12/47) when compared to the control group ($p \leq 0.001$). Home visitation records are shown in Table 1.

Table 1. Maternal and psychosocial characteristics of 57 cases of methamphetamine-exposed infants ascertained by home visitation.

Risk factors	Number (%)
No prenatal care	36 (63.2)
Single mothers	28 (49.1)
Father addicted	28 (49.1)
Member of family addicted	18 (31.6)
Mother depressed or suicidal	27 (47.4)
Unwanted pregnancy	26 (45.6)
History of incarceration in father or mother	36 (63.1)

Conclusions: In-utero methamphetamine exposure has been shown to adversely effect somatic growth of newborns and cause a variety of abstinent-like symptoms. They are also at greater risk for psychosocial problems such as abuse and neglect. References: AM B, Mk L et al. Home Intervention for In Utero Drug-Exposed Infants *Public Health Nursing* 1998;**15**:307–318. Eriksson M, Larsson G et al. Amphetamine addiction and pregnancy II Pregnancy, delivery and the neonatal period. Socio-medical aspects *Acta Obstet Gynecol Scand* 1981;**60**:253–9. Little B, Snell BLM et al. Methamphetamine abuse during pregnancy: outcome and fetal effects *Obstet Gynecol* 1988;**72**:541–4.

220. ADMISSIONS TO AN EMERGENCY DEPARTMENT DUE TO ECSTASY (MDMA) CONSUMPTION

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Objective: To determine the epidemiological and clinical characteristics of admissions to an emergency department due to the consumption of ecstasy (MDMA) and other amphetamine derivatives. Methods: Descriptive retrospective study carried out in the emergency department of a teaching hospital. During 30 months, the medical records of patients admitted to the emergency department because they claimed to have consumed ecstasy or because toxicological tests were positive for amphetamines were revised. Epidemiological and clinical data, complementary tests and the evolution of the case were collected. Toxicological tests included the identification of benzodiazepines, amphetamines, cocaine, opiates, methadone, cannabis, LSD, GHB and ketamine in urine and serum ethanol levels. Results: One hundred and twenty cases where admittance to the emergency department was directly due to the consumption of ecstasy were included. In another 73 cases, the reason for admittance was the consumption of another abusive drug, but toxicological tests also demonstrated the consumption of amphetamines. The average age was 23, and 70% were male. The predominant signs and symptoms were neuro-psychological and cardiovascular: anxiety (52%), psychomotor agitation (28%), palpitations (16%), trembling, myoclonia or hypertonia (23%), delirium or hallucinations (10%) and convulsions (7%). The physical examination revealed tachycardia (24%), tachypnea (15%), hypertension (6%), and an axillary temperature greater than 40°C (1%). A complete screening was carried out in 48 cases, with rhabdomyolosis ($CK > 300$ u/l) being present in 6%. An electrocardiogram was carried out in 46 patients and showed sinus tachycardia in 18%, ventricular tachycardia in 2%, and signs of acute myocardial ischemia in 1%. The medical record and/or the toxicological tests showed that 95% of patients had consumed other drugs of abuse as well as amphetamines. The average

stay in the emergency department was 5 h. Three patients had to be admitted to the ICU (1.5%), two of whom died. Conclusion: The consumption of ecstasy generates admissions to the emergency department whose predominant manifestations are on the central nervous and cardiovascular systems. Around 2% of these patients die.

221. GAMMA-HYDROXYBUTYRATE INTOXICATION DURING RECREATIONAL USE: DEFINING CLINICAL PICTURE AND DELIMITING RISK FACTORS

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Objectives: Gamma-hydroxybutyrate (GHB; street name: liquid ecstasy) is a relatively newly synthetic recreational drug that has been introduced in European countries during recent years. During recent months, we have attended at our Emergency Department (ED) an increasing number of patients with GHB overdose. We herein present epidemiologic, toxicological, clinical and outcome data of such patients. Patients and methods: During the last 30 months (between April 1 2000 and October 31 2002) we attended 191 patients whose main clinical complaints could be directly attributed to GHB. Data were collected from interview with the patients and/or accompanying people, and results of blood and urine analysis were also compiled. Toxicological screening in urine was performed in nearly all cases, and since January 1 2001 it included determination of GHB by mass spectrometry–gas chromatography. Results: Mean age were 23 ± 5 year-old (range 17–39), 66% were males, 81% of cases were seen on weekend days and 71% between 0 and 8 a.m. All patients complained of some degree of impairment of consciousness at the scene of drug consumption and, when arrived to ED, 75% remained with a Glasgow Coma Score (GCS) of 12 or less, and 16% with a deep coma (GCS 3 points). Three patients required mechanical ventilation during a brief period of time due to severe hypoventilation and blood oxygen desaturation, and one patient exhibited transient hemodynamic instability. Other remarkable findings were poorly or non-reactive midriasis in 48%, vomiting in 17%, sinus bradychardia in 15%, generalized seizures in 3%, mild hypokalemia in 20%, and moderate rhabdomyolysis in 19%. Sixty-three percent of patients had also consumed alcohol and 84% had simultaneously used other illicit drugs (amphetamine derivatives 42%, cocaine 27%, cannabis 11%, ketamine in 10%, benzodiazepines 5%, and opiates 2%). In one case, GHB was used to facilitate sexual assault. Outcome was good in all cases: complete consciousness recovery was achieved 42 ± 39 minutes after arrival to ED (range: 1–180), and 90% leaving ED in less than 6 h. No fatalities were observed. Conclusion: European emergencists and toxicologists must be aware about introduction of GHB in illicit circuits because, since it is not routinely detected by drug screening tests currently available in the vast majority of ED, only a high-degree of suspicion will allow to diagnose this emergent cause of coma in both, the scene of drug consumption and in patients arriving to ED wards.

222. DIAGNOSIS OF OPIUM BODY PACKING BY PLAIN X-RAY AND CT SCANNING

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Objective: Opium body packing is a common cause of admission to the Medical Toxicology ward. Since the body packers are drug smugglers, they are mostly brought to the hospital by police. Those that are alert usually deny body packing. Ultrasonography, plain X-ray and CT scanning are recommended for the diagnosis of body packing and stuffing. We compare the diagnostic value of these 3 techniques in opium body packing. Methods: A questionnaire was designed to record all clinical and para clinical findings of all body packers admitted to the ward between 10 October 2000 and 11 October 2002. Ultrasonography, plain X-ray and CT scan were performed for all body packers on admission and at intervals as clinically indicated. Castor oil was used as a cathartic in all body packers admitted, and naloxone was administered in symptomatic patients. The asymptomatic cases were kept under close observation both medically and forensically. The packets recovered in the feces were counted, weighed and collected by the police. Comatose patients with many packets who did not respond to medical treatment or developed bowel obstruction were referred for surgery. The surgically removed packets were also counted, weighed, and collected by the police. The results of the three imaging techniques were compared with the clinical findings and the number of recovered packets. Statistical analysis (Ki Square test) was performed using SPSS. Results: Out of 3281 poisoned patients admitted to the ward over the year, 490 patients

(15%) had narcotic poisoning, of which 25 patients (5%) were opium body packers. There was only one female body packer (a 16-year-old girl) with severe opium poisoning who underwent surgery and died a day later in ICU. Out of 24 male patients, 2 (30 and 69 years) also had surgery and died. The other 22 patients aged 17 to 58 (mean 31) years were treated medically and all survived despite severe intoxication in 18 of them. The body packers were either illiterate (28%), primary educated (32%), or secondary educated (40%). More than 44% of them were addicts. The number of packets varied between 1 and 48 (mean of 21) with weights of 6 to 102 (mean of 46) gm. Ultrasonography did not show any clear countable packets, whereas plain abdominal X-ray revealed the packets in 12 patients (48%) and abdominal CT scan was positive in 24 (96%) patients ($p < 0.001$). Conclusion: 1. Ultrasonography is of no value in diagnosis of opium body packing. 2. Plain abdominal X-ray is simple but not efficient. 3. CT scanning is the best diagnostic technique in opium body packing.

223. EPIDEMIOLOGY OF VOLATILE SUBSTANCE ABUSE (VSA) CASES REPORTED TO U.S. POISON CENTERS

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Background: The American Association of Poison Control Centers TESS database provides a broad picture of exposures in the U.S. involving data from all age groups and including cases reported by the lay public and health professionals. Method: All cases reported to the TESS database where 1) the reason for exposure was abuse, 2) the route of exposure was inhalation, and 3) the substance was a non-pharmaceutical, were evaluated for the years 1996 through 2001. Results: 13,226,505 patients were reported in TESS during the study period of which 11,670 met entrance criteria. Over the study period there was a mean annual decline of 9% of reported VSA with an overall decline of 37% from 1996 to 2001. The 8620 patients (74%) were male. VSA was reported primarily in children, with 6358 cases (54%) in children 13–19 yrs and 1803 (15%) cases in children 6–12 yrs. Fifty-two cases were reported in children ≤ 5 yr. 2330 (20%) VSA cases had a serious outcome, defined as either moderate effect ($n = 2000$), major effect ($n = 267$), or death ($n = 63$). The top five categories of substances abused were gasoline (41%), paint (13%), propane/butane (6%), air fresheners (6%), and formulin (5%). Serious outcomes were evenly distributed to all categories, similar to their exposure rates. However three categories were responsible for the majority of deaths: gasoline (45%), air fresheners (26%), and propane/butane (11%). While there was a decline in reported cases, there was no decline in major outcomes or fatalities. VSA was reported in all 50 states, with case distribution similar to population distribution. However, seven states had >2 times the expected rate based on their population, 3 western states, 2 mid-western states and two Appalachian states. The monthly occurrence rate was evenly distributed with a mean of 162 VSA cases/month (S.D. $\pm$ 10.85). There were four months that were >2 standard deviations from the mean, with two peak months (May 192/month and March 187/month) and two trough months (December 126/month and January 137/month). VSA cases were reported more frequently during weekdays than weekends. VSA was reported more frequently during the evening hours: peak hours of occurrence were 7 PM through 10 PM (mean 19 VSA cases/hour) and with >14 VSA cases/hour from 4 PM to 11 PM. Conclusion: This report presents a broad picture of VSA in the U.S. VSA, as reported to U.S. poison centers, appears to be on the decline, but continues to remain common. VSA is reported throughout the U.S. in all areas of the country. A small group of substances appears responsible for the majority of deaths.

224. GAMMA-HYDROXYBUTYRATE (GHB) WITHDRAWAL AFTER 7 DAYS OF FREQUENT USE

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Background: Withdrawal from GHB and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD) is described after discontinuation of long-term, chronic usage. The shortest duration of usage reported was 2 months of usage every 2–3 hours. We describe a unique case of GHB withdrawal precipitated by only 7 days of GHB use every 2–3 hours. Case report: A 29-year-old healthy woman with no significant medical history was brought to the ED for abnormal behavior over the last day. A vague history of over the counter cold medications and GHB use was obtained by EMS. Her vital signs were: BP, 145/95 mmHg; HR, 132/min; RR, 16/min; temperature, 98.7°F. Upon examination,

the patient had an altered sensorium, 7 mm pupils, and dry mucous membranes. She had active bowel sounds, no bladder distension, and no toxidromes. An EKG revealed sinus tachycardia with normal intervals. Her laboratory values were normal, and a urine drug screen was negative. During the subsequent 24 h she developed agitation, insomnia and auditory hallucinations without signs of any specific toxidromes and required a continual lorazepam infusion. Two days later, the patient had a clear sensorium and revealed her pattern of GHB abuse. Over the preceding year, she used single doses of GHB sporadically. However, 8 days prior, the patient began to use GHB as a sleep aid. Her frequency of dosing quickly escalated to 3 oz of GHB every 2–3 hours for a total of 7 days. She abruptly stopped taking GHB 24 hours prior to her presentation to the ED. While in the hospital she received a total of 72 mg of lorazepam. Conclusion: As GHB and its precursors increase in frequency as habitual drugs of abuse, the incidence of withdrawal from these drugs will likewise increase. Prior reports of withdrawal describe patients with frequent GHB/GBL use every several hours for durations as short as 2 months to as long as several years. However, this case illustrates that GHB withdrawal can occur with as few as 7 days of continual 2–3 hour dosing.

225. LARYNGOSPASM IN SEVERE GAMMA HYDROXYBUTYRATE (GHB) COMA

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Background: Acute GHB intoxication is known to cause severe central nervous system depression with varying neuromuscular activity ranging from areflexia to myoclonus. We describe a patient who ingested GHB and presented comatose, flaccid and areflexic except for laryngospasm. Case report: A 21-year-old man with no significant medical history was brought to the ED after ingesting GHB and then having a witnessed seizure-like event followed by unresponsiveness. He received parenteral dextrose, naloxone, and thiamine with no effect. Vital signs were: BP, 102/62 mmHg; HR, 116/min; RR, 12/min; temperature, 99.6°F; O_2 saturation, 87% on room air; and fingerstick glucose 86 mg/dL. Respirations were shallow and regular and his O_2 saturation increased to 98% on 100% inspired O_2. Physical examination revealed no evidence of head trauma. He had a Glasgow coma score of 3, 3 mm non-reactive pupils bilaterally, generalized flaccid muscle tone, absent rectal tone, and absent oculocephalic, corneal and gag reflexes. During otoscopic examination, the patient developed gagging. Repeat examination again induced gagging followed by apnea, cyanosis, and an O_2 saturation of 60%. Bag valve mask ventilation did not correct the hypoxemia. Direct laryngoscopy revealed a small piece of gum not large enough for airway obstruction in the oropharynx and was removed. Repeat laryngoscopy revealed vocal cords that spasmed close with attempted passage of an endotracheal tube. An emergent cricothyrotomy was performed to secure the airway. Subsequent laboratory and radiographic studies were normal except for the following: ethanol, 28 mg/dL and creatinine phosphokinase, 131 units/L. Otolaryngologic consultation confirmed normal cord function post cricothyrotomy. The patient regained normal mentation the next day and confirmed GHB ingestion shortly before this event. His urinary GHB level on presentation was 1400 mcg/mL. Conclusion: GHB ingestion can result in coma, total areflexia and muscular flaccidity but this case demonstrates that laryngospasm with apnea may still be present. Laryngospasm may be caused by the presence of a foreign body but is unexpected and unusual the setting of severe coma, muscle flaccidity, and areflexia. This case illustrates the sudden conversion of areflexia to persistent laryngospasm with apnea in a severely GHB intoxicated patient.

226. ALPHA-METHYLTRYPTAMINE REVISITED DUE TO EASY INTERNET ACCESS

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Background: Alpha-methyltryptamine (AMT) is a synthetic hallucinogenic indolealkylamine, initially studied as a monoamine oxidase inhibitor and formerly used as an antidepressant in the Soviet Union. Recreationally, it is available as a white powder that is insufflated or ingested. While AMT is structurally similar to n,n-dimethyltryptamine (DMT), a hallucinogen referred to as the "businessman's high" because its effects last about 30 minutes, AMT-induced hallucinations last about 16 h. Although popular in the 1960s, use of this drug is uncommon now. We report a patient who presented with sympathomimetic features who was found to have ingested AMT. Case report: A 17 year-old boy with no significant past medical or psychiatric history was brought in by ambulance after he was found running around the streets, nearly naked and shouting incoherently. In the ED, the patient required immediate sedation with 6 mg of

lorazapam intramuscularly before he could be evaluated. His heart rate was 160/min, blood pressure was 125/75 mmHg, respiratory rate was 18/min, temperature was 99°F (37.2°C), and his oxygen saturation was 99% on room air. He was extremely diaphoretic with pupils that were 6–7 mm and reactive, but the rest of the physical examination was normal. Routine laboratory tests, as well as cerebrospinal fluid analysis and CT scan of the head, were normal. A urine drug screen was negative for cannabinoids, cocaine, amphetamines, and phencyclidine. The next morning the patient stated he had taken AMT that he had purchased over the internet. He paid $150 US for 3 gm and was instructed to insufflate 100 mg, which was described as "the amount of the white powder that would fit on a dime." The patient was afraid to snort it and instead ingested it. His symptoms began approximately 15 minutes after ingestion. HPLC of the initial urine sample, performed by a reference laboratory, confirmed the presence of AMT and the absence of cocaine, phencyclidine, and amphetamines. Conclusion: AMT, a drug of abuse seen frequently in the 1960s may be regaining popularity because of ready access via the internet. Patients present with tachycardia, diaphoresis, and agitation and hallucinations. Supportive care including sedation with benzodiazepines appears to be effective therapy.

227. "HAPPY CANDY" INGESTION: HALLUCINATIONS IN A FOUR-YEAR-OLD CHILD CAUSED BY A PSILOCYBIN-LACED CHOCOLATE CANDY BAR

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Objective: We report a case of hallucinations in a 4-year-old child caused by ingestion of a psilocybin-laced chocolate candy bar known as "Happy Candy." The candy was obtained in Amsterdam, Holland, and illicitly transported to San Diego, California. Although intended for adult recreational use, the product poses a health hazard for children who inadvertently ingest the candy. Case report: A 4-year-old male with abnormal behavior was brought to the emergency department (ED) by ambulance. Two hours prior to evaluation, the child had eaten all five sections of a chocolate candy bar brought back illicitly by his parents from Amsterdam. They were told that the candy was laced with hallucinogenic mushrooms, and they should "take one section for laughs and two sections for a trip." They intended to share the candy with friends, and hid it in a kitchen cabinet. The parents found the child in the kitchen with the empty candy wrapper. The father induced emesis and called for an ambulance. The child received 15 grams of activated charcoal en-route. On arrival to the ED, his vital signs were: T 37.5 C, HR 102, RR 24, BP 117/83. The child was indeed very happy. He was smiling and laughing, but otherwise nonverbal. He was staring and reaching for inanimate objects, with apparent visual hallucinations. He had marked mydriasis but the remainder of the physical examination was normal. The patient received another 10 grams of activated charcoal and was admitted for observation. His hallucinations resolved within 12 h and he was discharged home the next day. Serum analysis by high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS/MS) confirmed the presence of psilocybin metabolite (psilocin) at 48 ng/mL. It was negative for LSD. Rapid urine immunoassay screening was negative for phencyclidine, opiates, barbiturates, methadone, benzodiazepines, cocaine, and cannabinoids, but presumptively positive for amphetamines. Confirmatory GC/MS on the same urine specimen was negative for amphetamine/methamphetamine. In addition, a second urine sample was negative for amphetamines by both immunoassay and TLC. Serum chemistries, including liver function tests, were normal. Conclusion: This case demonstrates the danger to children when psilocybin is prepared and packaged to appear as a chocolate candy bar. These products pose a pediatric safety hazard.

228. GAMMA-HYDROXYBUTYRATE COMA INDUCED BY "UNNOTICED" DRINKING IN A VERY YOUNG TEENAGER

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Background: Gamma-hydroxybutyrate (GHB) is a compound which meets many criteria of a neurotransmitter and, when used as a recreational drug, can enhance sociability and sensuality or induce euphoric and sedative effects. This substance is sold in Spain at parties and night-clubs, under the name of "liquid ecstasy". Although poisoning is frequent

in recreational use, our report concerns a rare case, as far as we know, of short-term coma, relating to "unintentional" taking of GHB in a 14-year-old young adolescent. Case reports: A 14-year-old girl was brought, from a disco, into the emergency department. She was unconscious, with a Glasgow coma score of 5; her pupils were 6 mm non-reactive to light and she showed signs of hypoventilation. Oropharyngeal tube was inserted for airway protection and supplemental oxygen delivered. BP was 117/64 mm Hg, HR 119 beats/min, and temperature 36.4°. There was no response to naloxone or flumacenil and additional respiratory support measures were established. There was no evidence of head trauma (normal CT scan). Biochemistry was normal and arterial blood gases were pH 7.32; pCO_2 52 mm Hg; pO_2 81 mm Hg. Forty minutes after arriving at the hospital she suddenly regained full consciousness. No benzodiazepines, barbiturates, tricyclic antidepressants, paracetamol or salicylates were found in blood and the routine toxicological urine analysis was negative for any drug of abuse or medicine. Ethanol blood level at the time she was admitted to hospital were only 19 mg/dL. The patient was discharged the following day. One week later, she was told that the 17 year-old-boy that was accompanying her on the night of the incident had, in an attempt to produce an aphrodisiac effect, added "liquid ecstasy" to her drink without her knowledge. A new analysis of urine (conserved frozen) confirms the GHB ingestion. Discussion: GHB intoxication is well-known in North America and Europe. In Europe cases of GHB or gamma butyrolactone acute poisoning have been described, at least in Spain, Great Britain, France, Italy, and Sweden. This case meets all the suggested and published criteria of GHB induced coma. However, the most worrying aspect of our report is the possibility that an adolescent may take a liquid drug of abuse in "unnoticed form," when another person is able to take advantage of the practically odorless and tasteless characteristics of GHB and its masking facility. Conclusion: Physicians should suspect GHB poisoning, in very young patients who go into an "unexplained" coma with normal CT scan.

229. EPHEDRINE-INDUCED CARDIAC ISCHEMIA: EXPOSURE CONFIRMED WITH A SERUM LEVEL

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Objective: Many nonprescription weight-loss preparations that claim to speed up metabolism contain ephedrine. Although cardiac ischemia and infarction have been previously associated with ephedrine use, few cases are confirmed by drug levels. Case report: A 22-year-old woman with no history of drug or tobacco use presented to the ED with tremulousness, nausea, vomiting, abdominal pain, and palpitations immediately after taking 3 Xenadrine® tablets (each pill reportedly contained 10 mg of ephedrine). The day prior, she began taking 2 tablets twice a day (twice the recommended starting dosage). In the ED, she was tremulous with a blood pressure of 138/96 mm Hg and a pulse of 133/min. An ECG revealed 1 mm of ST-segment depression in leads V3 and V4 and T-wave inversions in leads V1–V4. Although the patient reported a history of an "abnormal ECG" found on routine outpatient examination five months prior, a subsequent cardiac evaluation (including an echocardiogram with Doppler) revealed only trace tricuspid regurgitation. In the ED, the patient was diagnosed with an acute coronary syndrome. During her stay in the ED, she was treated with nitrate tablets (0.4 mg PO × 2), diltiazem (10 mg IV) for tachycardia, aspirin (165 mg PO), lorazepam (4 mg IV), a heparin infusion and intravenous labetalol (10 mg) for tachycardia. She was admitted to the hospital with the intention of having a stress echocardiogram the following morning. A repeat electrocardiogram obtained 4 hours after the first revealed resolution of her ST-segment depression and cardiac enzymes subsequently excluded myocardial infarction. Although she retained inverted T-waves throughout her hospital stay, their amplitude was markedly reduced two days after admission. A serum ephedrine level, drawn approximately 6–7 hours after ingestion, was 150 ng/mL (usual bronchodilator range 35–80 ng/mL). Cardiac echocardiography with Doppler revealed normal heart size and function. The patient was discharged from the hospital after discussion of the potential harmful effects of the product. Conclusion: Ephedrine containing products may cause unanticipated side effects such as cardiac ischemia in otherwise young and healthy individuals. Slight deviations from therapeutic dosing that result in levels just above the bronchodilator range, may result in cardiac toxicity.

230. SEVERE METHEMOGLOBINEMIA AFTER ACCIDENTAL INGESTION OF AMYL NITRITE

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Objective: Increases in intoxications with aliphatic nitrites called "poppers" among urban gay/bisexual men have been noticed recently[1]. The emergency physician is faced with a life-threatening situation requiring fast diagnosis and antidotal treatment. Standard diagnostic tools such as pulse oximetry do not provide adequate results and can lead to incorrect treatment. Cyanosis with no obvious cause which is unresponsive to oxygen treatment despite normal arterial oxygen tension is the hallmark of poisoning with methemoglobin-forming agents. A case with severe methemoglobinemia due to amyl nitrite poisoning is described. Case report: A 47-year-old male patient ingested 30 mL of a fluid called "jungle juice" containing amyl nitrite, which he had confused with Echinacea. When admitted to hospital, the patient was deeply cyanotic with tachypnoea and reduced level of consciousness, arterial blood samples were noticed to be chocolate brown. Pulse oximetry showed a saturation of 82% with 10 l O_2 administered via an oxygen-mask. Arterial blood gas-analysis showed a respiratory overcompensated metabolic acidosis with normal oxygen tension. The first methemoglobin level measured about 1.5 h after ingestion was 50%. Laboratory findings were normal apart from a moderate increase in serum creatinine and a minimal elevation of white blood cell count. One ampoule (300 mg, e.g., 4 mg/kg b.w.) of toluidine blue was administered intravenously. Skin color changed to a blue-grey cyanosis due to the color of toluidine blue and 20 minutes after antidotal treatment the MetHb-level was reduced to 12%. Unfortunately, the patient developed intense vomiting, probably a side effect of toluidine blue. Within 1 h, the condition of the patient had improved dramatically, MetHb-level had dropped below 2% and blood gases were normal. Three weeks after admission, the patient was discharged in good physical condition to a psychiatric hospital due for treatment of bipolar-psychosis. Conclusion: In cases of cyanosis unresponsive to adequate oxygen treatment by mask or mechanical ventilation, and fairly normal blood gases one has to bear in mind dyshemoglobinemia. Because congenital abnormalities in hemoglobin structure and inherited deficiencies in enzymes responsible for methemoglobin reduction is rare, side effects of drugs or intoxications causing methemoglobinemia should be considered. Antidotal treatment with MetHb-reducing agents such as methylene blue or toluidine blue at a dosage of 1–2 mg/kg b.w. or 2–4 mg/kg b.w.[2], respectively, should be administered over 5 minutes, when glucose-6-phosphat-dehydrogenase deficiency is not suspected. References: [1]Colfax GN, Mansergh G, Guzman R, Vittinghoff E, Marks G, Rader M, Buchbinder S. Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr* 2001;**28**:373–9. [2]Curry S. Methemoglobinemia. *Ann Emerg Med* 1982;**25**:375–80.

231. EPHEDRINE-INDUCED CARDIOMYOPATHY

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Objective: Dietary supplements containing ephedrine are widely used in the U.S. for weight reduction. Numerous reports describe cardiovascular complications associated with ephedrine, including AMI, severe HTN, myocarditis, and cardiac dysrrhythmias. Although dilated cardiomyopathy is well associated with the use of cocaine, amphetamine, and phenylpropanolamine, it is not well reported with ephedrine use. We report a patient who developed CHF and a dilated cardiomyopathy associated with the prolonged use of ephedrine. Case report: A 47-year-old man used Xenedrine, an over-the-counter (OTC) weight reduction agent containing ephedrine and caffeine for 12 months. His calculated daily dose was 80 mg of ephedrine. He presented to the hospital complaining of fatigue and paroxysmal nocturnal dyspnea (PND). Examination was notable for bibasilar rales and an S3 gallop. Chest X-ray (CXR) showed cardiomegaly and interstitial pulmonary edema and his electrocardiogram (ECG) was consistent with left atrial enlargement and poor R-wave progression. Routine laboratory studies, including cardiac enzymes, were normal. An echocardiogram showed an ejection fraction (EF) of 20–25% [left ventricular end systolic diameter (LVESD) 6.3 cm; left ventricular end diastolic diameter (LVEDD) 5.4 cm]. The patient was treated with digoxin, lisinopril and carvedilol with some clinical improvement. Three days later, a cardiac catheterization noted an EF of 15%, insignificant CAD, and was highly suggestive of a non-ischemic cardiomyopathy. The patient was advised to stop taking the Xenadrine. Seven months later, the patient's EF significantly improved (EF 45–50%, LVESD 5.6 cm, LVEDD 4.4 cm) Conclusion: Similar to other sympathomimetic agents, ephedrine may be associated with cardiomyopathy. The use of ephedrine as a non-prescription weight control agent should be discouraged. Clinicians need to familiarize themselves with the complications of ephedrine use.

232. COMPARISON OF RISKS OF SEVERE INTOXICATIONS BETWEEN SEROTONIN REUPTAKE INHIBITORS AND TRICYCLIC ANTIDEPRESSANTS

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Objective: Due to antagonistic action on several peripheral receptors, tricyclic antidepressants (TCAs) have a narrow therapeutic index. This leads to a high risk of severe symptoms and lethal outcome in the setting of overdose. Guided by increasing insight in the importance of the neurotransmitter serotonin in the pathophysiology of depression, a search for safer compounds have led to the development of selective serotonin reuptake inhibitors (SSRIs). These new substances show fewer adverse effects in therapeutic doses as well as less profound toxicity in overdoses. Although this has been generally accepted for several years, TCAs still dominate drug therapy of depression in Germany. Documentation of qualitative and quantitative data on overdose cases may help to accelerate an adjustment of antidepressant prescriptions. Methods: Data on prescriptions of antidepressant in Germany (1) were analyzed and compared with overdose cases reported to the GIZ-Nord poison center to evaluate the risk for overdoses and the severity of intoxications using the WHO poisoning severity score (PSS, 2). The pattern of symptoms caused by overdoses of antidepressants were analyzed in detail using the poison center's case records database (GIZiNDEX). Results: Between 1993 to 2001, prescriptions for antidepressants have doubled in Germany, mainly because of a wider range of diseases treated. While TCA consumption is growing slowly, prescriptions for SSRIs have increased by a factor of 4 between 1997 and 2001. Citalopram and sertraline have increased most strongly. Nevertheless, in 2001, total Defined Daily Doses (DDD) of TCAs are still 58% of total DDD of all antidepressants (SSRIs 29%). Overdoses with TCAs and SSRIs are both reported to the GIZ-Nord poison center with increasing frequency. In 2001, 75% of all antidepressant related cases documented in the poison center's database were caused by TCAs and 15% by SSRIs. The severity of symptoms were different in both groups: outcome was lethal in 15 cases of TCA poisoning and in no case of SSRI poisoning. More than 50% of all TCA cases are categorized as "severe" or "moderate" according to PSS while only 25% of the SSRI cases are classified this way. Critical analysis of citalopram related cases showed that severe symptoms were not observed below 3000 mg. Conclusion: With respect to the number of DDD, overdoses with SSRI were reported less frequent than overdoses with TCA. Normalized by the number of poison center calls SSRI intoxications were less dangerous than TCA intoxications. References: (1) Schwabe U, Paffrath D (eds., 2002). Arzneiverordnungsreport 2002. Berlin: Springer. (2) Persson HE et al. Poisoning Severity Score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998;**36**:205–213.

233. EPIDEMIOLOGY OF ANTIDEPRESSANT POISONING IN THE NORTH OF ENGLAND

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Objective: This study was performed to determine the epidemiology of antidepressant overdose in the northeast of England and to compare this to local patterns of prescribing in primary care. Methods: With ethics committee approval the records of all patients presenting with antidepressant poisoning in a 2-year period between January 2000 and December 2001 were obtained. The age and sex of the patient were recorded together with details of the overdose and outcome, including length of hospital stay. Data on local prescribing of antidepressants by general practitioners were obtained from the Prescription Pricing Authority. Results: During the 2-year study period, 621 patients presented with antidepressant overdose, representing 24% of all overdose patients. Of these 61% were female and 39% male. The age range was 16–81 years with a median age of 33 in both sexes. Thirty-nine patients (6.3%) had taken more than one antidepressant and 427 (73%) had taken other substances, including alcohol. Of all episodes, 47% involved a selective serotonin reuptake inhibitor (SSRI), 36% a tricyclic antidepressant, and 2% a combination of these. Hospital stay was short, with 86% discharged on the day of admission or the day after. Prolonged stay (>3 days) was more common in those taking a tricyclic antidepressant (11/224, 5%) than an SSRI (6/292, 2%, $P < 0.05$). The numbers of patients admitted to ITU were 15 (6.7%) for tricyclics and 1 (0.3%) for SSRIs. The proportion of overdoses involving SSRIs and newer agents has increased since similar local surveys performed over the last 15 years. There was a strong correlation between frequency of drug overdose and local prescribing of individual antidepressants ($R^2 = 0.87$, $P < 0.0001$). Conclusion: Antidepressant poisoning is common with an increasing proportion of cases involving SSRIs and newer

agents. This pattern of presentation closely reflects local GP prescribing patterns. As previously recognized, tricyclic antidepressant poisoning is more often associated with ITU admission and prolonged hospital stay.

234. TOXICOLOGICAL FEATURES IN A CONSECUTIVE SERIES OF PATIENTS WITH VENLAFAXINE OVERDOSE

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Objective: Venlafaxine, an antidepressant that selectively inhibits the reuptake of serotonin and noradrenaline, is increasingly prescribed and overdose is likely to become more common. Reported toxic features include seizures and serotonin syndrome, and fatalities have occurred[1–5]. This research was performed to quantify the frequency of toxic features following overdose in a consecutive series of patients presenting to hospital. Case series: With ethical approval information was obtained from case records of all patients with venlafaxine overdose presenting to Freeman Hospital in Newcastle between January 2000 and December 2001. ECGs were reviewed by an experienced physician when there was no history of ingestion of another potential cardiotoxic substance. Of 2603 episodes of poisoning, 59 (2.3%) included venlafaxine. These involved 57 different patients (35 females, 22 males, median age 40 years). There was reported co-ingestion of other substances, including alcohol, in 54 episodes (92%). For episodes with pure venlafaxine overdose and mixed overdose respectively, reduced conscious level (Glasgow Coma Scale <13) was present in 1 (20%) and 9 (17%), sinus tachycardia in 1 (20%) and 8 (15%) and seizures in 0 and 1 (2%). The single patient with seizures was a 48-year-old female a history of epilepsy. Her most recent seizure had been 3 weeks prior to this overdose, which also involved sodium valproate and temazepam. One patient required intensive care and mechanical ventilation because of coma and respiratory depression following a mixed overdose including nitrazepam, thioridazine, zopiclone, and alcohol. Review of the ECGs from the 5 pure overdoses and 7 cases where there was no cardiotoxic substance co-ingested revealed 3 cases (25%) of non-specific ST segment or T wave changes but no episodes of QRS (>120 ms) or QTc interval prolongation (QTc <470 ms in females or 450 ms in males). All patients recovered and were discharged within 36 h of admission. During the period of study, prescribing of venlafaxine in primary care increased almost 3-fold. Conclusion: Significant clinical complications are uncommon following venlafaxine overdose and may result from co-ingested medication. In the absence of a past history, seizures appear unusual. Non-specific ST and T wave changes are frequently observed, but cardiac repolarization delay appears uncommon. References: [1]Fantaskey A, Burkhart K. A case report of venlafaxine toxicity. *J Toxicol Clin Toxicol* 1995;**33**:359–361. [2]Coorey A, Wenck D. Venlafaxine overdose. *Med J Aust* 1998;**168**:523. [3]Zhalkovsky B. Seizure activity and enzyme elevations after venlafaxine overdose. *J Clin Psychopharmacol* 1997;**17**:490–491. [4]Setzer S. Acute venlafaxine overdose—a multicentre study. *J Toxicol Clin Toxicol* 1995;**33**:496–497. [5] Banham N. Fatal venlafaxine overdose. *Med J Aust* 1998;**169**:445–448.

235. COMPARATIVE TOXICITY OF CITALOPRAM, VENLAFAXINE, MIRTAZAPINE, AND NEFAZADONE IN OVERDOSE

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Objective: Citalopram is thought to be more toxic than other selective serotonin re-uptake inhibitors after overdose. Our aim was to compare the toxicity of citalopram with the newer antidepressants venlafaxine, mirtazapine, and nefazadone after overdose. Methods: Retrospective review of patients admitted to a Clinical Toxicology unit over a 2-year period. Data collection included clinical variables (pulse, blood pressure, temperature, coma score), ECG features (QRS and QTc duration), and peak creatine kinase (CK). Complications were defined as CK >130 u/L, QTc ≥ 450 ms, development of seizures, arrhythmias, severe tremor, or the need for admission to a critical care facility. Results: Two hundred twenty-five admissions were reviewed (96 venlafaxine, 88 citalopram, 29 mirtazapine, 12 nefazadone). Demographic details were similar in all groups. Venlafaxine overdose was associated with a significantly higher pulse rate than the other antidepressants ($p < 0.0001$) but other clinical variables were not significantly different. Mirtazapine and nefazadone overdose did not result in any complications. QTc prolongation occurred in 13 citalopram and 10 venlafaxine patients ($p = 0.27$). No arrhythmias were documented. Fourteen citalopram and 22 venlafaxine patients had

CK > 130 u/L. These results were not significantly different ($p = 0.27$). Severe muscle tremor occurred in 8 venlafaxine patients but was not seen following citalopram overdose ($p = 0.007$). Seizures occurred in 5 citalopram and 8 venlafaxine patients ($p = 0.57$), and the need for admission to critical care was similar in both groups (2 citalopram and 8 venlafaxine; $p = 0.17$). Conclusion: Mirtazapine and nefazadone appeared to be safe in overdose with no complications occurring. Venlafaxine was associated with tachycardia, tremor, and a trend towards a higher creatine kinase. The incidence of QTc prolongation, seizures, and need for critical care admission was similar with both venlafaxine and citalopram. No arrhythmias were reported in this series.

236. ACCURACY OF DIAGNOSIS OF QRS INTERVAL PROLONGATION IN TRICYCLIC ANTIDEPRESSANT POISONING

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Objective: Prolongation of the QRS interval on the ECG predicts toxicity in patients with tricyclic antidepressant poisoning, including seizures (QRS > 0.10 s) and ventricular arrhythmias (QRS > 0.16 s)[1,2]. This study was performed to measure the frequency of QRS prolongation in an unselected series of patients with pure tricyclic antidepressant overdose, and to determine how often this is recognized by admitting medical staff. Methods: The study had ethical approval and included all patients with tricyclic antidepressant overdose presenting to Freeman Hospital in Newcastle between January 2000 and March 2001 when other substances, including alcohol, had not been taken. A reference group of healthy unmedicated volunteers were also studied. All ECGs were coded and then analyzed for RR interval, QRS duration, and QT interval using a digitizer and a previously validated program. At least 3 complexes were analyzed from each lead and a mean QRS durations and QT intervals calculated as the mean of all measured values. Results were then compared with the interpretation of the ECG by the admitting doctor as recorded in the medical records. Results: There were 42 patients with tricyclic overdose meeting the entry criteria (22 females and 20 males, age range 16 to 59 years) and 158 healthy volunteers. QRS prolongation of greater than 120 ms was present in 4 patients (9.5%) and 1 healthy volunteer (0.6%). In the patients, this was correctly diagnosed by the admitting doctor in 1 case, with the ECG recorded as being normal in the other 3. QRS prolongation was diagnosed in 3 patients by the admitting doctor when this was not present using the digitizer method. Conclusion: Although this study is small, it suggests that clinically significant QRS prolongation is often not recognized by medical staff admitting patients with tricyclic antidepressant poisoning. Improved training is required if this valuable predictive ECG sign is to be recognized when it is present. References:
[1]Boehnert MT, Lovejoy FH: Value of the QRS duration versus the drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985;**313:**474–479. [2]Liebelt EL, Francis PD, Woolf AD. ECG lead $_{A}V_{R}$ versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med* 1996;**28**:515–519.

237. EPIDEMIOLOGY OF CHILDHOOD POISONINGS IN THE YEARS 1996–2001

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Objective: Childhood poisoning remains a significant health problem in Slovakia. Every year children make up the majority of cases. To obtain more information about the nature of childhood poisoning we performed a retrospective analysis of all children treated for poisoning in the largest children's hospital in Slovakia during the last six years. Methods: Acute poisonings were analyzed for age, sex, intent of exposure (accidental or suicidal), substances ingested, and clinical severity. All intoxications were classified in accordance with the Poison Severity Score. Results: During the 6-year period a total of 24430 children were hospitalized in the study hospital, of which 820 (3.9%) were treated for acute poisoning. Over half (51.1%) of the cases were female. Accidental poisonings (41.9%) were more common than suicidal poisonings. The most frequently involved age groups were those younger than 5 years of age and those aged 16–18 years. Pharmaceuticals were most often ingested (40.7%), but also alcohol, chemicals, and other substances were

Table 1. Substances involved in childhood poisonings.

	Cases involved n (% total cases)
Pharmaceuticals	383 (46.7)
Alcohol	192 (23.4)
Chemicals	67 (8.1)
Plants	59 (7.2)
Pesticides	45 (5.4)
Drugs of abuse	34 (4.1)
Mushrooms	31 (3.7)
Others	9 (1.0)

involved (Table 1). On arrival 78.8% of patients had some symptoms. The majority of them developed only mild toxicity (57.2%), moderate symptoms occurred in 21.0%, and severe symptoms in 0.8% of all overdoses. Five cases (0.6%) resulted in death. Gastric lavage was performed in 20.2% of patients. In 92% of cases there was consultation with our Toxicological Information Centre (TIC). Conclusion: To prevent further increases in childhood poisonings TIC should serve as a lead agency in developing effective prevention guidelines for drug procedures, pharmaceutical distributors, and parents: use of child-resistant containers, proper storage, and disposal of toxic household products and drugs, checking the house and yard for poisonous plants and mushrooms.

238. CLINICAL COURSE AND DRUG LEVELS FOLLOWING CITALOPRAM OVERDOSE IN AN INFANT

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Objective: Citalopram is a selective serotonin reuptake inhibitor commonly prescribed for depression in Europe and the US that has been described to cause seizures and QRS widening with overdoses in adults. Despite the frequent use of this drug, its clinical effects and overdose pharmacokinetics in the pediatric patient are not well described. We describe the clinical course and drugs levels following an accidental ingestion of citalopram by a 10-month-old female. Case report: A 10-month-old female took an accidental overdose of an unknown amount of citalopram, which was prescribed for the infant's grandmother's use. Upon realizing the child had consumed the drug, the patient's mother digitally induced emesis with return of a few pill fragments. The child was brought immediately to the emergency department and was noted to be well appearing upon triage 15 minutes following the ingestion. While baseline labs were being obtained, the child experienced a generalized, tonic-clonic seizure that lasted 2–3 minutes, requiring 1 mg of midazolam IM. The child had a subsequent seizure, requiring a second mg of midazolam IM, and fosphenytoin was loaded at 20 mg/kg IV (200 mg). After a third seizure, the child was endotracheally intubated using succinylcholine 1.5 mg/kg IV (15 mg) and an additional 1 mg of midazolam IV. Despite the use of benzodiazepines and phosphenytoin, the child had a recurrence of a seizure approximately 85 minutes following the drug ingestion and 30 minutes following the phosphenytoin loading dose. Therefore, administration of activated charcoal via nasogastric tube, IV midazolam infusion, and IV phenobarbital loading were carried out. The child was transferred to a nearby facility with pediatric intensive care facilities in stable condition. The child did not suffer any cardiovascular compromise, hypotension, or dysrhythmia. The QTc and QRS complexes were normal throughout this child's course. During the subsequent 48 h, the child's recovery was uneventful, and she was discharged home without sequelae. Initial plasma level from 1 h after ingestion was 1400 ng/ml. Five, 12, and 22 h post-ingestion levels were 583 ng/ml, 416 ng/ml, and 296 ng/ml respectively. This first level likely represents a predistributional level. Subsequent levels give an elimination half-life of approximately 15–20 hours. Conclusion: We report a case of citalopram poisoning in a 10-month-old infant with refractory seizures and an absence of cardiovascular events with subsequent excellent outcome. The elimination of the parent drug corresponds to an approximate t1/2 of 15–20 h in this single case. To our knowledge this case report represents the youngest child with intentional overdose for which pharmacokinetic data is available.

239. APNEA AND ALTERED MENTAL STATUS AFTER INGESTION OF SUPER GLUE REMOVER: A NEW CULPRIT

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Objective: Delayed toxicity associated with ingestion of acetonitrile-containing cyanoacrylate remover led to the development of comparatively less toxic products, typically containing acetone or isopropyl alcohol. We present a case of significant toxicity from an unexpected source after pediatric ingestion of super glue remover. Case report: An otherwise healthy 9 kg 20-month-old girl was brought to a community emergency department approximately 1 h after ingesting an unknown quantity of super glue remover. Upon arrival, she was apneic, regaining spontaneous respiratory effort only after vigorous suctioning. She was also noted to be cyanotic and lethargic, with a heart rate varying between 100–140 beats per minute. Finger-stick blood sugar was 98 mg/dL (5.43 mmol/L). On supplemental oxygen, pulse oximetry was 100%. The patient was subsequently intubated for airway protection due to central nervous system depression. Initial serum bicarbonate following transfer to a pediatric intensive care unit, obtained 3 h after ingestion, was 22 mEq/L. Initial serum lactate, obtained 7 h after exposure, was 1.9 mEq/L. Acetone was undetectable. Symptoms resolved within 12 h of ingestion. Repeat serum bicarbonate and lactate levels the next morning were 25 mEq/L and 1.1 mEq/L, respectively. Neither the product nor the company were listed in Poisindex®. No ingredients were legible on the product's label. The container of super glue remover was subsequently sent to the regional poison control center for chemical analysis. GCMS analysis demonstrated the product to consist entirely of gamma butyrolactone (GBL). Information subsequently provided by the distributor confirmed the product to be 100% GBL. Conclusion: Previous experience with cyanoacrylate remover, including super glue and artificial nail remover, has indicated products to typically contain acetonitrile, isopropyl alcohol, or acetone. The current case of an apneic, unresponsive child who presented cyanotic, without metabolic acidosis or detectable acetone levels, suggested the presence of another agent. GBL is endogenously converted to gamma hydroxybutyrate (GHB), a GABA analog with profound central nervous system depressant effects. GBL/GHB intoxication should be considered in cases of CNS depression following cyanoacrylate remover.

240. GUIDELINES FOR PREDICTING TOXIC DOSES OF PHARMACEUTICALS IN CHILDREN

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Objective: British and German standards for non-reclosable child-resistant packaging for drugs stipulate that packs should prevent children from extracting more than 8 dose units. Our previous study[1] highlighted that there was little evidence to support this standard. This study aimed to assess the best method of predicting toxic doses of medication in children and to define how this may be used to improve the criteria for child-resistant packaging. Method: The study evaluated data from paediatric pharmacology and paediatric trials; methods for estimating paediatric doses and toxicity from adult data; product formulation factors which may affect toxicity; and clinical factors which may alter toxicity. Infants under 6 months were excluded from the assessment due to the physiological differences of this sub-population. The value of case reports as a source of safe and toxic doses in children was assessed. Guidelines for using clinical trials data and case reports to predict safe doses in children were prepared, and tested on old and new medicines. Results: The guidelines provided a method for deriving the maximum dose below which medical intervention is unlikely to be needed to treat toxicity—the No Treatment Dose from different sources, ranked in recommended order of use, based on their reliability: the Maximum Tolerated Dose determined in phase 1 trial; human case reports of exposure (from Poison Centres, published literature, mortality data); human case reports for structurally and pharmacologically similar drugs; the normal paediatric Single Treatment Dose (STD); the adult STD, extrapolated to children. The outcome from this procedure was a mg/kg dose from which the No Treatment Dose for a 6-month-old could be calculated and compared with the size of solid dose units to decide whether specific packaging is required. The test showed the process was logical and workable for old and new medicines. For example, when the No Treatment Dose was calculated for olanzepine and nifedipine it was clear that for most of the solid dose units, more than one would be potentially toxic to a 6-month-old. Conclusion: It is possible to predict the highest safe dose of a medicine in children using a logical assessment of the data,

but not the toxic dose. This predicted dose could be used to give an evidence-based approach to defining the packaging criteria of medicinal products to improve child safety. Reference: 1. Bara V, Bates N, Wiseman H et al. Toxicological criteria for the selection of non-reclosable child-resistant packages for pharmaceuticals (submitted to EAPCCT).

241. RETROSPECTIVE CHART REVIEW OF INFANTS WITH METHEMOGLOBINEMIA IN A LARGE URBAN HOSPITAL, 1990–2000

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Objectives: The purpose of this review was to 1) describe the demographic characteristics of infants with methemoglobinemia (MetHgb), 2) list presumed etiologic factors for MetHgb, and 3) serve as a starting point for a prospective study of diarrhea-induced MetHgb in infants. Methods: We conducted a retrospective chart review of infants (less than 6 months of age) with a diagnosis of MetHgb. The study period spanned from January 1, 1990 to December 31, 2000. A standard instrument was created to collect the information. Results: A total of 32 patients met the inclusion criteria. Of these patients, 22 were Hispanic (69%). Ages ranged from 1 day to 5 months (mean 1.3 months, SD $\pm$ 1.5). Methemoglobin levels ranged from 4 to 54% (mean 12.9, SD $\pm$ 12.0). Eleven patients received methylene blue to treat the MetHgb. Methemoglobinemia was most commonly attributed to diarrhea (44%), and medication administration (56%). Conclusions: This review suggests MetHgb is quite uncommon. Two important features are evident from the data: 1) One is that the majority of the patients were of Hispanic origin and 2) a significant proportion of the patients had diarrhea-induced MetHgb. Further studies are needed to identify risk factors and incidence of diarrhea-induced MetHgb in infants.

242. MEDICAL ERRORS IN CHILDREN: POISON CENTRE DATA

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Objective: To evaluate the data of a Poison Control Centre (PCC) in order to assess incidence and risk factors of medical errors (ME) due to drug administration in children. Methods: Retrospective-observational study on a seven month period from August 1996 to March 1997. We examined 632 call records to Milan PCC due to ME in patients aged 0–14 years. Therapeutic error has been defined according to NCC MERP Taxonomy of Medication Errors. We considered: product that was actually given, age of the patient, dose, dosage form, route of administration, setting of error, symptoms, place of treatment, therapy, outcome. Drugs were classified according to ATC, the severity score according to PSS. Results: The total number of calls to PCC in that period was 25642; the total number of paediatric cases were 11545 and 632 were due to ME (2.46% of total calls, 5.47% of paediatric calls). Products which were given were NSAIDs 22.9%, respiratory drugs 14.8%, antibiotics 12.8%, central nervous system drugs 8.7%. The 229 patients were 0–12 months old, of which 20.5% were infants aged 0–30 days. The twenty percent of the cases occurred in the second year of life while 15.9% of the cases were related to children older than five years. The wrong drug was given in 38.4% of cases, while in 49.3% the improper dose was administered, resulting in overdosage; 5.5% of the cases were due to a wrong route of administration. 13.7% of the patients complained of symptoms related to ME: 14.9% of them scored 2 while 4.5% scored 3. In 350 cases (55.3%) the calls were made by a physician (270 were calls from hospitals). In 308 cases (48.7%) hospital treatment was advised and the suggested treatments were the following: activated charcoal 145 cases (22.9%), antidotes 3.1%, symptomatic therapy 21.9%. No deaths or sequelae were reported. Conclusions: Calls to PCC due to ME show the relevance of this problem in paediatric patients. Risk factors are mainly related to 1) age of the patient: the first year, particularly the first month of life, 2) use of over-the-counter products such as NSAIDs. ME in hospitals, when drugs acting on cardiac and nervous system are used, may be the most dangerous. Further studies are needed to improve data collection by PCCs in order to develop prevention strategies. References: Medication Error Reports. United States Pharmacopeia. N 71, January, 2000. Dexter, EM; Michell, L; Casey PB *Poisoning Severity Score* Proceedings XVI EAPCCT Congress Vienna, Austria April 12, 1994.

243. CHILDHOOD POISONINGS IN ICELAND: A ONE-YEAR SURVEY OF TOXIC EXPOSURES IN CHILDREN UNDER SEVEN YEARS OF AGE

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Objective: To assess the rate and nature of toxic exposures in children 6 years and younger in Iceland over 1 year as well as to compare their prevalence to the prevalence in the rest of the population. Methods: The research period was from 1 April, 2001, to 31 March, 2002. A prospective study was carried out in every hospital and health center in the country, and data from the Icelandic Poison Information Centre was collected for the same period. Results: Six hundred and sixty-eight exposures were recorded. This corresponds to 2.3% of all Icelandic children in this age group, whereas the prevalence is 0.55% in the rest of the population. Seventy-three percent of them were under 3 years old. Two hundred and fifty-six (38%) of the cases involved were exposures to pharmaceuticals and 412 (62%) involved non-pharmaceuticals. Ingestion was the most common route of exposure (90%). The majority of the exposures (98%) were accidental. Sixty-one children (9%) received some kind of treatment in a health-care facility and 13 (2%) required hospitalization. The Poison Information Centre was consulted in 92% of cases either by parents or health-care professionals. Conclusions: The prevalence of toxic exposures seems to be at least four times higher in this age group as compared with the rest of the population. The majority of the exposures are minor and can be treated at home. The Poison Information Centre seems to be consulted in the majority of toxic exposures involving children in this age group.

244. THE FETAL EFFECTS OF IBUPROFEN OVERDOSE DURING PREGNANCY

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Objective: To assess the fetal effects of exposure to ibuprofen overdose in pregnancy. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) is a frequently used analgesic that is readily available over the counter. Concerns have been raised that therapeutic use of NSAIDs is associated with an increased risk of miscarriage and renal dysfunction. Although most acute overdoses are of low toxicity, few data exist on the potential fetotoxicity of ibuprofen overdose during pregnancy. Method: Using standardized procedures, NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 100 women who took ibuprofen in overdose during pregnancy. Results: The results are shown in Table 1. The majority of liveborn infants ($66/73 = 90.4\%$) had no congenital anomalies. No pattern of anomalies was observed. Multidrug overdoses in which ibuprofen was the major constituent were taken by 68%, mainly compound analgesics and cold remedies with 28% taking paracetamol. The majority (86%) of overdoses occurred in the first trimester with only 9 (9%) reports of any significant maternal toxicity including 1 mother who was unconscious.Conclusion: The incidence of miscarriages (9% Vs 10–20%) and terminations (18% Vs 23%) is within the expected range. However, the incidence of congenital anomalies is higher ($7/73 = 9.6\%$ Vs 2–3% expected), but two exposures were second trimester, and the numbers are small. Although no pattern of malformations was seen, three were cardiac anomalies. As congenital heart anomalies are common 0.5–1% it is not possible to establish a causal relationship

Table 1. Outcome of pregnancy following ibuprofen overdose.

Total number of overdoses (multi-drug)	Liveborn infants			Termination of pregnancy	
	Normal	Congenital anomalies	Neonatal problems	Miscarriage	Elective termination
Ibuprofen 32	23	2	2	1	4
Ibuprofen + paracetamol 10	6	2	1	1	
Ibuprofen + multidrugs 58	27	3	7	7	14
Total	56	7	10	9	18

with the drugs taken in overdose. No cases of renal dysfunction were seen. In the majority of women who receive appropriate treatment at the time of the overdose the outcome of pregnancy is a normal baby. Reference: McElhatton PR, Garbis H, Schaefer C. Poisons and overdoses. In: Drugs during pregnancy and lactation. Ed. Schaefer C. Elsevier 2001; pp 206–213.

245. CARBON MONOXIDE (CO) POISONING IN PREGNANCY

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Objective: To assess the fetotoxic effects of CO exposure in pregnancy. CO is readily absorbed in the lungs and transferred across the placenta into the fetal circulation where accumulation is 10–15 times greater than in maternal blood. Maternal exposure to 100 ppm of CO for 4 hours has been associated with miscarriages, intrauterine death, premature delivery, lower birth weight, neurological deficits, and dysgenesis in surviving infants. Although there have been a number of reports describing normal infants much less is known about acute exposures or chronic exposures to low concentrations. Methods: NTIS has provided fetal risk assessment and collected outcome data on a prospective case series of 131 women exposed to CO during pregnancy using standardized procedures. Results: There were 5 miscarriages, 8 elective terminations, and 118 liveborn infants including 5 with malformations and 6 with neonatal

Table 1. Malformations and neonatal problems.

Weeks of exposure	Malformations	Neonatal problems	Causality
0–10	Gastroschisis,and short bowel syndrome		Possible
13	Heart murmur		Possible
13–14	Suspected heart murmur, PDA		Possible
0–36	Torticollis		Possible
0–40	Small right eye, clubfoot, ankyloglossia, developmental delay		Possible
20		Jaundice	Unlikely
0–29		Jaundice	Unlikely
9–11		Viral meningitis	Unlikely
8		IUGR*	Unlikely
0–6		IUGR*	Unlikely
12–16		Premature, breech, jittery	Unlikely

problems (details are shown in Table 1). Severe toxicity occurred in 7 mothers, 34 mothers suffered moderate toxicity, and 90 were asymptomatic. Twenty-six mothers (19.8%) had long-term exposures (>2 weeks), 4 of whom were exposed throughout pregnancy, but there was no loss of consciousness. None had hyperbaric oxygen. Conclusion: The incidence of liveborn infants with malformations is higher than expected ($5/118 = 4.2\%$ Vs 2–3%), but no pattern of malformations was seen, and it is based on small numbers. The incidence of miscarriages (3.8% Vs 10–20%) and terminations (6.1% Vs 23%) is lower than expected. However, a causal relationship could not be excluded for six of the miscarriages because of the stage of exposure and association with maternal features. These findings are comparable with those reported in the literature. If there is prolonged severe maternal toxicity (comatose), there is an increased risk of poor fetal outcome. At subclinical levels (no loss of consciousness), despite the fetus being more sensitive to COHb, there is no good evidence that there is a clear clinical syndrome and fetal outcome is usually normal. Such acute exposures are not necessarily an indication for termination of pregnancy and no additional prenatal diagnostic tests are required. Reference: McElhatton PR, Garbis H, Schaefer C. Poisons and overdoses. In: Drugs during pregnancy and lactation. Ed. Schaefer C. Elsevier 2001; pp 206–213.

246. ACUTE IMIDAZOLINE DERIVATIVES EXPOSURE IN CHILDREN

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Background: The imidazoline derivatives are alpha2-adrenergic agonists with decongestant properties. Products containing these drugs have been widely used in Brazil as over-the-counter eye and nasal preparations. Although intoxication due to overdose or accidental exposure can result in central nervous system depression, diaphoresis, bradycardia and/or respiratory depression, mainly in children, few case series have been reported in this age group. We describe the outcome of 72 children under 15 years old after acute imidazoline derivatives exposure, followed by our service, from January 1994 to December, 1999. Case series: Seventy-two patients (ages 2 months–13 years, median 2 years), were followed 1 to 72 h after being exposed to naphazoline (N = 48), phenoxazoline (N = 18), oxymetazoline (N = 5) and tetrahydrozoline (N = 1), via oral (N = 46), nasal (N = 24), or unknown (N = 2). Fifty-seven children developed clinical manifestations such as somnolence (N = 34/57), sweating (N = 20/57), pallor (N = 17/57), hypothermia (N = 16/57), bradycardia (N = 13/57), cold extremities (N = 9/57), agitation (N = 7/57), tachycardia (N = 6/57), vomiting (N = 5/57), irregular respiratory pattern and apnea (N = 5/57), and miosis/mydriasis (N = 4/57). Naphazoline was the most frequently involved (N = 47/48), followed by phenoxazoline (N = 5/18) and oxymetazoline (N = 2/2). The onset of clinical manifestations was rapid, beginning within 2 h after exposure in 32/57 children. Only supportive measures were employed, with 1-year-old child needing mechanical ventilation after accidental naphazoline ingestion. In most of the children resolution of the symptoms occurred within 24 h (N = 39/57). No deaths were observed. Patients exposed to naphafazoline (N = 47/48) had a higher risk of developing poisoning in comparison with those exposed to phenoxazoline (N = 5/18) (Fisher's exact test, $p < 0.001$). There were no significant effects of route of exposure on clinical features [oral (N = 34/46), nasal (N = 21/24); chi-square test, $p = 0.31$]. Conclusions: The use of imidazoline derivatives, specially naphazoline, should be strongly avoided in young children, and these medications should be kept out of their reach.

247. ACUTE POISONINGS WITH MEMBRANE STABILISING AGENTS: ANALYSIS OF THE PREDICTIVE PARAMETERS OF NON-RESPONSIVENESS TO CONVENTIONAL THERAPIES

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Objectives: Acute self-poisoning with membrane stabilizing agents (MSA) (chloroquine, flecainide, tricyclic antidepressants, betablockers or cocaine) are rare but may lead to cardiac arrest or severe cardiovascular failure. Our objective was to identify in the severe poisonings, the predictive factors for failure of usual medical therapies. Methods: Retrospective study of patients admitted in our intensive care unit (ICU) during the last 5 years, in relation to severe acute self-intoxication with MSA and who received cathecholamines. Results were expressed as median [extremes]. Comparisons between groups of dead and surviving patients were done using Chi-2 and Mann–Whitney tests. Determination and validation (sensitivity and specificity) of the predictive criteria of death were calculated on this study population. Results: 137 patients were included (34 years [14–84], 95 F/42 H). 38/137 patients (28%) died, of whom 32

Intoxicant	Total number of patients	Number of dead patients	Mortality rate
Chloroquine	63	17	27%
Tricyclic antidepressant	40	11	28%
Betablockers	23	5	22%
Flecainide	8	4	50%
Cocaine	3	1	33%
Total	137	38	28%

within 72 h. 21% presented a pre-hospital cardiac arrest, which was persistent on hospital admission in 25% of the cases. During ICU stay, 12% of the patients presented an intra-hospital cardiac arrest.We considered these following parameters as predictive of death in ICU, in case of ingestion of an intoxicant with MSA: 1)- persistent cardiac arrest on admission or 2)- refractory shock (defined by the persistence of a systolic blood pressure <90 mmHg, despite adequate 1,000 mL fluid loading, 375 ml 8.4% bicarbonate infusion in <8 h and >3 mg/h adrenaline infusion), in relation with cardiac failure (confirmed by echocardiography or right cardiac catheterization), in the presence of signs of respiratory failure ($PaO_2/FiO_2 > 150$ mmHg under controlled mechanical ventilation and adequate sedation) or renal failure (diuresis < 20 mL/h or serum creatinine concentration >120 μmol/l). Taken together, these criteria allowed us to identify the patients who died in ICU with a sensitivity rate of 87% and a specificity rate of 97%. Conclusion: Death following acute self-intoxication with SMA is high and difficult to prevent. Characterization of the predictive parameters of resistance to the usual medical therapies should allow improvement of the strategies of symptomatic management and resuscitation. It may promote consideration of exceptional therapies such as extra-corporeal cardiovascular assistance, in experienced multidisciplinary centers.

248. BETABLOCKER POISONINGS: PROGNOSTIC VALUE OF PLASMA CONCENTRATIONS MEASURED ON ADMISSION

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Objectives: Betablocker poisoning is rare and toxicity is dominated by cardiovascular symptoms. The only recognized prognostic factors are the ingested dose, the co-ingestion of other cardio-active drugs and the stabilizing activity of the betablocker (propranolol, sotalol, and acebutolol). Recently, rapid determination of the betablocker plasma concentration has become available, but its usefulness is still not validated. The objective of our study was to evaluate the prognostic value of betablocker concentration on admission to ICU. Methods: We performed a retrospective study of the patients admitted to our ICU in relation with betablocker self-poisonings. Plasma betablocker concentrations were determined using HPLC (REMEDI automate, Bio-Rad). Results were expressed as median [extremes]. Sub-group comparisons were done using Mann–Whitney and Chi-square tests, correlation study using Spearman tests and toxicokinetic–toxicodynamic relationships by using Prism (GraphPad) software. Results: Twenty-eight patients were included in a 15-month-period: age 41 years [19–61], 6M/22F, baseline treatment with cardio-active drug (43%) and multi-drug intoxication (68%). Betablockers were: propranolol (46%), atenolol (21%), and sotalol (11%). Thirty-six percent of the patients were hypotensive, 18% bradycardic, and 11% comatose. On ECG, there was a PR prolongation (61%) and QRS (32%) and QT (18%) widening. Treatment included glucagon (54%) and/or catecholamines (61%). Twenty-nine percent were ventilated, 21% developed cardiovascular failure, and 7% died. There was no significant correlation between the betablocker concentration on admission and the blood pressure, heart rate on admission

	Concentration >10 N (N = 11)	Concentration ≤ 10 N (N = 17)	p
Propranolol + acebutolol	73%	53%	0.4
HR on admission (/min)	62 [50–88]	64 [48–90]	0.7
SBP on admission (mmHg)	105 [90–130]	100 [74–130]	0.4
PR on ECG (msec)	200 [160–280]	180 [140–280]	0.1
QRS on ECG (msec)	80 [60–120]	80 [60–120]	0.9
$QT_{measured}/QT_{theoric}$ on ECG	1.05 [0.86–1.19]	1.05 [0.93–1.25]	0.3
HR (/min)	57 [0–70]	53 [0–73]	0.6
Lowest SBP value (mmHg)	81 [0–107]	83 [0–111]	0.8
Antidote	73%	59%	0.7

(r = 0.053; $p = 0.79$ and r = 0.22; $p = 0.26$) and the lowest values (r = 0.12; $p = 0.57$ and r = 0.20; $p = 0.35$). The lack of any prognostic value for betablocker concentration may be explained by both interindividual variability and/or the effect of active metabolites that were not quantified. Conclusion: Plasma betablocker concentration measurement on admission is useful for the diagnosis, although our study did not find these useful in prognosis.

249. EFFECTS OF SINGLE INTRAVENOUS HIGH DOSES OF BUPRENORPHINE AND NORBUPRENORPHINE IN ASSOCIATION ON ARTERIAL BLOOD GASES IN RATS

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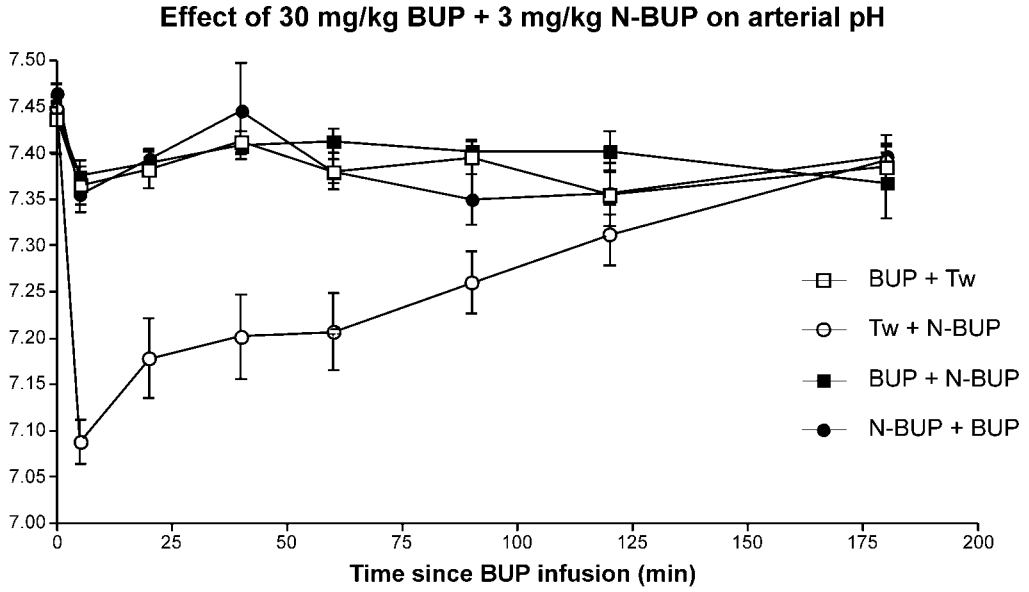
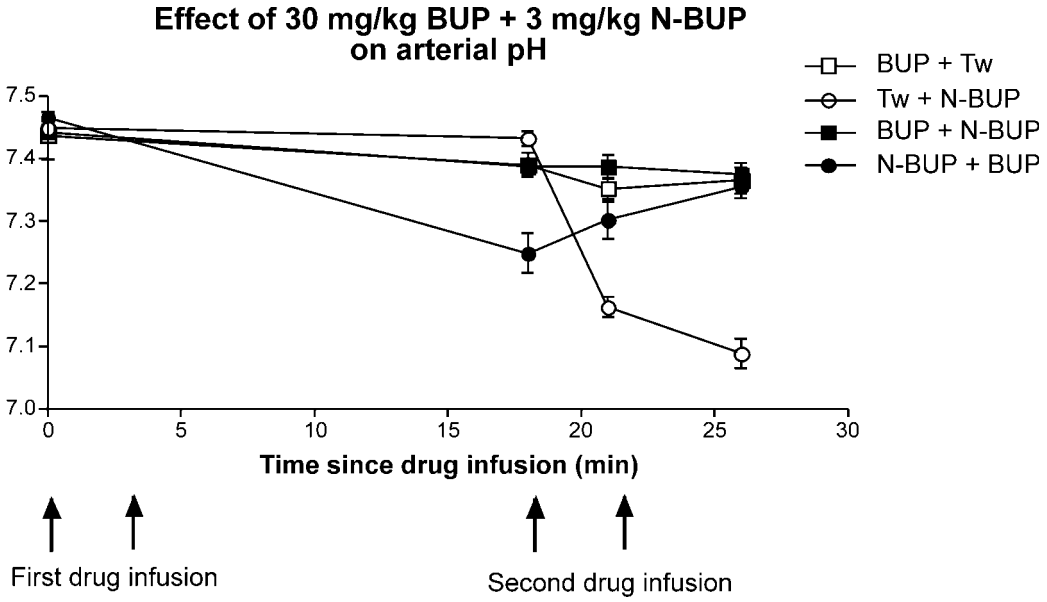
Objectives: High-dosage buprenorphine (BUP) is an efficient substitution treatment for opiate addiction, extensively prescribed in France since 1996. Despite its partial opiate agonist properties and its well-demonstrated ceiling effects, BUP may cause severe acute poisoning with coma and respiratory failure, in case of overdose, misuse, or association with benzodiazepines.[1] The mechanisms of BUP-related respiratory toxicity are still poorly understood. The role of norbuprenorphine (N-BUP), the main N-desalkylated BUP metabolite in BUP-associated respiratory effects is unknown. Our objective was to test the effects of the association of single high doses of BUP and N-BUP on ventilation in naive rats.



Methods: Catheterized restrained male Sprague–Dawley rats were randomized in four groups. The first group of rats received intravenously N-BUP (3 mg/kg) followed 15 min later by BUP (30 mg/kg), The second BUP (30 mg/kg) then N-BUP (3 mg/kg), the third BUP (30 mg/kg) then aqueous solvent and the fourth N-BUP (3 mg/kg) then aqueous solvent. Effects of treatments were analyzed using clinical parameters (scale of sedation and respiratory rate determination) and assessed by serial arterial blood gases obtained over 3 h (Radiometer ABL 300). Comparisons were performed using anova multiple comparison tests using Bonferroni's correction. Results: IV infusion of a single N-BUP dose was responsible of respiratory acidosis, whereas BUP infusion did not provoke any significant respiratory effect. There was a significant effect ($p < 0.001$) of combining BUP and flu on rat ventilation, with a decrease in pH and elevation in $paCO_2$ values, at all times of measurements following drug infusion. BUP significantly and rapidly reverses N-BUP induced respiratory acidosis. Administered 15 minutes before N-BUP, it also prevents its effects, in a dose-dependent manner.



Conclusion: BUP (30 mg/kg) protects or reverses N-BUP (3 mg/kg) induced respiratory effects. This interaction may play an important role in the pathogenesis of BUP toxicity and explain the importance of the mode of drug consumption in the mechanism of BUP-induced fatalities. Reference: Tracqui A. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol* 1998;**22**:430–434.

250. MERCURIC CHLORIDE NEPHROTOXICITY: AN ULTRASTRUCTURAL AND IMMUNOHISTOCHEMICAL STUDY IN THE RAT

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Objective: Acute renal failure secondary to nephrotoxic drugs is an important clinical problem associated with high mortality [1]. Mercuric chloride ($HgCl_2$) induces tubular injury both in experimental animals and in humans after only a single exposure [2]. "Stress proteins" are molecules (chaperones) that may protect the kidney against stressful conditions [3]. This study was designed to investigate the effects of $HgCl_2$ on the distribution of three stress proteins, HSP25, HSP60, and GRP75 in rat proximal tubules. Methods: Twenty-four Sprague–Dawley rats received different sublethal $HgCl_2$ doses, 1 mg/kg (T1 group) or 3.5 mg/kg (T3.5 group), or sterile saline (C) as control by a single i.p.injection. After 24 h, rats were killed and kidneys processed for electron microscopy and immunohistochemistry according to the ABC method. Morphometric analysis was also performed to quantify tubular atrophy and nucleolar changes between groups. Data were analyzed by ANOVA and Bonferroni's test. Results: Dose-dependent mitochondrial swelling, vacuolation, nuclear necrosis, and nucleolar segregation were observed. Table 1 shows data on 100 proximal tubules/group. In T1

Table 1. Effects of $HgCl_2$ in rat proximal tubules.

	C	T1	T3.5
Normal	86.6 ± 7.2	26.8 ± 5.3*	7.60 ± 3.1* +
Single cell damage	10.9 ± 4.6	45.9 ± 3.4*	23.1 ± 3.3* +
Focal atrophy	2.5 ± .08	14.5 ± 2.3*	39.9 ± 4.1* +
Extensive atrophy	0 ± 0	12.8 ± 2.2*	29.4 ± 4.2* +

Table 2. Nucleolar effects of $HgCl_2$ in rat proximal tubules.

	C	T1	T3.5
Segregation	3.5 ± .05	19.50 ± 1.91*	40.00 ± 1.63* +
Margination	27.50 ± 3.42	27.00 ± 5.03	39.50 ± 6.61* +

Data are means ± SD, *$p < 0.05$ vs C group; +$p < 0.05$ vs T1 group.

the damage was restricted to a single cell and focal atrophy was less than 15%. By contrast in T 3.5, focal atrophy increased to 40% and was extensive in about 30% of tubules. Two-hundred nucleoli/group were evaluated and in T1 nucleolar segregation was limited to about 10% but doubled in T3.5 where also margination was significant (Table 2). HSP25, HSP60, and GRP75 immunoreactions were moderate in control tubules, restricted to the brush border or basolateral side, respectively. After $HgCl_2$ exposure, all three proteins increased and changed their distribution. HSP25, a cytoskeletal chaperone, was detached from brush border and mainly perinuclear areas. HSP60 and GRP75, mitochondrial chaperones, were intense and scattered within the cytoplasm. Conclusion: $HgCl_2$ produces dose-dependent alterations in the rat proximal tubule and enhances specific renoprotective biomarkers. These data may be useful for toxicologists and assist understanding of the nephrotoxicity induced by a single mercury-exposure in vivo. References: 1. Lieberthal W. *Kidney Int* 1997;**52**:1102–1115. 2. Clarkson T. *Crit Rev Clin Lab Sci* 1997;**34**:369–403. 3. Beck F, Neuhofer W, Muller E. *Am J Physiol Renal Physiol* 2000;**279**:F203–F215.

251. NEUROTOXICITY OF THE GAMMA-HYDROXYBUTYRATE PRECURSOR, TETRAHYDROFURAN

Quang LS,[1,2] Vo T,[2] Hartman N,[2] Kalaria1H,[2] Werawattanachai1 N,[2] Shannon MW,[1,2] Maher TJ.[2] [1]*Division of Emergency Medicine/Department of Pediatrics, Children's Hospital Boston/Harvard Medical School, 300 Longwood Ave, Boston, MA 02115, USA;* [2]*Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, 179 Longwood Ave, Boston, MA 02115, USA.*

Objective: Gamma-hydroxybutyrate (GHB) remains a popular recreational drug of abuse in the U.S. However, since the regulation of illicit GHB as a federal schedule I drug in the U.S. in 2000, GHB has been substituted with several of its chemical precursors. In addition to gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), the most recent precursor to have appeared is tetrahydrofuran (THF). While two case reports of THF overdoses described coma, hypotonia, and respiratory depression, its toxicity as a GHB precursor relative to GBL, and 1,4-BD are unknown. The objectives of this study were to conduct dose–response evaluations of THF for neurotoxicity, calculate its Toxic Dose-50 (TD_{50}) for neurotoxicity, and compare its TD_{50} for neurotoxicity to those of GBL and 1,4-BD previously established in our laboratory. Methods: One hundred male CD-1 mice were administered THF 300–1000 mg/kg intraperitoneal (i.p.) and evaluated for neurotoxicity by the righting reflex and the rotarod test ($N = 10$ for each dose). The TD_{50} of THF (with 95% confidence intervals) for the righting reflex and rotarod test was calculated by the Litchfield-Wilcoxon Test (Pharmacologic Calculation System Version 4.2). The TD_{50} of THF for the righting reflex and rotarod test were then compared by the Z-statistic ($P < 0.05$) to those of GBL and 1,4-BD previously established in our laboratory. Results: The TD_{50} of THF for the righting reflex and rotarod test was 691.7 (587.2–814.8) mg/kg and 487.8 (436.9–544.6) mg/kg, respectively. These results for THF were statistically significant ($P < 0.05$) when compared to the righting reflex and rotarod TD_{50} of GBL [366.2 (273.6–490.2) and 99.0 (60.0–163.2) mg/kg, respectively] and 1,4-BD [567.4 (505.8–636.5) and 163.9 (153.5–175.0) mg/kg, respectively]. Furthermore, THF toxicity for the rotarod test was significantly reduced by the $GABA_B$ receptor antagonist SCH 50911(30 mg/kg i.p.), which we have also previously demonstrated in our laboratory with GBL and 1,4-BD. Conclusion: THF appears to be less neurotoxic than the GHB precursors GBL and 1,4-BD, as there was a significant rightward shift in the THF dose–response curves and higher TD_{50} compared to those of GBL and 1,4-BD. Furthermore, like GBL and 1,4-BD, THF neurotoxicity appears to be mediated by the $GABA_B$ receptor, which was reduced with the $GABA_B$ receptor antagonist SCH 50911. This research was supported by Orphan Medical, Inc. (Minnetonka, MN, USA), National Institute on Drug Abuse (NIDA) grant #

1RO3 DA15951-01, and National Institutes of Health (NIH) National Research Service Award (NRSA) # 1T32 HD40128-01.

252. A FAST AND SENSITIVE METHOD FOR GC–MS SCREENING IN ACUTE POISONING

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Objective: The diagnosis of acute intoxication needs a fast and reliable laboratory method supplying a validated report within 2 hours (*Hallbach 2001*). The most reliable technique today is still GC–MS analysis of blood and urine samples. In order to reduce the time required all analytical steps should be optimized. Therefore fast and appropriate derivatization methods should be used. *Maurer and Kraemer (1997)* accelerated the derivatization procedure by introducing brief microwave irradiation. Here a similar technique using an ultrasonic bath for acceleration of the derivatization steps was introduced. Methods: 2.5 mL of the urine sample were enzymatically hydrolyzed (56°C, 10 min) and then combined with further 2.5 mL unhydrolyzed urine. 1 mL of plasma (unprocessed) or 5 mL urine (processed) were extracted l/l (Toxilab A) and the extracts were dried with nitrogen. The residues were dissolved in 50 μl ethyl acetate and immediately analyzed on a 30 m DB 5-HT column (J&W) by GC–MS. After the first injection of each extract 15 μl MSTFA (N-methyl-N-trimethylsilyltrifluoracetamide) were added to the GC vial and incubation was performed in an ultrasonic bath for 3 minutes. Thereafter the derivatizated sample was analyzed under the same GC conditions. When the system is not actually used, a cleaning procedure automatically starts in a repeated sequence: 1 μl ethylacetate injected at 250°C and an end temperature of 300°C held for 18 min. Results: The total procedure (analyses of underivatisated and TMS-derivatizated extracts of plasma and urine) can be performed within 2 h using only one GC–MS apparatus. Crucial were the time for derivatization (3 vs. 30 min) and the improvement of the sensitivity by the use of a high-temperature GC column. The frequent use of cleaning runs at high temperature reduced the baseline signal noise, typically by a factor of 10 and allowed a very sensitive peak detection by the autointegrator. Therefore the full scan detection of substances like paracetamol, amphetamines, codeine and especially benzodiazepines (lorazepam, nordazepam, oxazepam, temazepam) was improved by both effects (ultrasonic derivatization and low baseline signal noise). Conclusions: The turnaround time was considerably reduced using a simple ultrasonic bath for derivatization. In combination with the use of a high-temperature column this new procedure provides a higher sensitivity and handling advantages compared with the use of standard columns and extraction procedures. References: Hallbach J, Külpmann WR, Maurer HH, Pragst F. Analytical strategies in the diagnosis of acute intoxications. *Clin Chem Lab Med* 2001; Spec. Suppl:73. Kraemer T, Weber AA, Maurer HH. Improvement of sample preparation for STA—Accelleration of acidic hydrolysis and derivatization procedures by microwave irridiation. *Proceedings of the Xth GTFCh Symposium in Mosbach 1997, Helm-Verlag, D-Heppenheim.*

253. INHIBITION OF CYTOCHROME P4502E1 PROTECTS PROXIMAL TUBULAR CELLS AGAINST OXIDANT STRESS

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Introduction: The generation of reactive oxygen species (ROS) has been implicated in the pathogenesis of renal ischemic reperfusion injury. The effects of oxidants stress in the activation of endogenous ROS generating system e.g., cytochrome P4502E1 (CYP2E1) remain unclear. The aim of this study was to investigate the effect of CYP2E1 inhibition on the cellular injury and death of renal proximal tubular cells (PT) exposed to H_2O_2. Methods: Porcine

	Control	H_2O_2	+CT	+DAS	+DSF
Cell viability (*% control*) ± SD (n = 6)	100	56.4 ± 2.6	91.7 ± 3.7	71.6 ± 4.4	70.1 ± 4.6
LDH (%) ± SD (n = 5)	3.5 ± 5.1	64.8 ± 19	13.6 ± 12	19.2 ± 4	21.7 ± 20
CYP2E1 activity ± SD (*mM/mg/min*) (n = 5)	2.19 ± 0.53	4.31 ± 0.58	2.59 ± 0.40	2.5 ± 0.51	2.46 ± 0.55

proximal tubular cells (LLC-PK1) were incubated with H_2O_2 (1 mM) in the presence or absence two CYP2E1 inhibitors (0.1 mM), diallyl sulfide (DAS), and Disulfiram (DSF) and 300 U/ml of catalase (CT). Cellular injury was determined using LDH release assay. CYP2E1 activity in LLC-PK1 was determined by conversion of *p*-nitrophenol to *p*-nitrocatechol.
Results: Exposure of LLC-PK1 to H_2O_2 significantly increased cell injury and death ($P < 0.001$). Catalase reduced cell injury and death in dose dependence manner ($P < 0.001$). Both inhibitors of CYP2E1 significantly reduced H_2O_2-mediated cell injury and death ($P < 0.001$). Incubation with H_2O_2 increased CYP2E1 activation in time and dose dependence manner that was significantly reduced by catalase, DAS and DSF ($P < 0.01$). Conclusion: We propose that CYP2E1 activation contributes to ROS-mediated injury of LLC-PK1 cells. Inhibition of CYP2E1 could be a novel approach in the prevention of ischemic reperfusion injury.

254. ACTIVATED CHARCOAL–YOGHURT MIXTURE IN A SIMULATED PARACETAMOL (ACETAMINOPHEN) OVERDOSE

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Objectives: Activated charcoal (AC) is used as primary gastric decontamination treatment for many poisonings. However, getting children to drink the recommended dose (1 g/kg) AC–water slurry is difficult. In these cases it would be valuable, if the charcoal was administered mixed differently than the recommended water slurry. The general recommendation is that AC should not be mixed with anything but water (1). An AC–yoghurt mixture is often successfully used in pediatric poisonings in some Nordic countries, but no in vivo investigations have been performed using the AC–yoghurt mixture. In vitro, yoghurt reduced the maximum adsorption capacity of paracetamol to AC by 15–17% ($p < 0.05$) compared to controls without yoghurt (2). Methods: A randomized crossover study on 15 volunteers, using paracetamol 50 mg/kg in 125 mg tablets (mean dose 3875 mg) as a simulated overdose. Each study day volunteers were given a standard meal 1 h before paracetamol, then AC 1 h later in two preparations: day A 50 g as AC–water slurry and day B 50 g AC-granules poured on top of 400 mL yoghurt. Paracetamol concentrations were measured using HPLC. The areas under the time–concentration curve (AUC) of the AC–yoghurt mixture preparation were compared to that of the 50 g AC–water slurry preparation (control) and used to estimate the efficacy of each preparation. The palatability of both preparations was evaluated using a visual-analogue scale (100 mm). The volunteers were asked

Table 1. Palatability evaluated on a visual-analogue scale (100 mm) and time (minutes) spent consuming the activated charcoal water slurry and activated charcoal–yoghurt mixture, median values [95% CI].

	Appearance	Smell	Flavor	Texture	Ability to swallow	Overall impression	Duration of administration
AC–water slurry	57 [45–73]	95 [91–97]	69 [51–84]	39 [27–55]	41 [21–60]	57 [47–69]	3 [2–6]
AC–yoghurt mixture	47 [25–62]	91 [86–94]	66 [51–77]	34 [20–43]	35 [24–47]	43 [29–55]	12 [7–19]

to evaluate the appearance, smell, flavor, texture, ability to swallow and overall impression of the mixture. The time spent consuming the AC was registered. Results: There was no significant difference ($p > 0.05$) in AUC between the AC-water slurry and the AC poured on top of yoghurt. Median values and 95% CI for the AUC's were (in mg/l*minutes): day A 6532(4569–8073) and day B 7082(5420–8744).
There were significant differences in overall impression ($p < 0.05$) and in duration of administration ($p < 0.02$).
Conclusion: The two AC preparations showed equal absorption reduction. Mixing AC with yoghurt rather than water did not improve the palatability in adults. References: (1) Jones A, Dargan P. *Churchill's Pocketbook of Toxicology.* Churchill Livingstone, London, 2001. (2) Hoegberg LCG et al. Effect of yoghurt on the adsorption of acetaminophen (paracetamol) to activated charcoal, simulated in vivo studies. (Abstract). 'EAPCCT, XXII International congress 22–25 May, 2002, Lisbon, Portugal.'

255. ECG ABNORMALITIES IN CO-PROXAMOL (PARACETAMOL/DEXTROPROPOXYPHENE) POISONING

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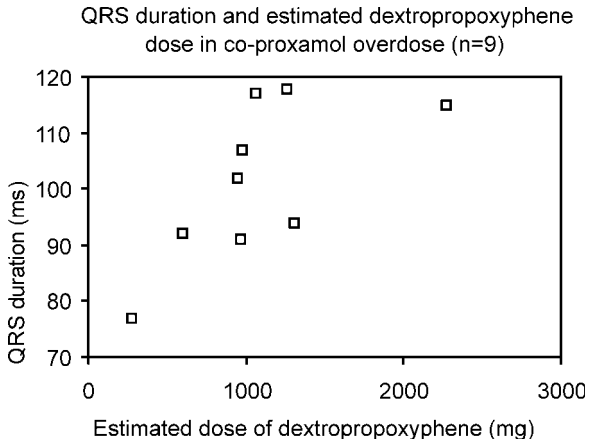
Objective: To describe the ECG changes following co-proxamol (paracetamol 325 mg, dextropropoxyphene [propoxyphene] 32.5 mg) overdose and to examine the relationship between estimated dextropropoxyphene dose and ECG changes. Background: Co-proxamol is a common cause of drug-induced death in the UK, and the most common product ingested among 1331 hospitalized patients in Royal Infirmary of Edinburgh (from July 2000 to July 2002) who took an opioid as part of their ingestion (co-proxamol cases 270, 23.3% of total). ECG changes following dextropropoxyphene ingestion have been reported in animals [1] and man [2], and changes reported in animals include PR, QRS, and QTc interval prolongation [3]. In man there are case reports indicating dextropropoxyphene causes widening of the QRS complex [4]. These findings are normally attributed to drugs that have actions on fast sodium channels. Methods: Hospital records for patients admitted to the Royal Infirmary of Edinburgh from July 2001 to July 2002 were retrospectively examined as a case series. Patients were included if they had an ECG in the first 24 h following exposure to co-proxamol. Patients who had co-ingested drugs known to cause cardiac conduction abnormalities were excluded. Nine eligible cases were identified in a preliminary analysis. Dextropropoxyphene ingested dose was estimated from paracetamol level at the time of presentation, using back extrapolation to time of ingestion and an estimated half-life of paracetamol of 2.5 h. Relationship between estimated dextropropoxyphene ingestion and ECG changes was examined. In patients who had more than



one ECG performed the maximum perturbation in ECG findings were used. The mean age of the 10 patients was 34.5 years (95% CI, 29.8 39.1). Mean interval between overdose and ECG 6.7 h (3.45–9.93) with a maximum of 19 h. In the patient group the mean PR interval was 181.8 (159.7–203.9) milliseconds. Mean QRS was 101.3 (91.8–110.8) milliseconds. QTc (Bazett's) was 427 (413.4–440.6) milliseconds. The calculated dextropropoxyphene dose was statistically significantly correlated with QRS duration ($r = 0.676$, $P = 0.045$). There was no significant correlation between PR or QTc in this group. Conclusions: QRS was significantly prolonged in co-proxamol overdose, this prolongation being statistically significantly correlated with estimated dextropropoxyphene dose. In this series none of the patients developed cardiological toxicity, but the findings support that hypothesis that dextropropoxyphene causes ECG abnormalities in man, and ECG findings correlate with overdose size. These findings have clinical relevance to the management of patients with co-proxamol poisoning. References: 1. Nickander et al. *Hum Toxicol* 1984;**3**(Suppl):13S–36S. 2. Whitcomb et al. *J Clin Invest* 1989;**84**:1629–1636. 3. Holland DR, Steinberg MI. *Toxicol Appl Pharmacol* 1979;**47**:123–133. 4. Stork et al. *J Toxicol Clin Toxicol* 1995;**33**:179–183. We would like to thank Mashhad University, Iran for financial support for R. Afshari.

256. HEXAFLUORINE® VERSUS STANDARD DECONTAMINATION TO REDUCE SYSTEMIC TOXICITY AFTER DERMAL EXPOSURE TO HYDROFLUORIC ACID

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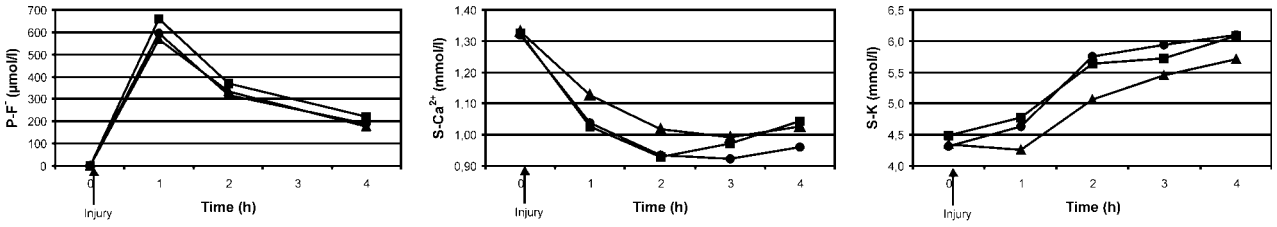
Objective: Dermal exposure to hydrofluoric acid (HF) may cause burns and systemic toxicity, i.e., fluoride intoxication, electrolyte disturbances, and arrhythmias. Hexafluorine® (Prevor, France) is a new product marketed as a sole decontamination liquid for HF skin exposure (1). The documentation of Hexafluorine is scanty and a recent study (2) indicates that its ability to reduce HF burns is at the most equal to water. The present study was performed to evaluate Hexafluorine's capacity in reducing HF-induced systemic toxicity. Methods: Sprague Dawley rats (300–325 g, n = 39) were anaesthetized, catheterized in the femoral artery and shaved on the back. A filter paper (35 × 60 mm) was soaked into 50% HF and applied on the back of each rat for three minutes. Thirty seconds after removal of the papers, the animals were randomly rinsed during 3 minutes with either 500 mL Hexafluorine (original rinsing equipment—group H, n = 13), 500 mL water (using the same rinsing equipment—group W, n = 13) or 500 mL water followed by a single application of 2.5% calcium gluconate gel (group Ca, n = 13). Blood samples were analyzed for S–Ca^{2+}, S–K (before injury and 1, 2, 3, and 4 h after) and P–F^- (1, 2, and 4 hours after injury). In a preceding pilot study, eight animals who received water rinsing had normal ionized fluoride values in plasma of < 2 μmol/l before the HF exposure and a P–F^- value > 600 μmol/l 1 h after ($p < 0.001$). One-way analysis of variance was used to evaluate differences between treatment groups. If $p < 0.05$, correction for multiple comparisons with Tukeys method was performed. The animal ethics committee approved the study. Results: Five animals died before completion of the experiment, one from group Ca and two from each of the other groups. The results of the P–F^-, S–Ca^{2+}, and S–K analyses are shown below:



● = group H, ■ = group W, ▲ = group Ca.

Significant difference was only reached at 1 h in S–K, between group W and group Ca. There was a trend toward milder hypocalcemia and hyperkalemia in group Ca compared to the other groups. Conclusion: In this model of HF toxicity hexafluorine was no more effective in reducing systemic toxicity caused by HF than standard decontamination. On the contrary, a consistent tendency toward poorer effect with Hexafluorine was observed. We consider that water rinsing followed by topical calcium should remain the standard decontamination for skin exposure to HF. References: 1. Mathieu L. Nehles J, Blomet J, Hall AH. *Vet Hum Toxicol* 2001;**43**:263–265. 2. Höjer J, Personne M, Hultén P, Ludwigs U. *J Toxicol Clin Toxicol* 2002;**40**:861–866.

257. EFFECTS OF SMOKING AND WOLLASTONITE INHALATION ON RESPIRATORY FUNCTION OF HEART AND LIVER MITOCHONDRIA IN RATS

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Objective: Cigarette smoking and chronic Wollastonite exposure have been implicated as a cause of morbidity and mortality from both neoplastic and nonneoplastic disease (Witschi et al., 1997; Hanke et al., 1984). This study evaluates the individual and combined effects of 6 months smoking and Wollastonite inhalation on respiratory function of heart

Table 1. Respiratory function of mitochondria after 6-months exposure to smoking and Wollastonite inhalation.

Wilcoxon test		Heart (n = 6)				Liver (n = 10)			
		C	W	S	W + S	C	W	S	W + S
RCR (S_3S_4)	K-Median	7.2	5.5**	5.4**	5.2**	6.4	4.5**	5.9	4.9
	25th percentile	6.7	4.6	5.3	4.6	5.1	4.0	5.4	4.7
	75th percentile	7.6	5.7	6.0	5.5	7.5	5.3	6.2	5.5
S_3 (nAtO mg prot^{-1} min^{-1})	Median	158.9	165.0	115.3*	95.1**	50.3	40.8*	48.3	51.2
	25th percentile	141.2	104.8	101.2	85.3	43.3	36.9	44.3	45.3
	75th percentile	197.5	176.6	133.8	104.1	51.5	45.8	55.0	59.6
OPR (nmol ATP mg prot^{-1} min^{-1})	Median	413.0	437.4	313.7*	250.8*	132.4	106.1*	125.0	134.5
	25th percentile	347.3	279.6	285.7	222.1	124.1	93.1	106.7	119.9
	75th percentile	522.8	461.7	355.4	272.7	137.7	120.6	144.9	165.2

and liver mitochondria in male Fisher 344 rats. Methods: "Kentucky" research cigarettes and commercially available Wollastonite ($CaSiO_3$) dust were used. Mitochondrial function was measured polarographically by oxygen consumption using a Clark electrode and NAD glutamate as substrate. Results: The parameters of mitochondrial respiratory function are shown in Table 1. In heart mitochondria, all groups showed significant decrease of respiratory control ratio (RCR) in comparison to control. State 3 oxygen consumption (S_3) and ATP formation (OPR) were significantly inhibited with smoking and much more with synergistic exposure to Wollastonite. In liver mitochondria, RCR was significantly inhibited with Wollastonite exposure, but less with combined exposure to Wollastonite and smoking. State 3 oxygen consumption and ATP production were inhibited in Wollastonite exposure only. Conclusions: In this study, the heart was found to be a target organ of smoking. The inhibitory effect of smoking on mitochondrial function was enhanced with Wollastonite inhalation. In contrast, the liver was found to be a target organ of Wollastonite inhalation. The inhibitory effects of Wollastonite on mitochondrial function were eliminated by concomitant smoking. References: Witschi H, Joad JP, Pinkerton KE. The toxicology of environmental tobacco smoke. *Ann Rev Pharmacol* 1997;**37**:29–52. Hanke W, Sepulveda MJ, Watson A, Jankovic J. Respiratory morbidity in Wollastonite workers. *Br J Ind Med* 1984;**41**:474/479. Technical assistance: Butasova L.

258. HEXAFLUORINE® SKIN DECONTAMINATION OF 49% HYDROFLUORIC ACID: PRELIMINARY STUDY IN AN IMMATURE DOMESTIC PIG

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Objective: To determine a 49% hydrofluoric acid (HF) skin exposure period that will allow sufficient time to intervene with decontamination before a visible skin lesion develops. Also, to evaluate and compare the efficacy of Hexafluorine skin decontamination to that of tap water when both are delivered similarly at 500 mL over 3 minutes following exposure to 49% HF at specified times. Methods: This study was approved by the Animal Use Committee and used 12 separate sites on the shaved and depilated back of an anesthetized 16.3 kg immature domestic pig. Each test skin site was exposed to 400 μL of 49% HF using a 25 mm Hill Top Chamber. HF exposure times, delay times to decontamination, and type of decontamination are listed below. Endpoints: subjective skin reaction scores (standard Draize scale) and digital photographs taken before HF exposure, after HF exposure, and at each post-decontamination observation point (2 minutes–4 hours). Results: All HF-exposed skin sites with no decontamination developed severe HF burns. For HF-exposed skin sites receiving decontamination, those treated with Hexafluorine resulted in less severe burns than those treated with tap water, but tap water resulted in less severe burns than no decontamination. Efficacy (reducing the extent of HF burns) was best demonstrated when skin was exposed to 49% HF for 10 seconds followed by decontamination with Hexafluorine after a 30-second delay. Conclusion: Based on dermal scoring and visual observations, this preliminary study using an immature pig model demonstrated decontamination with Hexafluorine was more efficacious than tap water for decreasing the severity of burns produced by dermal contact with 49% HF. Further studies are planned

Site number	HF exposure time (seconds)	Delay to decontamination (seconds)	Type of decontamination
1	30	N/A	None
2	15	N/A	None
3	10	N/A	None
4	5	N/A	None
5	10	60	Tap water
6	10	60	Hexafluorine
7	5	N/A	None
8	5	10	Tap water
9	5	10	Hexafluorine
10	10	N/A	None
11	10	30	Tap water
12	10	30	Hexafluorine

to evaluate and compare the effect of longer decontamination delay times on the relative efficacy of Hexafluorine and tap water following 10-second exposures to 49% HF.

259. A COMPARISON OF PARACETAMOL CONCENTRATIONS MEASURED IN PLASMA AND SALIVA IN OVERDOSE

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Background: Measurement of paracetamol concentration in plasma is carried out routinely in paracetamol overdose. Paracetamol concentration can also be measured in saliva.[1] Objective: In order to assess whether paracetamol concentrations measured in saliva are similar to those in plasma following paracetamol overdose, we compared the concentration of paracetamol measured in plasma and saliva samples taken concurrently in patients presenting with acute paracetamol poisoning. Methods: Fifty-seven patients (age 16-80 years) admitted to our unit following an overdose of paracetamol or paracetamol containing products within the previous 24 h were recruited to the study. All patients consented verbally to participate in the study, which had local ethics committee approval. A saliva sample was collected using the salivette system (Starstedt Ltd) at the same time as the plasma paracetamol sample. Paracetamol concentrations were measured by HPLC. Data are expressed as mean ± SEM, with confidence intervals for paracetamol

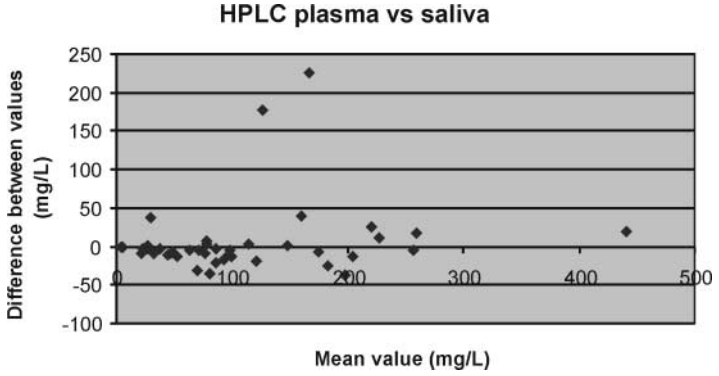

Figure 1.

concentrations. The correlation between plasma and saliva measurements was calculated and agreement between the methods plotted as the mean paracetamol concentration against the difference between the measurements (Fig. 1). Results: Sixteen patients were excluded from the study analysis [plasma paracetamol concentrations were not detected ($n = 4$); insufficient saliva or plasma obtained for assay ($n = 12$)] and 41 patients (age 27 ± 2 yrs) were included. Paracetamol concentrations in plasma and saliva were similar in the study group [110.2 (100.3–120.1) mg/L vs 112.1 (102.1–122.1) mg/L; $r = 0.86$] (Fig. 1). However, there were 2 cases where the paracetamol concentration was markedly higher in saliva than plasma (38 vs. 216 mg/L and 53 vs. 279 mg/L). Summary: There appears to be agreement between the measurement of paracetamol concentrations in plasma and saliva. However, in at least 2 patients in our study, the paracetamol concentration was five fold higher in saliva than in plasma. The high salivary concentrations in these patients may reflect paracetamol product fragments in the mouth, either as a result of vomiting or where tablets may have been crushed or chewed. Conclusion: The measurement of paracetamol concentrations in saliva may provide a useful tool in assessing the kinetics of paracetamol following overdose. However, we have not shown sufficient agreement between plasma and saliva measurements of paracetamol concentrations to support replacement of plasma measurements with saliva measurement in the clinical setting. References: [1]Kamali F et al. Salivary secretion of paracetamol in man. *J Pharm Pharmacol* 1987;**39**:150–152.