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1 EFFECTS OF POISONS ON THE AUTONOMIC NERVOUS SYSTEM

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The autonomic nervous system is divided into three anatomical divisions: sympathetic, parasympathetic and enteric nervous systems. The enteric nervous system receives inputs for sympathetic and parasympathetic systems and is unable to act independently. The autonomic nervous system controls smooth muscle activity (visceral and vascular), the rate and force of cardiac contraction and a variety of metabolic, endocrine and exocrine processes. The principal neurotransmitters are acetylcholine and noradrenaline. Preganglionic neurons are cholinergic. Ganglionic transmission occurs via nicotinic acetylcholine receptors, although excitatory muscarinic acetylcholine receptors are also present on post-ganglionic cells. Post-ganglionic parasympathetic neurons are cholinergic while most post-ganglionic sympathetic neurons are noradrenergic and a few are cholinergic (e.g. sweat glands). Acetylcholine receptors are sub-divided into nicotinic (nAChR) and muscarinic (mAChR) subtypes. nAChR mediate fast excitatory synaptic transmission at the neuromuscular junction, autonomic ganglia and at a number of sites within the central nervous system. mAChR mediate acetylcholine effects at post-ganglionic parasympathetic synapses (mainly the heart, smooth muscle and endocrine glands) and contribute to ganglionic excitation. All mAChR (M_1, M_2, M_3) are activated by acetylcholine and blocked by atropine. Adrenoceptors are divided into α and β subtypes. There are two main α adrenoceptor subtypes (α_1, α_2), and three β subtypes (β_1, β_2, β_3). Activation of α_1 receptors produces vasoconstriction, relaxation of gastrointestinal smooth and increased salivary secretion. α_2 receptors are inhibitory for neurotransmitter release at autonomic nerve endings, platelet aggregation and contraction of vascular smooth muscle. β_1 stimulation increases the rate and force of cardiac contraction, β_2 activation produces bronchodilatation, vasodilatation, relaxation of visceral smooth muscle and muscle tremor while β_3 receptor stimulation increases lipolysis. Cholinomimetic agents: Cholinomimetic agents are divided into those which are direct acting and those which are indirect acting. Direct acting agents bind to and activate the muscarinic and/or nicotinic receptors while indirect acting agents inhibit acetylcholinesterase which hydrolyses acetylcholine. As a result the concentration of acetylcholine in the synaptic clefts and neuroeffector junctions increases and stimulates the cholinoreceptors. Examples are given in the Table. Effects of overdose: Poisoning with most direct acting cholinomimetics produce symptoms within 30 to 60 minutes of drug ingestion. Common symptoms include salivation, lacrimation, nausea, vomiting, headache, visual disturbances, diarrhea, bradycardia and hypotension. Similar effects can be seen with organophosphate and carbamate insecticides. Bradycardia, hypotension and syncope are more common with organophosphate intoxication. Management: Atropine is the mainstay of management for direct and indirect acting agents but the doses required to produce symptomatic benefit tend to be higher for acetylcholinesterase inhibitors. Pralidoxime is a specific antidote for acute organophosphate poisoning which acts to regenerate enzyme activity. It is most effective when given within the first 24 hours after exposure but later administration may be effective for overdose with highly lipid soluble compounds. Symptomatic therapies include diazepam for convulsions, salbutamol for bronchospasm and oxygen with assisted ventilation for pulmonary edema. Antimuscarinic agents: Examples of drugs which have antimuscarinic activity are listed in the Table. Effects of overdose: These compounds competitively antagonize the effects of acetylcholine at the receptor producing a variety of well described unopposed sympathetic effects—'red as a beet', 'dry as a bone', 'blind as a bat', 'hot as a hare' and 'mad as a wet hen'. Other effects include hypotension, widening of the QRS complex, arrhythmias, urinary retention, hallucinations and muscle paralysis. Management: Treatment is largely supportive and symptomatic—adequate ventilation, propranolol for tachycardia, bicarbonate for the tachyarrythmias and diazepam for convulsions. Physostigmine is used occasionally for tertiary amines, e.g. atropine, hyoscine and H_1 antihistamines when causing hyperthermia, delirium and symptomatic tachycardia but is best avoided in tricyclic

overdosage as it can cause atrioventricular block, asystole, bronchospasm and seizures. Sympathomimetic agents: Direct and indirect acting sympathomimetics are listed in the Table. Effects of overdose: Sympathetic agents represent a number of compounds with varying selectivity for alpha and beta receptors. Some act directly on adrenoceptors, some increase catecholamines at the nerve endings and some act by both mechanisms. Most increase blood pressure and predispose to headache, confusion, seizures, coma and intracerebral hemorrhage. Methylxanthines and alpha$_2$ agonists cause hypotension. Heart rate also tends to increase except for those compounds which stimulate the alpha receptor when heart rate declines by stimulation of the baroreceptor mechanism. A variety of indirect acting agents have important central effects such as anxiety, restlessness, agitation, talkativeness and euphoria. In addition, amphetamines and cocaine cause tremor, fasciculation, rigidity, cerebral vasculitis, myocardial ischaemia, infarction and hyperthermia. Other serious consequences include rhabdomyolysis, myoglobinuria, renal failure and brain damage. Management: Treatment is largely supportive; cold packs for hyperthermia, beta blockade for tachycardia and hypertension, intravenous diazepam for convulsions and nitrates for angina. Sympatholytics: Only overdoses with beta adrenoceptor antagonists represent a significant clinical problem. Examples are listed in the Table. Effects of overdose: The main cardiovascular effects are hypotension, sinus bradycardia and heart block. Central nervous system effects include convulsions, apnea and coma. Management: At present glucagon is the beta agonist of first choice to reverse the cardiovascular complications but other measures include atropine to increase heart rate, pacing and balloon pumps to improve cardiac output and symptomatic treatment with diazepam for convulsions and salbutamol for bronchospasm.

Examples of agents which affect the autonomic nervous system

Parasympathetic		**Sympathetic**	
Cholinomimetics	**Antimuscarinics**	**Sympathomimetics**	**Sympatholytics**
Direct	Direct	Direct	Direct
Amanita muscaria	Atropine	Adrenaline ($\alpha\beta$)	Labetalol ($\alpha\beta$)
Beletus	Hyoscine	Phenylephrine (α_1)	Prazosin (α_1)
Clitocybe	Tricyclic antidepressants	Clonidine (α_2)	Yohimbine (α_2)
Inocybe	H_1 antihistamines	Isoprenaline (β)	Propranolol (β)
Betel nuts	Phenothiazines	Dobutamine (β_1)	Atenolol (β_1)
	Class 1A antiarrhythmics	Salbutamol (β_2)	ICI 118551 (β_2)
	Belladonna alkaloids		
Indirect	Indirect	Indirect	Indirect
Organophosphates		Tricyclic antidepressants	Reserpine
Carbamates		Cocaine	Adrenergic neuron blockers
Nerve gas		Amphetamines	
Drugs for myasthenia gravis		Ephedrine	
		MAO inhibitors	

2 EFFECTS OF POISONS ON ION CHANNELS

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The concept and role of ion channels: The cell membrane constitutes a bilayer boundary of phospholipid molecules which is non-permeable to ions and water. Therefore, cell membranes exhibit a selective permeability to ions which is responsible for creating an electrical potential across the membrane. Proteins embedded in the phospholipid bilayer and spanning the entire bilayer can serve as ion channels by providing a hydrophilic environment. The different protein or phospholipoprotein channels are selective, favoring the passage of one ion over another. Moreover, for each ion (Na^+, Ca^{++}, K^+ or Cl^-) there are different types of channels with specific roles. In addition to the channels, other protein complexes serve as a major supplementary transport system through the cell membrane and provide for neutral exchange

of some ions and small organic molecules along their concentration gradient (passive ion transport: Na^+-Ca^{++} or Na^+-H^+ exchanges) and for transporting ions against their electrochemical energy gradient (active transport: Na^+-K^+ ATPase or Ca^{++} ATPase). Some protein complexes penetrate only the outer cell membrane and may serve as receptor sites for neurotransmitters and hormones, while others, such as the adenylate cyclase system, protrude through the inner cell membrane and may be involved in various enzymatic activities. When ion channels are opened, ions cross the cell membrane according to their concentration gradient. Physiologically, Na^+ and Ca^{++} tend to enter the cell generating an inflow current which induces membrane depolarization. Conversely, K^+ tends to go out the cell generating an outward current resulting in hyperpolarisation or repolarisation. The ion transfer across the channels is regulated. The opening of the channel is activated either by changes in membrane polarity (voltage operated channels or VOC) or by the binding of an appropriate ligand on its receptor (receptor operated channel or ROC). The opening and closing of the channel are regulated by a 'gating mechanism' including 2 gates, m and h, which are influenced by the electrical field and time. During each action potential, membrane channels cycle through 3 states: closed resting, open and closed inactive. The membrane proteins appear to be responsible for most of the known biological activities of membranes. Ion movements and action potential: Ion movements across the cell membrane generate electrical currents which are responsible for the electrical activity (action potential) of the cell. Depolarization occurs when positively charged Na^+ and Ca^{++} ions enter the cytosol to generate inward ionic currents. Repolarisation occurs when outward currents, largely due to K^+ efflux and possibly also to inward movements of Cl^- ions, restore the membrane potential to its resting level of electronegativity. For contractile cells, such as myocardial cells and smooth muscle cells, the changes of cytosolic Ca^{++} concentration determine the cycles of contraction (increase of Ca^{++}) and relaxation (decrease of Ca^{++}). Myocardial cells contain only Ca^{++} VOC. These channels are also regulated by G proteins and can be activated by isoprenaline either directly by binding (direct G-protein pathway) or indirectly (phosphorylation pathway) by activating adenylate cyclase. In smooth muscle cells, Ca^{++} can enter into the cytosol either through VOC or ROC, the latter being activated by alpha-mimetic drugs (noradrenaline). Ion channels as targets of toxicity: Numerous drugs or poisons exert their action by an effect on ion channels. The target organs of poisons blocking fast Na^+ channels are myocardial contractile cells and CNS cells. These poisons have a membrane stabilizing effect and include local anesthetics (xylocaine, lidocaine), class I antiarrhythmics, some beta-blockers, tricyclic antidepressants, chloroquine, tetrodotoxin, carbamazepine, amiloride and barbiturates. The target organs of poisons blocking the slow Ca^{++} channels are the cells or tissues whose activities are dependent on the influx of Ca^{++}, namely myocardial contractile cells, vascular smooth muscle cells and the sinoatrial and atrioventricular nodes. These drugs include the class IV antiarrhythmics: verapamil, diltiazem, dihydropyridines. Blockers of K^+ channels include the class III antiarrhythmics (amiodarone) and sulfonylureas. Some drugs act by activating channels: barbiturates and benzodiazepines activate Cl^- channels, the alpha-mimetic drugs activate the Ca^{++} ROC and beta-mimetic drugs activate the Ca^{++} VOC. Toxic effects: Despite the complexity of the mechanisms involved, most of the electrophysiological, pharmacological and toxic effects of these poisons can be explained by their action on ion channels. Blockade of the fast Na^+ channels results in decreased automaticity, conduction and contractility, favoring the occurrence of ventricular dysrhythmias by a reentry mechanism. Other effects such as an anticholinergic, beta blocking or alphalytic effects are specific to the drugs and not related to an action on the ion channels. The blockade of slow Ca^{++} channels results in reduced contractility and conduction, with a decrease in blood pressure and cardiac output and marked vasodilation. Blockade of K^+ channels results in bradycardia with prolongation of repolarisation and an increase in the duration of the QT interval. Therapeutic issues: From a theoretical point of view, two strategic options can be used in order to counteract the blockade of ion flow through the channel. The first option is to increase the ion concentration gradient in order to force the influx of the ion into the cell. In this way, hypertonic Na^+ salts may reverse some toxic effects, especially cardiac conduction disturbances, in poisonings with Na^+ channel blockers and Ca^{++} salts may reverse some toxic effects of Ca^{++} channel blockers. However, these effects are often inconstant and transient. The second option is to promote cell contraction by increasing the intracellular Ca^{++} concentration through other pathways. For cells with VOC, the opening of Ca^{++} channels can be stimulated by the phosphorylation of membrane proteins. This pathway uses adenylate cyclase which acts according to the following sequence: adenylate cyclase transforms ATP into cAMP which activates a protein kinase which induces membrane protein phosphorylation. Beta-mimetic drugs and glucagon stimulate adenylate cyclase. Phosphodiesterase inhibitors act by decreasing the breakdown of cAMP. For cells with ROC, the influx of Ca^{++} can be increased directly by the stimulation of the channels opening by alpha-mimetic drugs. Conclusion: Many poisons act on ion flow through ion channels. These effects account for the symptoms and explain the therapeutic options which may be used in order to reverse the toxic effects.

3 ROLE OF INDIRECT FACTORS IN POISON-INDUCED CARDIOVASCULAR DISTURBANCES

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Introduction: Cardiovascular disorders following acute poisoning may be caused by several factors. Their prompt recognition is mandatory as it can probably influence outcome. Direct factors are related mainly to adverse effects of some toxic substances on cardiac contractility, cardiac conduction or on vascular tone. Numerous indirect factors can also be identified. Hypoxia: The central role of hypoxia is illustrated by the severity of the cardiovascular disturbances observed after cyanide or carbon monoxide exposure. Acute respiratory failure may also lead to progressive hypoxia through central hypoventilation, pneumonia or noncardiogenic pulmonary edema. In many instances, hypoxia will further aggravate cardiac dysrhythmias or cardiovascular collapse. Neurological disorders: The influence of neurological disorders has been studied less frequently. They are often in close correlation with respiratory depression. The relationship between the severity of CNS manifestations (seizures) and cardiotoxicity has been documented for tricyclic antidepressants. In the most severe forms of intoxication, brain edema or hemorrhage (e.g. methanol) may lead to brain death and irreversible cardiocirculatory collapse. Thermoregulation: Problems of thermoregulation also interfere with the cardiovascular system. Hypothermia is frequent following ethanol or psychotropic drugs abuse and is a leading cause of cardiac arrhythmias or collapse which could occur during rewarming. More recently, the importance of hyperthermia has been recognized after evidence of cardiovascular failure following heat stroke, neuroleptic malignant syndrome, exposure to psychoactive substances (e.g. cocaine, ecstasy) or recent antidepressant drugs (serotonin syndrome). Hypovolemia: Hypovolemia is another possible reason for cardiovascular impairment. While hemorrhagic shock remains exceptional, gastrointestinal fluid losses (e.g. colchicine, mushroom poisoning) may contribute to hypotension. Septic shock is also unusual and would occur after some delay. Metabolic and ionic changes: These changes have also to be taken into account. The severity of metabolic acidosis (e.g. lactic acidosis with metformin, formic acidosis with methanol) may influence cardiac dysfunction. Hypokalaemia and hyperkalemia are the most life-threatening ionic disorders. They may be caused by specific mechanisms (redistribution) which have to be correctly diagnosed and treated. Conclusion: The role of indirect factors in poison-related cardiovascular disturbances perfectly illustrates that acute poisoning is a general disorder with multisystem consequences.

4 POISON-INDUCED ARRHYTHMIAS: MECHANISMS, DIAGNOSIS AND MANAGEMENT

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Background: Cardiac arrhythmias are an important cause of mortality in poisoned patients. It is of particular concern that serious arrhythmias can develop very rapidly and that patients may die without prompt and appropriate medical intervention. Classification:: Arrhythmias can be classified as slow (bradyarrhythmias) or fast (tachyarrythmias). Bradyarrhythmias: These include sinus bradycardia and nodal rhythms as well as all degrees of heart block. The most common toxic causes are beta-blockers, calcium channel blockers and cardiac glycosides. Cyanide and organophosphates are less common causes. Mechanisms include direct inhibition of the positive chronotropic effects of noradrenaline (beta blockers), reduced conduction velocity in the sinus node and AV node due to delayed calcium entry (calcium channel blockers) and increased cholinergic effect at the level of the AV node (digoxin, organophosphates). Bradycardias may not need specific treatment provided the cardiac output is adequate to maintain tissue perfusion and renal function. Non-specific treatment with adequate doses of intravenous atropine or isoproterenol is often effective. Occasionally, temporary transvenous ventricular pacing is required. Specific therapy is sometimes appropriate, e.g. glucagon for beta-blockade poisoning, digoxin-specific F(ab) antibody fragments (Digibind®) for digoxin poisoning or calcium gluconate for poisoning with calcium channel blockers. Tachyarrhythmias: These are more difficult to diagnose and treat. Supraventricular tachycardias: These may be caused by a wide range of agents including amphetamines and related compounds (including ecstasy), other sympathomimetic amines (e.g. phenylpropanolamine), anticholinergic drugs, beta agonists (e.g. salbutamol) and phosphodiesterase inhibitors such as theophylline. Supraventricular tachycardia is characterized on the 12 lead ECG by narrow QRS complexes with normal morphology, unless there is aberrant conduction. Drug-induced supraventricular tachycardia generally carries a good prognosis and often does not need specific treatment. However, use of carotid sinus massage or other physical treatments to increase vagal tone may be useful. If these fail and the patient has features of impaired cardiac output, beta-blockers or calcium channel blockers can be employed, although these may contribute to toxicity. In extreme cases, supraventricular tachycardia may respond to DC cardiover-

sion or the intravenous administration of adenosine. Ventricular tachycardia: This is the most serious manifestation of poisoning with cardiotoxic drugs. There are three major causes. The first is impaired conduction velocity in the bundle of His because of sodium channel blockade. Agents that commonly cause this include class I anti-arrhythmic agents (e.g. quinidine, lignocaine, and flecainide) and tricyclic antidepressants. It may also occur with very high doses of antipsychotic drugs, opioids (particularly dextropropoxyphene), barbiturates, and those beta- blockers that have membrane stabilizing activity. Severe sodium channel blockade is manifest on the 12 lead ECG as prolongation and distortion of the QRS complex due to the delayed conduction velocity in the specialist conducting tissues. When the QRS complex duration exceeds 160 ms there is a high risk of ventricular tachycardia. When these features are present immediate treatment should include intravenous infusion of sodium bicarbonate until the arrhythmia is reverted, and the ECG becomes normal or the arterial pH is more than 7.6. Hypoxia and electrolyte disturbances should also be corrected vigorously. This will be sufficient for many cases of arrhythmia. Anti-arrhythmic drugs should generally be avoided because they can worsen the sodium channel blockade. The second major cause of ventricular tachycardia is abnormally delayed ventricular repolarisation. Causes include class I and III antiarrhythmic drugs, antipsychotic agents (particularly thioridazine and pimozide), tricyclic antidepressants, antihistamines such as terfenadine and astemizole, chloral hydrate, erythromycin and halofantrine. Delayed repolarisation is manifest on the ECG as QT prolongation and this may provoke the ventricular tachycardia known as *torsade de pointes*. This arrhythmia is particularly common when the underlying heart rate is slow and the corrected QT interval is $>$500 ms. *Torsade de pointes* is generally self-limiting, causing repeated episodes of syncope. However, without adequate treatment it can degenerate to ventricular fibrillation causing cardiac arrest and sudden death. Treatment is by aggressive correction of acid-base status, electrolytes and hypoxia. Patients with recurrent attacks or persisting QT prolongation should be treated with intravenous magnesium or by increasing the underlying heart rate using ventricular pacing or isoproterenol infusion. It is particularly important to avoid those anti-arrhythmic drugs that worsen repolarisation abnormalities such as those from Vaughan-Williams Singh classes Ia (e.g. quinidine) or III (e.g. amiodarone). The third cause of drug-induced ventricular tachycardia is increased ventricular excitability. The most important cause is poisoning with cardiac glycosides such as digoxin. This is due to increased intracellular sodium resulting from blockade of the Na^+/K^+ exchange pump. The results are ventricular arrhythmias including extrasystoles, tachycardia and fibrillation. Combinations of tachyarrythmias and bradyarrythmias may be seen, e.g. paroxysmal atrial tachycardia with atrioventricular block. Serious toxicity is usually associated with hyperkalaemia. The most effective treatment for ventricular tachycardia or ventricular fibrillation in the context of digoxin toxicity is the use of digoxin-specific F(ab) antibody fragments (Digibind®). Cardiac arrest: Patients who suffer cardiac arrest as a result of drug poisoning often have normal underlying hearts and their prognosis for survival is significant and those who do survive may have a normal life expectancy. Prolonged and vigorous attempts at cardiac resuscitation are therefore appropriate and there are reports of patients surviving after more than one hour of cardiopulmonary resuscitation.

5 POISON-INDUCED HYPOTENSION AND SHOCK: DIAGNOSIS AND OVERALL MANAGEMENT

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Causes of shock and diagnosis: Physicians confronted with intoxicated patients frequently have to deal with hypotension or shock. In order to manage severe hypotension or shock, it is relevant to know the mechanisms involved and to find out which agent(s) is (are) involved. Does the patient have hypovolemic, distributive, or cardiogenic shock? Hypovolemic shock may exist, e.g., in a diuretic intoxication or after a hemorrhage following ingestion of a corrosive substance. Distributive shock may be observed in cases of reduced peripheral vascular resistance induced by systemic vascular relaxation, for example, after exposure to medication with adrenergic receptor blockade or central motor tone depression. Cardiogenic shock may be due to toxic effects inducing cardiac failure (backward and/or forward failure), and/or arrhythmias. On physical examination, attention should be paid to blood pressure, heart rate, heart rhythm, jugular venous distension and pressure, and pulmonary vascular congestion. Further, mental status, skin temperature, capillary refill, and urine output should be monitored in order to evaluate organ perfusion. An electrocardiogram is obligatory to be informed about ischemia or myocardial infarction, conduction defects, arrhythmias, and pre-excitation effects. Routine biochemical analysis should include potassium, calcium, magnesium, sodium, lactate, glucose, creatinine, and

urea concentration, cardiac and liver enzymes, and arterial blood gas. A chest X-ray may be necessary to diagnose pulmonary vascular congestion. In the case of an unknown agent causing severe hypotension or shock, it may be necessary to obtain additional diagnostic information. Invasive monitoring may be needed in severe hypotension with insufficient organ perfusion not responding to initial treatment. Management: A patient with shock should be admitted to intensive care. Hypovolemic and distributive shock should initially be treated with fluid infusion, and acid-base and electrolyte disturbances should be corrected. If the mean arterial pressure does not improve (or not enough), dopamine or norepinephrine should be considered. Primary cardiac failure with hypotension and without systemic vascular dilatation should initially be treated with medication having especially positive inotropic activity on the heart (e.g. dobutamine). Cardiac failure in combination with systemic vascular dilatation may need medication having positive inotropic effect on the heart and vasoconstrictive properties (e.g. dopamine or the combination dobutamine and norepinephrine) in combination with fluids. A pulmonary artery balloon flotation catheter including a thermodilution system for cardiac output measurement may be helpful in unclear situations or in a patient not responding to the initial therapy. With this information appropriate treatment can be instituted and evaluated. The treatment of heart failure induced by arrhythmias in cases of intoxication generally needs a different approach from those caused by primary cardiac diseases. Ventricular fibrillation should be treated with defibrillation. Arrhythmias caused by intoxication, such as atrial fibrillation or tachycardia, and ventricular tachycardia with hemodynamic consequences, should preferably be treated with electric conversion if the nature of the intoxication is unknown. Pharmacologic treatment is second line therapy in these patients. If the mechanism of the arrhythmia is known or the patient does not respond to electric conversion, and a suitable antiarrhythmic drug, not negatively interfering with the course of the intoxication, is available, one might consider administering this antiarrhythmic drug. Special attention should be paid to medicines which interfere with conduction velocity and/or suppress or increase the spontaneous firing rate of pacemaker tissues in all phases of intoxication. Arrhythmogenic activity can be increased by hypotension, hypoxia, and acid-base and electrolyte disturbances, and also by altered sympathomimetic and anticholinergic activity. Reduced membrane responsiveness may cause slowing of conduction velocity and a reduced response to cardiac pacing. Bradycardia with hemodynamic failure can be treated with atropine or isoproterenol intravenously, or cardiac pacing. High degree Mobitz II or complete block should be treated with cardiac pacing. Failure to respond to cardiac pacing may be due to hyperkalemia, hypoxia, acidosis, or membrane-depressant agents. These patients require a cardiopulmonary bypass or intra-aortic balloon pump to maintain adequate circulation. Conclusions: Severe hypotension and shock are life-threatening events for which treatment is immediately required. As the causes of poison-induced hypotension or shock are various, a sound knowledge of the mechanisms involved is necessary for adequate treatment. Adequate organ perfusion must be maintained or restored in order to prevent multiple organ failure.

6 INVASIVE HAEMODYNAMIC MONITORING AND THE MANAGEMENT OF SHOCK—A STEP TOO FAR FOR THE POISONED PATIENT?

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There has been increasing use of invasive haemodynamic monitoring but awareness of potential complications and limitations is not universal. More experienced intensivists are less likely to use invasive monitoring than less experienced staff (J-L Vincent—personal communication). Arterial lines ('A' lines): The main complications are infection, vascular insufficiency and bleeding. Arterial spasm and pulselessness are common after a new-site insertion. Radial artery pressure underestimates central pressure in hypotensive septic patients receiving high-dose vasopressor therapy. Therefore management of hypotensive subjects based on radial pressures, may lead to excessive vasopressor administration, with the known associated risks.[1] Central venous catheters (CVC): The chance of CVC- sepsis was about 10% when used for the treatment of severely ill patients.[2] Tunneling decreases the risk and chlorhexidine gluconate is the preferred antiseptic. A study of 1303 cannulations showed arterial puncture in 5.2%, arrhythmias in 1.6%, cardiopulmonary arrest in 0.1%, and pneumothorax in 0.5% patients. The tip of the CVC was incorrectly located in 11.2% of patients. Swan-Ganz catheters: Complications of Swan-Ganz catheters include perforation of a vessel, infection and wedging in the pulmonary vasculature, causing pulmonary infarction. Sadly, rupture of the pulmonary artery or one of its branches during a Swan-Ganz catheterization is a complication that remains lethal in about 50% of cases. There are also problems with interpretation of results, such as from samples where the tip migrates too distally and become 'arterialised'.[3] Also

mathematical coupling of equations can overestimate the haemodynamic or oxygen delivery action of drugs.[4,5] An alternative and better method of establishing oxygen kinetics is use of end-tidal CO_2 measurements, which use a non-invasive probe in the patient's exhaled air.[5,6] The thermodilution method of assessing cardiac output is inaccurate in low-flow states and may not be reliable in the critically ill patient.[7] Electrical impedance methods can replace this, though require evaluation in poisoned patients.[8] In addition, esophageal Doppler monitoring seems to be at least as useful as a PA catheter in critically ill patients.[9] Corrected flow time given by the Doppler technique was a better indicator of preload than pulmonary capillary wedge pressures obtained by Swan-Ganz catheterization. If a Swan-Ganz catheter is used, improved training in its use and interpretation of the data it generates is required.[10] For less severely poisoned patients, telemetric pulse oximetry monitoring may represent a cost-effective approach to ensuring that patients, for example with opioid toxicity do not deteriorate clinically. Jugular bulb catheters: Whilst the risk of bacteremia is negligible, the incidence of subclinical internal jugular vein thrombosis is considerable.[11] Non-haemodynamic determinants of outcome in the intensive care environment: An adequate blood pressure to perfuse critical organs is likely to result in better outcome in poisoned patients than prolonged cardiovascular shock. However, minimizing the effects of skin breakdown, and diagnosis of conditions such as acute mesenteric ischaemia, abdominal sepsis, pulmonary complications, complications of enteral and parenteral nutrition in critically ill patients are also important in determining outcome. The commonest toxicological causes of admission to our intensive care unit are tricyclic antidepressants, opioids, carbon monoxide and anticonvulsants. Less common causes are late paracetamol poisoning, poisoning with alcohols, amphetamines and cardiac drugs such as digoxin. All may present with systemic hypotension. However, for the opioid poisoned patient, it is appropriate timely administration of appropriate quantities of naloxone that alter outcome.[12] Tricyclic antidepressant poisoning within ITU has a low mortality rate,[13] and it is important to differentiate between intensive supportive treatment and invasive haemodynamic monitoring, the latter of which is probably not required except in the most severe cases. In contrast, fulminant hepatic failure due to paracetamol requires effective monitoring of haemodynamic, septic and cerebral complications.[14] Conclusions: Invasive haemodynamic monitoring carries a number of substantial risks. It is not a substitute for good clinical bedside skills and should be used in only a tiny minority of seriously poisoned patients. The non-haemodynamic predictors of outcome in seriously poisoned should not be forgotten. We should develop innovative techniques that will reduce the need for invasive haemodynamic monitoring in the future[10] and make use of the ones already available. For less severely poisoned patients who meet admission criteria, a monitored care unit should be explored as an alternative to the ITU.[15] References: [1]Dorman T, Breslow MJ, Lipsett PA, *et al.* Radial artery pressure monitoring underestimates central arterial pressure during vasopressor therapy in critically ill surgical patients. *Crit Care Med* 1998;**26**:1646–1649. [2]Martin C, Bruder N, Papazian L, Saux P, Gouin F. Catheter-related infections following axillary vein catheterization. *Acta Anesthesiol Scand* 1998;**42**:52–56. [3]Nishikawa T, Dohi S. 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7 INVASIVE HEMODYNAMIC MONITORING AND MANAGEMENT OF SHOCK—A STEP TOO FAR FOR THE POISONED PATIENT?

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Introduction: Severe hemodynamic disorders were reported following intoxications with several drugs and xenobiotics. These disorders may be caused by metabolic changes, a direct toxic effect (heart or blood vessels) or induced by influencing receptors. Known clinical symptoms include hypertension, hypotension, myocardial depression, signs of distributive or cardiogenic shock and arrhythmias. The mechanisms resulting in hemodynamic changes in drug overdose may be different from those of therapeutic drug dosage. Therefore, the treatment of adverse effects in intoxicated patients may need a different approach. Management: Essential to the management of intoxicated patients with severe hemodynamic instability is the knowledge of the drug(s)/xenobiotic(s) involved and the underlying mechanisms. Non-invasive hemodynamic variables such as blood pressure, heart rate and rhythm are normally obtained variables in the treatment of intoxicated patients. However, invasive monitoring may be needed in intoxications with a combination of possible mechanisms. The treatment of hypotension caused by peripheral vasodilatation is different from the treatment of hypotension due to primary cardiac failure. By means of a pulmonary artery balloon flotation catheter (with a thermodilution system for cardiac output measurement) and an arterial line, invasive hemodynamic variables (pulmonary artery blood pressure, central venous blood pressure, pulmonary capillary wedge pressure, cardiac output, indexed systemic and pulmonary vascular resistance, right and left ventricular stroke work index, and systemic arterial blood pressure) can be obtained. Obtained invasive hemodynamic variables may result in a better understanding of the underlying mechanisms of hemodynamic instability, and a more appropriate treatment based on the pathophysiology of the patient. Conclusions: The scientific evidence demonstrating the benefit of the use of pulmonary artery catheters is limited by the lack of prospective, randomized, controlled, clinical data in intoxicated patients. However, we feel that the use of pulmonary artery catheters can be useful in hemodynamically unstable intoxicated patients, but are not a tool for routine use. In complex intoxications with severe cardiovascular compromised patients, a pulmonary artery catheter can guide the treating physician to the correct diagnosis and management.

8 POISONING DUE TO BETA-RECEPTOR AND CALCIUM CHANNEL BLOCKERS

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Introduction: Beta-blockers (BB) and calcium channel blockers (CCB) are among the most frequent causes of poisoning by cardiovascular drugs. BB antagonize the effects of catecholamines by competitive inhibition at the beta-adrenoreceptors. Some BB may exert a membrane stabilizing effect (propranolol) or an antiarrhythmic III effect (sotalol). In overdose, BB lose their cardioselectivity and exhibit a marked negative inotropic effect. CCB decrease the entry of calcium into cells through the voltage-dependent channels. This results in vasodilation and inhibition of cardiac conduction, especially in the sinoatrial and atrioventricular nodes. According to the selectivity of their effects CCB are classified into 3 groups: verapamil which has a predominant effect on the heart, the nifedipine-like group which has a predominant effect on the vascular smooth muscle and diltiazem which has an intermediate action. In overdose, the selectivity tends to disappear and all CCB may exert a negative inotropic effect. Because BB and CCB are rapidly absorbed, toxic effects usually appear within 1 to 2 hours of ingestion. However, symptoms may be delayed if a sustained-release preparation has been ingested. Diagnosis and clinical features: The most frequent findings in BB poisoning are bradycardia and hypotension. In large overdose, severe hypotension, coma, convulsions (especially with propranolol) and respiratory depression may occur. Cardiorespiratory arrest is usually caused by asystole or ventricular fibrillation. Sinus bradycardia or a first degree atrioventricular block are common. In severe poisonings, complete atrioventricular block, right or left bundle-branch blocks may be seen. Intraventricular conduction disturbances with wide QRS complexes are more frequent with BB which have membrane stabilizing effects. Sotalol increases strongly the QT interval and may induce ventricular dysrhythmias, especially, *torsades de pointes*. Hypoglycemia and hyperkalemia are uncommon. Hypotension due to vasodilation and/or myocardial depression is the most common feature in CCB poisoning. Sinus bradycardia and junctional bradycardia may be observed with all CCB but a high degree atrioventricular block is more frequent with verapamil and diltiazem. Occurrence of CNS disturbances is mostly related to cerebral hypoperfusion. Hyperglycemia and metabolic acidosis may be observed. Severe shock and cardiac arrest by asystole is more frequent in verapamil and diltiazem poisonings. Several factors may increase the toxicity of BB and CCB: coingestion of other cardiotoxic drugs, ingestion of sustained-release preparations, underlying cardiovascular diseases, metabolic disturbances such as

hypoxemia, hyper or hypokalaemia, metabolic acidosis. Management: Because BB and CCB poisonings may be rapidly life-threatening, patients should be admitted in an intensive care setting for rapid evaluation and management. General measures include intravenous access, fluid resuscitation, ECG and blood pressure monitoring, blood gases, glucose and electrolyte analyses. Plasma concentrations are not useful for clinical management. Gastric lavage and activated charcoal may be considered if a substantial dose has been ingested less than 1 hour previously. Forced diuresis and enhanced elimination are not indicated. Repeated doses of activated charcoal may be considered in patients who have ingested sustained-release preparations, though the efficacy of this treatment has not been confirmed by clinical trials. The goal of treatment is to restore an adequate tissue perfusion and oxygenation by increasing myocardial contractility, heart rate and/or mean arterial pressure. Initial non-specific therapy includes vascular filling, oxygenation and mechanical ventilation if needed. Vascular filling should be performed carefully in order to prevent subsequent pulmonary edema. Atropine is often the initial drug given for bradycardia but it has mostly little or no effect. Glucagon seems to be the drug of choice in BB poisoning. Glucagon activates adenylate cyclase independently of beta-receptors and promotes the formation of cyclic AMP which has a direct inotropic effect on the heart. It should be given in a bolus dose of 2 to 10 mg over 1 minute, followed by an infusion of 2 to 5 mg per hour. The usefulness of glucagon in CCB poisoning has not been demonstrated. Calcium is an inotropic agent and, based on some experimental studies and clinical reports, has been recommended in CCB poisoning. However, there is still no clinical evidence that calcium is the treatment of choice and, especially, calcium has no effect on the vasodilation and only little effect on the cardiac conduction disturbances. The usefulness of calcium in BB poisoning has not been established. In case of failure of glucagon or calcium, catecholamines should be rapidly used. Isoproterenol is indicated in severe bradycardia and in BB poisonings. High doses are often needed in order to reverse the toxicity. In CCB poisonings, the choice of the catecholamine depends on the mechanism of hypotension. Adrenaline is indicated in order to increase inotropism if myocardial failure is the major factor. Norepinephrine is the drug recommended in cases of severe vasodilation which are frequent in these poisonings. Sodium salts are only indicated if membrane stabilizing effects are present. Other drugs such as phosphodiesterase inhibitors have been used in anecdotal cases. Cardiac pacing is rarely indicated. In poisonings with severe hypotension not responding rapidly to treatment, monitoring of haemodynamic parameters (Swan-Ganz catheter or echocardiography) is indicated in order to determine the precise mechanism of shock and to adapt the treatment. Conclusion: BB and CCB poisonings are potentially life-threatening and need rapid evaluation and treatment. Apart from glucagon in BB poisoning, there is no drug of choice or specific antidote. Treatment should be adapted according to symptoms and take into account the mechanism of cardiovascular failure: severe bradycardia, decrease of myocardial contractility and/or severe vasodilation.

9 POISONING FROM MEMBRANE STABILIZING AGENTS

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Membrane stabilizing activity (MSA) (quinidine-like) is an interaction between a drug and the membrane lipid bilayer, which leads to inhibition of the fast inward sodium channel. While MSA is a primary mechanism of action for type Ia and Ic antiarrhythmics and local anesthetics, it is an unintended effect for many other drugs. Sodium channels, which open in response to membrane depolarization, are known as voltage-gated. Most MSA drug interactions occur with the voltage-gated sodium channels. MSA drugs preferentially inhibit sodium channels in the activated or inactivated states but not the resting state. As heart rate increases, sodium channels spend relatively more time in the activated or inactivated states resulting in greater sodium channel inhibition from MSA drugs. In nonpacemaker myocytes, inhibition of the fast inward sodium channel reduces the maximal upslope of phase 0 (V_{max}) leading to a prolonged action potential and QRS EKG interval (conduction block). If the conduction block is severe, unidirectional block and re-entrant circuits may lead to re-entrant rhythms (ventricular tachycardia). In pacemaker myocytes, spontaneous depolarization during phase 4 is partly due to inward sodium flux and is inhibited by MSA drugs (bradycardia). Sodium channel blockade reduces the amount of sodium available to exchange with calcium and thereby reduces intracellular calcium levels. Lower intracellular calcium reduces the strength of muscle contraction (decreased contractility). Sodium channel blockers may also block potassium and calcium channels resulting in more severe cardiovascular impairment. Many drugs from different classes and with different structures exhibit MSA, but display similar toxicity and response to therapy. MSA drugs responsible for substantial numbers of severe poisonings include: class Ia and Ic antiarrhythmics, local anesthetics (i.e. cocaine), verapamil, tricyclic antidepressants, antihistamines, propoxyphene, certain beta adrenergic

receptor blockers (i.e. propranolol, oxprenolol and acebutolol) and certain phenothiazines (i.e. thioridazine, mesoridazine?). Excessive levels of MSA drugs may induce severe toxicity (conduction block, bradycardia, ventricular dysrhythmias, decreased contractility, as well as CNS and respiratory depression and seizures). When toxicity from MSA drugs fails to respond to general supportive care, other measures may be required. Other measures generally believed to be safe and effective include sodium loading and alkalinization. A number of animal studies and case reports suggest a beneficial effect of sodium and bicarbonate individually and additively. QRS intervals may be shortened, hypotension improved and ventricular dysrhythmias terminated with these therapies. However, not all MSA drugs respond well to one or the other of these therapies. One recommended approach to MSA toxicity refractory to supportive care is alkalinization with 1–2 mEq/kg boluses of hypertonic sodium bicarbonate until toxicity is controlled or a pH of 7.55 is attained. Thereafter, further sodium loading (i.e. with hypertonic saline) with 100–200 mmoL sodium over 10–30 min should be tried. When hemodynamically stable, ventricular tachycardia is refractory to the supportive care, sodium loading and alkalinization, other antiarrhythmics are considered. Limited experimental work suggests that lidocaine may be effective in terminating ventricular tachycardia due to certain MSA drugs (i.e. cocaine, quinidine). Lidocaine has fast on-off binding kinetics and may reverse toxicity from slow on-off MSA drugs through competition for the sodium channel. Since increased heart rates worsen MSA drug toxicity, physostigmine may be expected to be beneficial by slowing the heart rate. However, two notorious case reports of asystole following its use in tricyclic antidepressant poisoning make many hesitant to try this. While anecdotal reports suggested that phenytoin may be effective in tricyclic antidepressant poisoning, experimental animal data suggests no beneficial and possibly even adverse effects. Further reading: Bou-Abboud E, Nattel S. Relative role of alkalosis and sodium ions in reversal of class I antiarrhythmic drug-induced sodium channel blockade by sodium bicarbonate. *Circulation* 1996;**94**:1954–1961. Callaham M, Schumaker H, Pentel P. Phenytoin prophylaxis of cardiotoxicity in experimental amitriptyline poisoning. *J Pharmacol Exp Ther* 1988;**245**:216–220. Henry JA, Cassidy SL. Membrane stabilising activity: A major cause of fatal poisoning. *Lancet* 1986;**1**:1414–1417. Jaeger A, Raguin O, Liegeon MN. [Acute poisoning by class I anti-arrhythmia agents and by chloroquine]. *Rev Prat* 1997;**47**:748–753. Kolecki PF, Curry SC. Poisoning by sodium channel blocking agents. *Crit Care Clin* 1997;**13**:829–848. Kulling PE. Treatment of cardiac membrane stabilizing dysrhythmias. *J Toxicol Clin Toxicol* 1996;**34**:131–134. Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med* 1980;**9**:588–590. Sanchez-Chapula J. Electrophysiological interactions between quinidine-lidocaine and quinidine-phenytoin in guinea-pig papillary muscle. *Naunyn Schmiedebergs Arch Pharmacol* 1985;**331**:369–375. Winecoff AP, Hariman RJ, Grawe JJ, *et al*. Reversal of the electrocardiographic effects of cocaine by lidocaine. Part 1. Comparison with sodium bicarbonate and quinidine. *Pharmacotherapy* 1994;**14**:698–703.

10 ACUTE DIGITALIS POISONING: PROGNOSIS AND MANAGEMENT

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Digitalis poisoning is a rare life-threatening event with a mortality rate before the availability of specific treatment of about 15%. Digitalis poisoning may result from an overdose of either digoxin or digitoxin. The nature of the cardiac glycoside will dramatically modify the duration of life-threatening events, in the range of 36 hours for digoxin and of 5 days for digitoxin. Furthermore, digitalis poisoning may result either from the ingestion of a single high dose of digitalis or from a too high dose during a chronic treatment. This presentation will be focused on the prognosis and the management of acute digitalis poisoning resulting from the ingestion of a single high dose of cardiac glycoside. At the time of presentation several prognostic factors can be determined in order to assess the likelihood of life-threatening cardiac events. These prognostic factors include: the age, the sex, a past history of cardiac disease, an atrioventricular block whatever its degree, and hyperkalemia. According to these prognostic factors, the probability of death ranges from about 2% to 75%. In our experience a serum potassium level greater than or equal to 6.4 mmol/L, in a digitalis poisoning without any factors of potassium overload is associated with a mortality rate of about 90%. The death of acute digitalis poisoning is mainly related to the occurrence of cardiac events either conduction abnormalities or ventricular arrhythmias. Supportive treatment including atropine, endocardial pace-maker, and anti-arrhythmics are efficient. However, their use was not associated with an improvement in the prognosis of digitalis poisoning. Digoxin-specific Fab fragments have been shown efficient in digitalis poisoning regarding the reversal of conduction abnormalities, ventricular arrhythmias, and hyperkalemia. However, there are no prospective studies comparing the mortality rate of acute digitalis poisonings treated with or without Fab fragments. Furthermore, the mortality rate of digitalis poisonings treated with

specific Fab fragments in previous large series appears quite similar to that observed without Fab fragments. In a retrospective study we observed an improvement in the prognosis of digitalis poisoning only when Fab fragments were used as first line antidote in patients without life-threatening cardiac disturbances. Fab fragments are expensive and the minimal efficient dose of Fab fragments remains a matter of debate. Our data suggest that a curative dose (equimolar neutralization) is recommended for patients with life threatening intoxication while a prophylactic dose (half-equimolar neutralization) should be recommended if the patient had poor prognosis factors without acute life-threatening toxicity. However, some patients may require an additional dose of Fab fragments more especially if digitalis poisoning results from the ingestion of digitoxin.

11 POISON CENTERS AT THE MILLENNIUM AND BEYOND

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Introduction: Professor Louis Roche and several visionaries founded the European Association of Poisons Control Centres and Clinical Toxicologists (EAPCCT) in 1964 with the goal of improving the care of the poisoned patient. Nearly four decades later the primary mission of the Association remains the same, but what the original founders envisioned has undergone a major evolution. Poison centers are now abundant throughout the entirety of Europe. Telephones were once a luxury to some, now the prevalence of mobile phones and facsimile machines make poison center advice readily available to inquiring medical professionals, the lay public and the hearing-impaired. Poison centers, staffed previously by volunteers and those drafted into service, now employ poison information specialists and clinical toxicologists who are trained formally. Centers operate 24 hours per day, every day of the year. Poison treatment information was nonexistent or disorganized, often found in personal files, a limited number of texts and microfiche. Now computers and the Internet have revolutionized the storage of and access to poison treatment information. In the recent past, poison information and treatment advice were provided *secundum artem*, now most decisions are based on sound principle, research and professional expertise. Most importantly, the morbidity and mortality associated with poisonings continues to decrease as testimony to the commitment of many to the EAPCCT. The challenges that were the initial frontiers of poison information dissemination in 1964 have been surmounted. However, the evolution of the contemporary poison center and the problems of today seem insignificant compared to the challenges that face poison centers in the future. Discussion: Two things are incontestable: the future is inherently unpredictable with absolute certainty and the poison center of today will not be adequate in the future. While the future is uncertain, to predict the future accurately is to create the future of poison centers. The future is too important to be left to chance and efforts must be made to determine poison centers destiny by eliminating uncertainty and creating new opportunities. However, before poison centers can identify new opportunities and set a course for the future, the first step is to understand that the poison center product is an intangible entity referred to as 'knowledge.' Knowledge is the sum of poison center staff experience and information. Toxico-informatics or converting information to knowledge is the most formidable challenge that poison centers face in the near future due to the exponential growth of information. For example, during the period of 1750–1900 it required 150 years for available information to double; 1900–1950 saw information double in 50 years; from 1960–1992 information doubled at least once every five years; it is estimated that information will double every 73 days by 2020! Poison centers must proactively prevent the information explosion from incapacitating centers and find ways to filter the information to make it usable. Poison centers must become proactive rather than reactive. Poison centers rely on case reports and the scientific literature that report the events of yesterday. Imagine a world where toxicosurveillance occurred in real-time! Poison centers create thousands of medical records everyday that chronicle the toxicity of new medications, chemicals and natural products. Yet, these records are unusable because they are not standardized. Furthermore, the records are rarely compiled in a central repository. If there was harmonization of poison center records and global consolidation of effort, real-time toxicosurveillance could occur. Networking poison centers, harnessing the power of technology through the use of computer artificial intelligence or machine-learned paradigms would allow the early detection of toxidromes, prediction of adverse drug reactions and improve patient care through the use of real-time data. Knowing the marketplace, being aware of basic scientific research and understanding population demographics will help to identify and solve problems of the future. For example, as the role of genomic imprinting as a cause of disease becomes more apparent, the prediction of disease will be easier. It is estimated that more than 4,000 genetic diseases and disorders will be brought under control by 2025. How will genetic engineering enhance the treatment of toxicological problems (toxicogenomics?) and what genetic-induced toxicological problems

should be anticipated from these discoveries? Today, poison centers focus poison prevention efforts on the pediatric population. However, the population is aging (currently, 14% of the population is ≥65 years and by 2030 over 20% of the population will be ≥65 years!) and perhaps, education efforts should be redirected to address the needs of the elderly. What will the poison center of the future look like? Will a limited number of 'super centers' provide global service? Should the 'European model' of a comprehensive toxicology service, embracing a poisons information service, an in- and out-patient treatment service and analytical support, and covering the clinical, occupational and environmental aspects of toxicology, be the model adopted worldwide? Some predict that 90% of the world's languages will disappear as information creates a global culture. If English becomes the dominant language in clinical toxicology, as it already has in business, aviation and most of the scientific world, the concept of poison center consolidation may become reality. As the world becomes 'e' literate and technology allows seamless 'telecommuting', the virtual poison center may replace the traditional poison center as a resource for poison and drug information, especially considering the low morbidity associated with most poisoning exposures. Conclusions: The easiest way to anticipate the toxicological problems of the future is to recognize the transgressions of the past. The next several decades will witness the appearance of environmental problems and disease patterns occurring as a consequence of wanton disregard for society and the environment. Toxicology societies must conduct organizational brainstorming to anticipate future toxicological challenges. Once problems are identified, viable solutions can be developed.

12 SUBSTANCES OF ABUSE IN THE YEAR 1900: WAS IT REALLY ALL THAT DIFFERENT?

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As we enter the new millennium, the toxicologist is confronted by a number of recently introduced drugs of abuse such as gamma-hydroxybutyrate (GHB), 1,4-butanediol, flunitrazepam and methylenedioxymetamphetamine (MDMA). Yet apart from these newer 'synthesized' (and in some cases 'designed') drugs, the most commonly abused agents in the year 2000 (i.e. heroin, cocaine, marijuana, and ethanol) are derived from naturally-occurring substances and have been used for their mood altering effects for hundreds, and in some cases thousands of years. The use and abuse of these drugs has had a major impact on society in the past as well as the present. In an attempt to provide a perspective of the 'perils' of drug abuse in history, an investigation into drugs of abuse at the turn of last century (the Year 1900) will be offered. Just two years before the centennial celebration, in 1898, heroin was first synthesized from opium and promoted as a non-addictive morphine substitute. Interestingly, cocaine, which was also freely and legally available at this time, was heralded as a cure for opium and morphine addiction. During the last part of the 19th century cocaine could be found in a new French wine called 'Vin Mariani', the American-made Coca-Cola and numerous patent medications. Despite a medical interest in the antagonistic features of cocaine and heroin at that time, patients who took this approach to treat their underlying opiate addiction were at risk of exchanging one type of drug habituation for another. Not surprisingly, by the turn of the century, the increasing public demand for cocaine led to the first great cocaine epidemic and cocaine would soon be referred to as 'Public Enemy Number 1.' The criminality of drug possession and distribution would come later. A detailed review of the medical literature from the centennial year 1900 exploring the epidemiology, clinical presentations and treatment modalities for opiate, cocaine and ethanol abuse time reveals striking similarities to ongoing problems that we encounter today. Despite the proliferation of pharmaceuticals and other chemicals during the 20th century, three major drug abuse scourges of the Year 2000 remain heroin, cocaine, and ethanol. An understanding of the use and abuse of these substances 100 years ago provides perspective on how far we have come, or not come, in tackling the myriad of problems associated with substance abuse.

13 SIGNIFICANCE OF SUBSTANCE DISORDER IN ADOLESCENT SELF-POISONING

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'I saw the best minds of my generation destroyed by madness, starving hysterical naked, dragging themselves through the negro streets at dawn looking for an angry fix.' Allen Ginsberg's Howl, 1956.

Introduction: Substance use is common in patients presenting with self-harm. However the significance of substance use may differ in various age groups. If we identify substance use in our patients, does substance use increase their risk of self-harm and should we be treating them for their substance use? Adolescents are likely to be high risk takers and experiment with drugs for recreational purposes. While this activity may vary between countries, a number of social influences conspire to ensure that high rates of substance use are the norm in western countries. Surveys of Australian school leavers embarking on a one week holiday, show that most expected to be drunk most or every night of their

holiday and 27% of young men and 17% of young women expected to be 'stoned' most nights or every night.[1] Substances abused by adolescents include alcohol, recreational drugs, therapeutic drugs, plants and occasionally animals. Adolescents who demonstrate high substance use can be characterized as being low on self-esteem and high on sensation-seeking.[2] While there is no doubt that high use of substances carries significant intrinsic risks, their use in an adolescent should be seen as a marker for other psycho-social dysfunction. Diagnosis: In hospital patients screening questionnaires are useful in determining the extent of dependence for some drugs (e.g. CAGE) but patients commonly under-report other substance use when compared with the results of urine drug screens. The incidence of recording a positive history for substance use is increased if a preformatted chart is used. However admitting doctors appear to over-report for substance abuse or dependence compared with use alone when compared with DSM IV criteria. In our review of 740 adolescents with self-poisoning we assessed the admitting residents diagnosis for substance disorders against a gold standard of psychiatric assessment. Using a structured history form the admitting resident could identify most patients with a substance disorder but overdiagnosed the condition (Sensitivity = 0.909, Specificity = 0.602, PPV = 0.396, NPV = 0.958) (Table). The clinical issue is which group should receive intervention: all those who present with substance co-ingestion, those with an MO diagnosis of substance disorder or those with a DSM IV diagnosis? Risk: Substance abuse is a marker of psycho-social disorder. It is a high risk activity with potential effects on an individual's health and social function. In addition to the direct toxicological effects, substance-induced disinhibition may have a role in subsequent self-harm. Substance use has both an association and causal relationship to depression and other psychiatric disorders. Despite this adolescent substance abuse has a low predictive value for suicide/self-harm. In adolescents who present with self-harm the diagnosis of substance disorder by either resident (OR = 1.44 CI 0.81–2.5) or psychiatrist (OR = 1.61 CI 0.85–3.03) is not predictive for repeat presentation within the next year. However, certain subsets do have increased risk, such as adolescent males presenting with deliberate self-harm with a history of narcotic abuse, have a high rate of successful suicide.[3] There may be value in addressing substance use in addition to other interventions in specific subsets of our patients. Intervention: While politically it seems attractive to offer broad-based drug education to adolescents, such programs have not been shown to be effective. One possible reason is that the key predictors of social drug use are all outside the ambit of drug education programs.[4] Brief targeted intervention/education has been shown to be effective in a number of groups ranging from substance-dependent to recreational use in adolescents. In most clinical settings it is the only intervention that can be delivered in a practical and cost effective way. It would seem appropriate to offer such interventions to our patients. However, it remains to be proven whether this will influence outcomes such as representation or subsequent suicide. This is likely if substance disorder is just a marker for other psycho-social dysfunction. Conclusion: The majority of adolescents with a history of substance use are not substance abusers or substance-dependent. The vast majority will not present with self-poisoning. Adolescents who present with self-poisoning and have a history of substance abuse or dependence are at higher risk of subsequent self-harm. Assessment and management should include, in addition to normal medical and psychiatric care, a structured history, and occasional use of a urine drug screen for drugs of abuse. While there is no evidence for a broad-based approach, the self-harm presentation provides a 'vulnerable' window to offer brief intervention. Such interventions may not impact on subsequent episodes of self-harm unless other psycho-social disorders are also addressed. References:

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Diagnosis (+) of substance abuse or dependence by admitting MO or psychiatrist in 740 cases of self-poisoning age 13–19 years (1991 and 1999)

Diagnosis by admitting MO	**Diagnosis by Psychiatrist**	
+379	+150	−229
−361	+ 15	−346
740	165	575

14 NONPRESCRIPTION PSYCHOACTIVE DRUGS: ABUSE CHARACTERISTICS AND SURVEILLANCE

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One component of the substance abuse problem in the United States, particularly among adolescents, is the abuse of nonprescription (OTC) drugs. Many commonly available OTC drugs including sympathomimetics (ephedrine, phenylpropanolamine, psuedoephedrine), antihistamines (cyclizine, diphenhydramine, dimenhydrate, meclizine), antitussives (dextromethorphan, codeine) and stimulants (caffeine) are abused for the psychoactive effects that occur when they are taken in greater than the recommended therapeutic doses.[1–4] The abuse of these drugs have numerous unique aspects that include widespread relatively uncontrolled legal availability, the almost universal exposure of children and adolescents to the drugs for the symptomatic relief of common illnesses, and regulatory issues involving their nonprescription status.[5] OTC drug abuse is often overlooked because the public and many health professionals are not aware that these drugs are abused. It may also be overlooked because there is a little data available regarding the frequency and the patterns of abuse and because abuse of OTC drugs is not pandemic. The abuse of OTC drugs appears to generally be limited and episodic in nature. It usually spreads within and between communities by word-of-mouth, and may become a temporary fad. Media reports can stimulate and perpetuate abuse locally and expand it to other areas. It is likely that the continued growth of Internet communications will significantly expand the scope of OTC drug abuse. Abuse appears to be most common in adolescents, usually in combination with alcohol. Both single substance and combination drug products are abused. The abuser selects OTC drugs rather than illicit drugs based on factors including perceived safety, the lack of legal consequences, and few social consequences associated with their abuse. The abuse and dependence liability of OTC drugs is controversial and it appears that episodic abuse infrequently results in chronic abuse and dependence. The self-reported use of OTC drugs increases steadily during adolescence in contrast to the use of alcohol, cigarettes, and cannabis.[6] The abuse of OTC drugs does not appear to facilitate progression to illicit substances such as cocaine, amphetamines, or opiates, but supporting evidence is lacking. There is a paucity of information about OTC drug abuse, due in part to its low incidence compared to the abuse of illicit substances. Traditional data collection methods such as the Drug Abuse Warning Network (DAWN) have focused on illicit and prescription drugs even though their purpose includes assessment of the use of OTC drugs contrary to approved labeling. The Toxic Exposure Surveillance System (TESS) data has also been used to evaluate OTC drug abuse, although it focuses primarily on unintentional human exposures.[7] The collation of data from a number of sources is important to accurately characterize the nature, extent, and potential toxicity of OTC drug abuse. Surveillance systems should include case identification (e.g. DAWN, TESS), published cases, spontaneous reports to regulatory agencies and pharmaceutical companies, state and local substance abuse programs, the media, and Internet newsgroups. Surveillance should also include targeted surveys to groups such as school counselors, nurses, and drug treatment centers, as well as the identification and interview of OTC drug abusers. Abuse has been most successfully evaluated using a novel method of surveillance based on looking at clusters where abuse is reported. This method involves coordinating information from different sources focused on a geographic area. Cluster evaluations should be considered as a more widely used method of surveillance. It is important to further evaluate the role of OTC drugs as substances of abuse in adolescent populations. The most important issue is how to collect data that provides the most accurate picture of this type of drug abuse. This information is necessary for designing potential solutions for related problems, implementing prevention strategies, and making appropriate regulatory decisions about these drugs. The issues of access, abuse patterns, and public perception of OTC drugs require a different approach to assessment and prevention when compared to illicit drugs of abuse.

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15 'COPS' WORKING WITH 'DOCS' TO COMBAT TRAUMA ASSOCIATED WITH SUBSTANCE ABUSE

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This presentation will describe an easily reproducible, multi-disciplinary effort to combat violence associated with illicit drug markets that are prevalent in many US communities. Introduction: Urban violence is a common public health problem that plagues many communities throughout the United States. In many circumstances, crimes are associated with the buying, selling or use of illicit drugs. In 1994, the city of Richmond, Virginia was the second most violent city in the US based on its per capita homicide rate, and forty percent of the homicides that year were associated with illegal drug trafficking. Of particular concern is the growing number of adolescents involved in violent crimes either as a witness or participant. It is our observation that children at increasingly young ages are utilized as look-outs, couriers or even sellers of illicit drugs, and studies have confirmed the association between substance abuse and violent crimes in adolescents and young adults. Program development: Violence associated with trafficking and use of illicit drugs is a concern for many interested parties, including but certainly not limited to law enforcement, emergency medical services (EMS), poison control centers, emergency departments (ED) and trauma centers. With leadership from the Department of Criminal Justice Services, a program affectionately called 'Cops and Docs' was organized to enhance participants' understanding of the roles that all these disciplines play in response to drug-induced violence, and to develop collaborative approaches to prevention. In addition to regular meetings, both police officers and medical staff have 'cross-trained' with each other to facilitate information exchange and to experience each other's difficult role in dealing with drug-related violence. In addition, data from the ED, poison center and vice detectives are shared and reviewed in order to identify new drugs of abuse, new uses for old drugs or new at-risk populations. Goals and objectives: The overall goal of the program is reduce the use and trafficking of illicit drugs, and the trauma that often accompanies these activities. By attending hospital rounds, police officers are able to experience the tremendous efforts necessary to save life or limb, and provide valuable advice on preservation of evidence during both resuscitation and definitive care. Police presence in the hospital (other than for interrogation) 'working' with doctors is also intended to show injured participants in criminal activities (both victim and perpetrator) that the police are concerned with their health and recovery. Likewise, the medical staff are learning about the environments that these types of trauma victims come from and are being discharged to. It is hoped that this demonstration of concern for the victims and their families will increase trust of the healthcare providers and improve compliance with medical advice. Joint community educational programs are planned for high-risk areas and populations. These efforts will combine the expertise of law enforcement with medicine to emphasize both the legal and medical dangers associated with illicit drugs.

16 DRUGS OF ABUSE AND SELF-HARM IN EDINBURGH: 1999

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Background: Drug abuse is a growing problem and is of interest to a wide range of professional groups. In toxicology an important concern is the contribution of drug abuse to the overall workload of clinical units. In the City of Edinburgh (population ~500,000) all cases of overdose and self-harm are admitted to a single clinical unit within the Royal Infirmary. Case series: From January to the end of October 1999 there were 2596 admissions to the unit, of which 462 (17.8%) were either as a direct result of drugs of abuse, or self harm in patients regularly abusing drugs at that time. Forty-five per cent of these patients were aged 16 to 25 years and 65% of the total were male. The 462 individual admissions reported an average of 1.8 agents per admission. Methods and results: Urine toxicology screens were performed in 121 patients; 4.7% of total admissions, and 26.2% of drugs of abuse patients. The indication for screening in 43 patients was uncertainty about the agent ingested, most being related to recreational use. The agents detected were: benzodiazepines 24, opioids 13 (18% methadone), cannabis 11 and amphetamine derivatives 5. In this group an average of 1.23 agents were ingested per patient and there were no cases of cocaine exposure. In the remaining 78 patients 1.84 agents were detected per patient. These were more commonly 'intentional' use for purposes of self-harm. The agents detected in this group were benzodiazepines 53, opioids 43 (39.5% methadone), cannabis 27, amphetamines 17 and cocaine 4. The agents stated to have been abused were compared to those actually detected in the 78 patients

in whom this was possible. Fifteen patients claimed to have taken substances that were not detected in their urine, but in only 5 of these was no drug of abuse detected. In 55 patients one or more substances were detected in urine that were not reported by the patient. In 54 patients substances were detected that the patient had reported. In only 9 (16.6%) was there complete concordance between history and laboratory findings. Conclusions: Patients were most likely to fail to report ingestion of cannabis (81%) and cocaine (75%). Failure of reporting was less for other drugs of abuse at 60% for benzodiazepines, 41% for amphetamines and 26% for opiates. These data emphasize the importance of confirming history with biochemistry in this patient population, and confirm previous reports from others on the unreliability of history in drug abusers. In Scotland abuse of benzodiazepines and opioids is a significant contributor to self-harm admission.

17 AN OVERVIEW OF CONTEMPORARY HERBAL DRUGS USED IN THE NETHERLANDS

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Objective: Over the last decade the use of herbal drugs of abuse, so-called *smart products, smart drugs* or *ecodrugs*, has increased in the Netherlands. Many of these products have psychoactive effects. The increased availability of these products (sold in so-called *smart shops*) and the continuing appearance of new products on the market, has lead to increased awareness of the possible negative health aspects associated with the use of these products. At present the Dutch Inspectorate for Health Protection, Commodities and Veterinary Public Health is testing whether the activities and products of these smart shops are in compliance with the laws on public safety and health. The National Poisons Control Centre (NVIC) of the National Institute of Public Health and the Environment (RIVM) made an overview of these products as a practical aid to the Inspectorate in evaluating the various smart products. Methods: Field studies (e.g. visiting smart shops) were made in order to make an inventory of the products. Subsequently, these products were categorized according to their alleged/desired effects and (active) herbal ingredients. For those herbal ingredients the following items are described: the various product appearances, usage, alleged/desired effects, a description of the herbal origin (most of these products are derived from plants) and the pharmacology and medical toxicology of these ingredients and products. A considerable part this information was acquired through literature research. Results: Many of the smart products appeared to be based on one or more herbal ingredients. Of these ingredients a total of 31 herbal drugs were discerned as toxicologically or pharmacologically relevant. Categorization of these drugs resulted in four groups of smart products, based on their main supposed effects: energizers (e.g. ephedrine-containing products used as 'herbal ecstasy', guaraña, colanut, betelnut, qat), relaxing herbs (e.g. kava kava, wormwood, St. John's wort), aphrodisiacs (e.g. yohimbe, damiana, hydrocotyle) and products with hallucinogenic properties (e.g. psilocybin containing mushrooms, belladonna-alkaloid-containing plants, mescaline-containing cacti, nutmeg, nitrous oxide, gammahydroxybutyric acid or GHB). GHB already has lead to life-threatening intoxications and was banned from the smart shops. With these drugs, the following acute effects were most often reported to our Centre: agitation, hallucinations, disorientation and vision disorders. Conclusion: Monitoring of the use of these smart products and their health effects should make clear to which smart products most attention should be paid from a medical point of view.

18 ANABOLIC SUBSTANCES: ANABOLIC STEROIDS, CLENBUTEROL AND GHB REPORTED TO SPANISH CONTROL POISON CENTRE

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Objective: Anabolic substances are used mainly to increase muscular bulk and body weight and as stimulants, not only among athletes but in also young people seeking cosmetic improvement. The purpose of this study was to ascertain the clinical features and etiology of anabolic substance poisoning registered by the Spanish Control Poison Centre. Anabolic androgenic steroids such as testosterone, other anabolic steroids such as nandrolone, mesterolone and stanozolol, as well as other anabolic substances such as clenbuterol (beta$_2$-adrenergic-agonist with anabolic properties) and gamma hydroxybutyrate (GHB) with anabolic qualities were included. Methods: Human intoxications by anabolic substances registered by the Spanish Poison Centre from January 1st 1991 to December 31st 1998 were studied. The following parameters were analyzed: type of product, age and gender of the patients, routes of exposure, signs and symptoms, etiology, drug dependence antecedents and sources of these agents. Results: Twenty-five cases were regis-

tered. Seven children aged from 24 months to 8 years old were exposed accidentally (orally). The products implicated were clenbuterol 4, mesterolone 2 and testosterone 1, due to prescription confusion or medication errors. Eighteen adults aged from 18 to 50 years old were exposed (male: 14, female: 3, unknown: 1). The substances registered included: testosterone 1, nandrolone 2, GHB 2, stanozolol 3, clenbuterol 10; only 50% were intentional: stanozolol 3, clenbuterol 3, GHB 2 and nandrolone 1. All but 2 exposures were oral, with one case of intravenous exposure (testosterone) and one by inhalation (clenbuterol). One patient had drug dependent antecedents. Most of the clinical manifestations corresponded to clenbuterol (tachycardia, palpitations, headache, muscle tremors and gastrointestinal symptoms such as nausea and vomiting) and GHB (one case with severe agitation and one with serious CNS depression). The sources of these substances were as follows: medicines (anabolic steroids, clenbuterol), illicit (GHB) and the accidental ingestion of contaminated beef liver. Conclusions: Although anabolic substance use is becoming more frequent, few cases were reported to our Service. The most frequent poisoning cases related to the accidental ingestion of clenbuterol in children and adults (respiratory drug or contaminated food). Since the vast majority of clinical presentations were related to the intentional etiology in adults, the real problem of anabolic drug abuse is most likely underrepresented in poison centre data.

19 A STUDY OF DRUG RELATED DEATHS IN THE STRATHCLYDE REGION OF SCOTLAND OVER THE 14-YEAR PERIOD 1985–1998

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Objective: This paper summarizes the findings from a study of drug related deaths (DRDs) that occurred within the Strathclyde region of Scotland. This area has a population of approximately two and a quarter million. The effects of changes in medical treatment and legislation on the frequency of DRDs were evaluated. Methods: There are various definitions of a DRD in the literature and, therefore, a definition of a DRD for the purpose of this study is described. The post mortem and toxicology reports provided information relating to the cause of death and results of toxicological analyses respectively. Data pertaining to the deceased's medical history, the circumstances of the death and examination of the locus were included in the sudden death reports issued by Strathclyde Police Force. The Department of Forensic Medicine and Science receive all biological samples from post mortem examinations occurring in the West of Scotland and carry out routine analysis for the presence of alcohol and drugs using immunoassay, gas liquid chromatography and high-pressure liquid chromatography. All positive samples are confirmed and quantified by gas chromatography mass spectrometry following extraction from a non-hydrolyzed sample. Results: During the period 1985–1998, the number of Strathclyde samples received by our department for drug analysis increased substantially. A total of 847 DRDs were reported to the various Procurators Fiscal within the Strathclyde jurisdiction. Approximately 80% of deaths occurred in the city of Glasgow with the majority of deaths involving males in their mid-twenties. Toxicological analysis revealed that heroin was the primary drug misused and polydrug use was prevalent. In particular, the concurrent use of heroin with benzodiazepines was evident. Temazepam was the favored benzodiazepine for mixing, however, due to a legislation change resulting in a decrease in this drug's availability in 1996, diazepam became the benzodiazepine of choice. An increase in methadone deaths following the introduction of the methadone maintenance program in Glasgow seems to have subsided. This has resulted from an increase in the number of pharmacies who carry out supervised administration of this, now widely available, drug. It was apparent that a group of individuals who were at high risk from overdose were those who had been recently released from prison. Conclusion: The number of DRDs has increased substantially in the Strathclyde region. Increasing supervision of methadone consumption has led to a decrease in methadone deaths. DRDs amongst recently released prisoners account for a substantial proportion of DRDs per annum.

20 THE CLINICAL SYNDROME OF 'BODY PACKING'

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Body packers, or mules, are persons who attempt to carry drugs concealed within a body cavity, most commonly across international borders. Typically indigent and non-drug users themselves, mules ordinarily harbor cocaine or heroin in their gastrointestinal tract. However, transport of virtually every illicit mind-altering substance has been reported. Although the frequency with which body packing occurs is unknown, Customs agents at major international airports routinely profile passengers from certain 'high-risk' destinations. Estimates from some sources place the number as high as several passengers per plane from these destinations. The medical hazards of body packing are related primarily to the large volume and high purity of the concealed drug and secondarily to the difficulty in diagnosing and managing

victims of packet disruption or mechanical bowel obstruction. A typical body packer usually ingests undiluted drug that has been carefully wrapped in a leak proof, protective covering, such as a condom. Each packet contains approximately 10 g of drug, and a body packer typically ingests approximately 100 packets. This represents several hundred times the lethal dose for the individual and, although it rarely occurs, rupture of even a single packet may prove catastrophic. The clinical presentation of body packers to the hospital varies based on the agent carried and the rate and degree of drug release. For example, gradual cocaine leakage may produce hyperarousal and sympathetic overactivity, while fulminant cocaine poisoning, including seizures and cardiovascular collapse, may occur with frank packet rupture. The decision to investigate the routine recreational-drug intoxicated patient for body packing is usually based on the history of the presenting illness. However, patients may present prior to the development of any symptoms, particularly if law enforcement is involved. Abdominal radiography, while specific, may lack the sensitivity to serve as an adequate screening test. Once identified, urine drug screening may be helpful to determine the packet content in asymptomatic patients. The management of the drug-intoxicated body packer is based on standard toxicological principles, with additional emphasis on aggressive gastrointestinal decontamination; whole bowel irrigation with a polyethylene glycol-electrolyte lavage solution is generally recommended. Heroin intoxicated body packers are successfully managed with mechanical ventilation and/or opioid antagonists and whole bowel irrigation. However, those manifesting cocaine toxicity should be deeply sedated and have immediate surgical packet removal. The difference relates to the inadequacy of pharmacologic and supportive therapy for serious cocaine poisoning as well as the unacceptable delay to complete bowel clearance with whole bowel irrigation. Although reported, the use of upper endoscopy to retrieve packets risks their tearing and the subsequent development of toxicity. Patients with mechanical bowel obstruction should not receive whole bowel irrigation but rather should have their packets removed expeditiously to avoid packet disintegration. The endpoint of gastrointestinal decontamination must be determined in concert with the patients account of the event as well as radiographic confirmation of an emptied gastrointestinal tract. This is best performed using a standard gastrointestinal series with water-soluble contrast including small and large intestinal follow-through. Computed tomography may ultimately prove to be comparable but its exact role is currently undefined.

21 MANAGEMENT OF THE PREGNANT BODY PACKER

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Objective: The medical management of body packers has been well described. However, there are no reports, to our knowledge, which discuss the management of pregnant body packers. We are reporting the first such case requiring medical management of a pregnant body packer. Case report: A 24-year-old female suspected of transporting ingested contraband material was brought by law enforcement officials from Philadelphia International Airport to our emergency department for diagnosis and possible purgation. The patient admitted ingesting cocaine-containing pellets several hours earlier in Jamaica prior to boarding a commercial airliner bound for Philadelphia. The patient denied knowledge of the precise number of cocaine-containing pellets she had ingested and further indicated that she was pregnant. Pregnancy was verified by serum beta sub-unit testing and the patient underwent purgation with polyethylene glycol solution administered per ora (2 liters per hour until clear effluent). Forty-eight cocaine-containing pellets (approximately 2.5 cm in length, multiply wrapped with latex and plastic wrap) were purged from the patient's bowel. The question of possible retained pellets remained a concern since retained pellets could pose a serious threat to the health of both the mother and fetus. While various modalities exist for the qualitative verification of large numbers of intra-luminal contraband drug-containing packages, the optimal diagnostic modality to determine the presence of relatively small numbers of retained packages in the gastrointestinal tract has never been determined. Decisions regarding quantitative verification of retained contraband in the pregnant patient are especially problematic as ultrasound techniques may lack sensitivity and abdominal radiographs may pose a risk for the developing fetus. In this case (following informed consent) it was elected to obtain a single flat abdominal radiograph in order to ascertain the presence or absence of retained drug-containing pellets. No pellets were identified and the patient was discharged in the custody of law enforcement officials. Conclusion: Since unnecessary X-rays should be avoided in all patients, the risk to benefit ratio for obtaining X-rays must be carefully weighed. While adequate doses of polyethylene glycol solution are expected to result in total purgation of all intra-luminal gastrointestinal contraband, this may not always be the case. Abdominal ultrasound may not be reliable in discerning small numbers of contraband packages and computerized tomography for this purpose is contraindicated in pregnancy. A single, flat abdominal X-ray may be considered to rule out the presence of retained contraband

material, however, the optimal modality and protocol for verifying the completion of purgation in the pregnant body packer remains controversial.

22 OPIUM BODY PACKING IN MASHHAD, IRAN

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Introduction: Opium smuggling by intra-abdominal concealment (body packing) is common in the eastern part of Iran. Afghanistan which is the main producer of opium in the world has a long border (>800 km) with the eastern side of Iran. There was no good control on the border particularly during the Iraq-Iran war. Therefore, opium addiction increased dramatically in Iran. Since 1992, there have been more drug smuggling controls and thus, the gastrointestinal tract of some people was abused for opium transport. Leaking and rupturing of the body packs induces severe and even fatal opium poisoning in the carriers. Reports of cocaine and heroin body packing leading to intoxication have been published,[1,5] but opium body packing has been reported only rarely.[6] Patients and Methods: All files of suspected body packers who were referred to the hospital between 1st September 1992 and 31st August 1999 were reviewed. Relevant data including sex, age, clinical and paraclinical findings, treatment measures, number and weight of packs, days of hospitalization and outcome were recorded. Abdominal x-ray was performed in all cases, but ultrasonography and CT scan was done when there was difficulties in diagnosis. Urine morphine concentration was estimated by the computerized polarization fluorometric immunoassay (TDx Analyzer, Abbott). Gastric aspiration and lavage, cathartics ($MgSO_4$ and/or castor oil), whole bowel irrigation and endoscopy were carried out as clinically indicated. Results: Over the 7 years, 1284 (1249M & 35F) cases of suspected body packing were brought to the Emergency Clinic of Poisoned Patients by the police and or emergency ambulance. Of these, 96 males (7.5%) aged 18–45 years were found to be asymptomatic with no signs of packing on abdominal X-ray and no detectable urine morphine concentration. Of the remaining 1188 body packers (1153M & 35F) aged 12–72 years (means of 42 and 26 years for the M and F, respectively), 792 (81.8%) were treated in the Emergency Clinic and were discharged within 24 hours after the packages were cleared from their bodies. Urine morphine concentrations of this group varied between 0 and 250 μg/L. The collected packets (varied between 2 and 254 in each case) were all opium (except 5 heroin packets of 5–20 g in 2 cases), which were packed and sealed in plastic bags weighing 8–42 g. The opium and or heroin body packing was mainly made by ingestion and in only 7 cases, was it done by inserting the packages rectally. The remaining 216 patients were transferred to the Poisons Treatment Ward and or ICU. Of these, 30 (26M & 4F) patients without any signs of intoxication underwent surgery for heavy packing; only in 2 patients was intestinal obstruction diagnosed before surgery. The highest amount of opium (2850 g in 254 packets) was discovered in one of these patients, who expired 2 days later in ICU due to severe intoxication (urine morphine concentration of 1250 μg/L). The other 215 patients all recovered and were discharged uneventfully. Of the 186 patients (15.7%) who showed signs of opium poisoning, 79 underwent surgery (in addition to administration of naloxone and supportive therapy) with 11 (8M & 3F) fatalities. Of the 107 patients who were treated medically, only 6 (4M & 2F) died. The urine morphine concentrations in these patients were high (780–1450 μg/L). The overall mortality rate of the opium body packers was 1.43%, but the mortality rate of the poisoned patients was 9.14%. Discussion: The body packers usually swallow multiple packages of cocaine, heroin, opium or other illicit drugs for purpose of transport across the borders with the intent to sell or receive compensation for transporting the drug.[1,2] Inserting the packages rectally or vaginally is less common as was observed in this study. Rupture or leakage of these packets can be lethal as happened in 18 of our patients despite intensive medical and surgical treatment. Discovery of these individuals is difficult and treatment of the symptomatic patients may require some suspicion, if the history is not obvious.[1–3] Radiological examination may provide evidence of the abdominal packages and aid the diagnosis, as it was performed in all cases in this study. Opium body packing is even more common in the southern east part of Iran. In a report from Kerman,[7] 221 (216M & 5F) opium body packers were studied prospectively in one year (Feb.1996 to Jan.1997). Heroin was also found in 54 of them. The smugglers were taken care of initially in the Prison Infirmary, where 202 of them defecated the packages after ingestion of 30–50 g castor oil. Of the 19 patients, transferred to the University Hospital, 15 were severely intoxicated and 6 of them died despite intensive medical and surgical treatment. Initial treatment is similar to that for opioid ingestion. However, additional treatment such as surgery may be required in cases involving large amounts of retained packages as was done in the above studies. Conclusion: Opium body packing may induce severe intoxication with high mortality. Emergency physicians should be aware of the problem. Abdominal plain radiography, ultrasonography and CT scan are valuable diagnostic modalities in the

assessment of body packers. Estimation of morphine concentrations is very helpful to confirm the diagnosis and to estimate the severity of intoxication. Administration of a cathartic may be effective in asymptomatic mild to moderate opium body packing. In addition to naloxone and intensive care therapy, surgery is indicated in heavy body packing causing severe intoxication. Surgery may also be effective in non-intoxicated heavy opium body packing particularly when there are signs of intestinal obstruction. References: [1]Utecht MJ, Stone AF, Macarron MM. Heroin body packers. *J Emerg Med* 1993;**11**:33–40. [2]Mc Cleave NR. Drug smuggling by body packers: Detection and removal of internally concealed drugs. *Med J Aust* 1993;**159**:750–754. [3]Sporer KA, Firestone J. Clinical course of crack cocaine body stuffers. *Ann Emerg Med* 1997;**29**:596–601. [4]Wetli CV, Rao A, Rao VJ. Fatal heroin body packing. *Am J Forensic Med Pathol* 1997;**18**:312–318. [5]Heinemann A, Miyashi S. Body packing as a cause of unexpected sudden death. *Forensic Sci Int* 1998;**92**:1–10. [6]Nihira M, Hayashida M, Ohno Y. Urinalysis of body packers in Japan. *J Anal Toxicol* 1998;**22**:61–65. [7]Sotoudah Nejad AR, Aghaci M, Poursaidi B, Vahedian Ardakani J. Evaluation of body packing syndrome in Kerman. *J Kerman Med Sci University* 1997;**4**:91–96.

23 VOLATILE NITRITE ABUSE: MECHANISMS OF TOXICITY, FEATURES AND MANAGEMENT

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Background: The volatile alkyl nitrites, for example amyl and butyl (predominantly isobutyl) nitrite, are popular recreational drugs. They are marketed as aphrodisiacs or 'room odourizers' in glass ampoules or bottles under various pseudonyms: 'Poppers' (amyl nitrite), 'Liquid gold', 'Rush', 'Heart-on', 'Thrust' (isobutyl nitrite). These agents are used to improve sexual performance, both enhancing and prolonging orgasm and/or as a smooth muscle relaxant to relax the anal sphincter. They also are claimed to promote a sense of increased well-being with temporary 'detachment' from reality. Bottles of volatile nitrites carry the instruction that they should not be inhaled directly, though this is usually the precise intention of the purchaser. These products may also be ingested. Mechanisms of toxicity: The alkyl nitrites cause vasodilation via nitric oxide mediated vascular smooth muscle relaxation. Vasodilation accounts for many of the effects observed or described by users following volatile nitrite abuse. However, clinically the most important mechanism of nitrite toxicity relates to the ability of these agents to cause methemoglobinemia, via oxidation of heme iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. The precise mechanisms are not understood fully but both direct and indirect mechanisms have been proposed. Direct oxidation of heme iron by nitrite involves a reaction between oxygenated hemoglobin and the nitrite ion, giving rise to methaemoglobin, nitrate and superoxide anion. Indirect heme oxidation utilizes the superoxide anion and involves the production of nitric oxide and hydrogen peroxide. Hydrogen peroxide acts as a nitrite scavenger and terminates these reactions so that nitrite-induced methemoglobinemia is essentially a stoichiometric process. In the presence of methaemoglobin, two mechanisms contribute to tissue hypoxia. Firstly, oxidized heme iron cannot bind oxygen, and secondly, oxidation of one or more of the heme iron atoms of hemoglobin distorts the heme tetramer such that the remaining iron atoms bind oxygen avidly but release it less efficiently, in effect shifting the oxygen dissociation curve to the left. Features: The clinical features of volatile nitrite intoxication reflect their action as potent vasodilators with headache, flushing, blurred vision, postural hypotension and syncope. Vasodilation is followed by reflex vasoconstriction with sinus tachycardia. With continued exposure, methemoglobinemia results. Vasodilation and perhaps mild methaemoglobin formation account for the 'desirable' effects described by those who abuse volatile nitrites for enhanced sexual pleasure or self-exhilaration. These include an altered perception of reality, momentary loss of identity, inner calm and increased skin perception. Irritant effects including burning in the nose and eyes, cough and facial dermatitis are recognized, and transient ECG changes (T wave inversion and ST segment depression) have been reported. Methaemoglobin concentrations less than 20% are usually asymptomatic though they cause slate-gray 'cyanosis' due predominantly to the presence of pigmented methaemoglobin. When 20–40% total hemoglobin is replaced by methaemoglobin, there may be dizziness and headache, features not dissimilar to those caused by vasodilation. Higher methaemoglobin concentrations reflect increasing tissue hypoxia and are unusual following volatile nitrite abuse unless inhalation is substantial or ingestion has occurred. However, in these circumstances, life-threatening methemoglobinemia may result. It is important to remember that individuals with cardiopulmonary disease or anemia, who are more susceptible to an hypoxic insult, may develop features at lower methaemoglobin concentrations that those seen in otherwise healthy individuals. Management: The vasodilatory effects of volatile nitrite abuse are not usually severe and are managed supportively. Most patients who present to the acute medical services have methemoglobinemia. This diagnosis should be considered in any patient who appears cyanosed where the degree of cyanosis is disproportion-

ately greater than the degree of respiratory distress, and is unresponsive to oxygen therapy. It should be remembered that pulse oximetry is unreliable in the presence of methemoglobinemia and arterial blood gas analysis reveals normal partial pressures of oxygen and carbon dioxide and a normal *calculated* hemoglobin oxygen saturation. In healthy adults methaemoglobin concentrations less than 30% total hemoglobin are unlikely to warrant specific treatment. At higher methaemoglobin concentrations, or where clinical features suggest tissue hypoxia, antidotal therapy with intravenous methylene blue 2 mg/kg body weight should be given over 5–10 minutes. Treatment is effective within 30 minutes and a second dose is required rarely. It should be remembered that higher doses of methylene blue may exacerbate methemoglobinemia and/or induce hemolysis. Methylene blue is an inefficient antidote in the presence of glucose-6-phosphate dehydrogenase deficiency as antidotal efficacy is NADPH-dependent. Conclusion: Volatile nitrites are popular recreational drugs. Inhalation and ingestion can lead to significant methemoglobinemia. Prompt diagnosis and appropriate antidotal treatment with intravenous methylene blue can be life saving.

24 VOLATILE SUBSTANCE ABUSE (VSA) IN THE UK

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Background: Volatile substance abuse (inhalant abuse, solvent abuse, anesthetic abuse, 'glue sniffing') is the deliberate inhalation of vapor in order to become intoxicated. This definition does not embrace deliberate inhalation of vasodilators such as nitrites, or insufflation of drugs such as cocaine. Although morbidity associated with VSA is well recognized, the major risk is that of sudden death ('sudden sniffing death'). Death may occur because of physical injury whilst intoxicated, fire/explosion due to abuse of flammable materials, suffocation associated with use of a plastic bag, asphyxiation due to inhalation of vomit, or direct toxicity, probably cardiotoxicity. All VSA-related sudden deaths are thought to be accidental deaths. Methods and Results: Information has been gathered on VSA-related sudden deaths directly from coroners, the UK Office for National Statistics, press cutting agencies, and other bodies. There were 1691 UK VSA-related sudden deaths, 1971–97. Although the average age at death has increased slightly in recent years, most (63%) deaths have occurred in those aged under 19 years. Such deaths are more common in males (87% overall), although in 1997 23% of deaths occurred in females. There is no clear explanation for this gender difference. VSA now accounts for 1 in 50 of all UK deaths in the age range 15–19 years. Purified liquefied petroleum gas (LPG, largely butane) is now the substance encountered most commonly in fatalities. Discussion: VSA is not illegal in the UK, although driving a motor vehicle, for example, whilst intoxicated is against the law. VSA may occur if there is occupational access to volatiles, but is most common in adolescents. UK prevalence surveys suggest that 3–10% of young people experiment with VSA (similar numbers of males and females) and that some 1% are current users. Similar or higher prevalence rates have been reported from many other countries (30–50% in some places). VSA-related deaths continue in the UK (reduced from 152 in 1990 to 73 in 1997) despite continuing governmental action aimed at prevention, which includes legislation designed to restrict availability. Most recently sale of LPG cigarette lighter refills to those aged under 18 years has been made illegal. There are no systematic reports of VSA-related deaths from countries other than the UK, although case examples and small series of fatalities are reported regularly as are examples of VSA-related morbidity. It seems from these reports that the substances abused, the way they are abused, and the age and sex distribution in fatalities, are similar between countries.

25 VOLATILE SUBSTANCE ABUSE IN SPAIN

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Objective: Inhalant misuse is the intentional inhalation of volatile substances in order to obtain euphoric, disinhibiting and exciting effects. Solvents, glues, adhesives, paint, varnish, paint remover, dry cleaning agents, spray paints, nail polish remover, typewriter correction fluid and aerosol propellants are common sources of volatile substance abuse in Spain. In recent years an increase in abuse of volatile substances, not only among those who abuse other drugs, but also in teenagers and children groups, has been reported. We reviewed retrospectively the cases of inhalant misuse reported to our Service. Methods: Human intoxications from inhalation of volatile substances registered by the Spanish Poison Centre from January 1st 1991 to December 31st 1998 were studied. Data were analyzed relative to type of product, composition, age, signs and symptoms, and dependent drug antecedents of the patients. The outcome including

complications after treatment was also investigated. Results: The age of the 79 cases ranged from 8 to 50 years, decreasing until 1998 (mean age: 7 to 21 years) gradually. Of the patients, 11.4% presented dependent antecedents to other abuse drugs and 68.3% were symptomatic. Clinical presentation affected the following systems: CNS (66.6%), gastrointestinal (27.7%), cardiovascular (16.6%), respiratory (9.2%), peripheral nervous system (7.4%), renal (5.5%), hematologic (3.7%), hepatic (3.7%) and other (29.6%). The commercial products more frequently inhaled were solvents (30.3%) and glues/adhesives (24%). We noted the increasing use of medicines with ethyl chloride—local anesthetic inhalation—(8.8%) and one case of aerosol bronchodilator (with fluorocarbons as propellants). The composition most often involved was aromatic hydrocarbons (46.8%), halogenated hydrocarbons (16.4%), aliphatic hydrocarbons (11.3%), ketones (10.1%), local anesthetic inhalation (ethyl chloride) (8.8%), ethers (2.5%), nitrous oxides (2.5%) and aliphatic nitrites (1.2%). Conclusions: In Spain some juvenile groups, even without drug dependent antecedents, inhale volatile substances as abuse drugs due to their effects on the CNS. The high incidence in this population seems to be related to easy accessibility and low costs of these products (e.g. household products). Although the principal compositions of these sources (household and industrial products) are hydrocarbons, an increasing use of drugs such as local anesthetics and aerosol bronchodilators was detected. Based on statistical studies of epidemiology in the Spanish population (essentially from adolescents and childhood), the community and authorities should develop strategies to prevent these exposures or the later use of other substances of abuse.

26 COCAINE—HISTORY OF USE, MANUFACTURE OF PREPARATIONS AND RELATED KINETICS

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History of cocaine use in the Americas: Cocaine has been a recreational drug and a drug of abuse for thousands of years. History offers ample evidence. George Washington used cocaine to ameliorate his tooth pain. Samuel Clemmens and Robert Louis Stevenson publicly supported the perceived beneficial effects of cocaine. Cocaine became popular in the US in the late nineteenth century. In 1891, coca wine became a best seller (two ounces of fresh coca leaves to each pint of Bordeaux wine) when a shrewd Corsican named Angelo Mariani managed to acquire the endorsement of three Popes, 16 Heads of State and 8,000 physicians. Parke Davis sold at least fifteen products containing cocaine. By the turn of the century, though, the drug had acquired a grotesque new imagery—elongated fingernails to carry cocaine to the nostril, nasal douches, and hypodermic needles. Despite the opposition of drug companies, the government began to crack down and by the 1920s, public revulsion against drugs bordered on hysteria. Cocaine was driven underground. Drugs stayed on the fringe of society in the 50s. But in the early 60s, an obscure Harvard lecturer named Timothy Leary began feeding students LSD and advising them to 'turn on, tune in, and drop out.' Fired by Harvard, he promptly became a counter-culture deity. The baby boom generation knew little about drugs, and although the dark side of drug abuse emerged slowly, illicit drug use had became entrenched in this society. The 1970s marked the Second Coming of cocaine, the perfect drug for the new morality-success, the high-performance ethic. Cocaine fit the tight line between high performance and self-indulgence. The easy availability of crack cocaine stimulated an epidemic which continues today. Yet cocaine makes the difference between subsistence and poverty for many South Americans. In Bolivia there is no law that prohibits either the cultivation or the marketing of coca. A law-abiding family can earn $200 a year for harvesting the leaves of *Erythroxylan coca*. Miners in Bolivia chew coca daily to suppress hunger and induce a sense of euphoria that helps them ignore the cold. Manufacture of preparations: Cocaine enters most countries as a hydrochloride salt which is obtained from treating the coca leaves with hydrochloric acid. Because the salt is soluble in water, it can be injected intravenously or absorbed via the nasal mucosa. However, because it decomposes upon heating, chemical manipulation is required to make a stable compound that can be heated and inhaled. Freebase and 'crack' are the same chemical forms of cocaine but they are manufactured by different techniques. Freebase is made by dissolving cocaine hydrochloride in water, adding a base such as ammonia and then a solvent such as ether. The cocaine base is dissolved by the ether which is subsequently evaporated. This method of preparation removes many of the water-soluble adulterants. One of the complications is the potential for burns. Too frequently, a flame is used to more rapidly evaporate the ether and explosions may result. Crack is made by an easier and less dangerous method and has become the most popular form to use. Cocaine hydrochloride is dissolved in water, mixed with baking soda and then heated. The cocaine base precipitates in a soft amorphous mass. The mixture becomes hard as it dries and a cracking sound is heard which reoccurs again when the substance is smoked. 'Bazooka' is a crude preparation of coca leaves mixed with water, kerosene and sulfuric acid. This paste is smoked in South America, but has not become popular in the United States.

Kinetics: The pharmacokinetics and pharmodynamics of cocaine are dependent on the method of use and the physiochemical form of the drug. Cocaine is a weak base (pKa = 8.6) and crosses the cell membranes rapidly. Following inhalation or intravenous injection, cocaine rapidly enters the systemic circulation and the brain. Cocaine is more slowly absorbed from the nasal mucosa due to concurrent vasoconstriction. Euphoria occurs in 3 to 5 minutes following nasal insufflation and within seconds following inhalation or injection. When inhaled or injected, peak arterial concentrations greatly exceed maximal venous concentrations. The rapid entry into the brain causes the intense euphoria and addictiveness of the inhaled product. The drug is well absorbed orally but undergoes significant first-pass metabolism resulting in a 40% bioavailability. Enzymatic and nonenzymatic hydrolysis to benzoylecgonine accounts for 45% of cocaine metabolism and enzymatic hydrolysis to ecgonine methyl ester accounts for an additional 40%. Both of these metabolites are relatively inactive. A small amount of the parent drug undergoes hepatic microsomal oxidation to norcocaine, which has significant pharmacologic activity. As cocaine is metabolized in part by the cholinesterase enzyme, persons with acquired or congenital deficiency of plasma cholinesterase are likely to metabolize the drug more slowly and may be at greater risk for toxicity.[2] The actions of the metabolites explain the clinical signs and symptoms of cocaine use. Cocaine, norcocaine, ecgonine methyl ester and benzolyecognine all cause cerebrovascular vasoconstriction when suffused over the brain or administered into cerebral circulation. Cocaine and norcocaine are potent vasoconstrictors, convulsants, and sodium channel antagonists. Ethanol is frequently consumed with cocaine. In the presence of ethanol, cocaine is transesterified to a benzoylecgonine ethyl ester, cocaethylene. Cocaethylene inhibits dopamine transport and produces the same behavioral effects as cocaine in laboratory animals. Cocaine users report enhanced and prolonged euphoria when using both agents simultaneously. When mice are pretreated with ethanol prior to cocaine administration, the concentration of the benzoylecgonine metabolite is decreased, and cocaine and norcocaine concentrations are increased which may explain the increased toxicity of this combination.[3] Cocaine blocks the dopamine transporter system and increases free dopamine in the brain. Other agents also increase dopamine in the brain (amphetamines, chocolate, gambling, sex). PET scans have demonstrated changes occurring in dopamine-binding sites following acute and chronic use of cocaine.[4] References: [1]Boghdadi MS, Henning RJ. Cocaine: Pathophysiology and clinical toxicology. *Heart Lung* 1997;**26**:446–485. [2]Hoffman RL, Morascco R, Goldfrank LR. Administration of purified human plasma cholinesterase protects against cocaine toxicity in mice. *J Toxicol Clin Toxicol* 1996;**34**:259–266. [3]Henning RJ, Wilson LD, Glauser JM, Lavin E, Sebrosky G, Sutheimer CA. Cocaine plus ethanol is more cardiotoxic than cocaine or ethanol alone. *Crit Care Med* 1994;**22**:1896–1906. [4]Volkow ND, Wang GL, Fischman MW, *et al*. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 1997;**386**:827–830.

27 COCAINE OVERDOSE: CLINICAL MANIFESTATIONS AND TREATMENT

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Although recent data suggest that the use of cocaine is declining, it is still the leading cause of illicit drug-related visits to the Emergency Department. The complications of acute cocaine intoxication result from its ability to modulate neurochemical transmission by blocking the reuptake of biogenic amines. Animal models demonstrate that inhibition of dopamine reuptake is responsible for the psychomotor agitation, which commonly accompanies cocaine use. Blockade of norepinephrine reuptake produces cocaine's hypertensive effects, while blockade of epinephrine reuptake produces tachycardia. While the serotonergic effects of cocaine are not as well characterized, inhibition of serotonin reuptake is most likely responsible for the anorexia and hallucinations associated with cocaine use. Furthermore, cocaine enhances central nervous system arousal by potentiating the effects of excitatory amino acids. Studies with excitatory acid antagonists demonstrate that these neurotransmitters are the most likely etiology of cocaine-induced seizures. Additionally, cocaine has a direct proarrhythmic effect on the myocardium which results from sodium and potassium channel blockade, and most resembles the type I antiarrhythmic agents. Finally, cocaine effects of unclear etiology include enhanced platelet aggregation, impaired thrombolysis, and accelerated atherogenesis. The metabolites of cocaine may contribute to clinical toxicity as well. A minority of cocaine undergoes demethylation in the liver to form norcocaine, which has effects that are essentially indistinguishable from the parent drug. Approximately half of a given dose of cocaine undergoes non-enzymatic degradation to benzoylecgonine. This metabolite is a direct vasoconstrictor with a much longer half-life than the parent drug. Whereas other metabolites may have clinical toxicity, these effects are not well described. In the presence of ethanol, however, cocaine (benzmethylecgonine) is transesterified to benzethylecgonine, a metabolite also known as ethylcocaine or cocacethylene, which has potent and long-lasting effects similar to cocaine. The above mechanisms produce multiple organ toxicity that largely results from hyperthermia, vasospasm, and increased vessel

shear force from the combined effects hypertension and tachycardia. Bland or hemorrhagic infarctions of all vascular beds have been described, but seem to predominate in the central nervous and cardiovascular systems. Rhabdomyolysis with multiple electrolyte abnormalities and resultant renal insufficiency commonly occurs. However, hyperthermia, with subsequent DIC, multiple organ failure and cerebral edema is the gravest complication of cocaine use. Currently there is no specific antidote for cocaine poisoning. As such, treatment is largely supportive, with specific attention given toward control of behavior. Sedation (with a benzodiazepine) is the safest method of control, with strong support from animal models and clinical practice. Active external cooling is also required when temperatures exceed 41°C. Although some authors have used haloperidol with reported success, animal experience advises against this practice because of its potential to exacerbate hyperthermia, lower seizure threshold and produce malignant dysrhythmias. Hypertension and tachycardia usually respond to sedation and cooling. In the event that specific antihypertensive therapy is required, beta-adrenergic antagonists and mixed alpha- and beta-adrenergic antagonists are absolutely contraindicated. Phentolamine or another direct-acting vasodilator can be used. Coronary syndromes typically respond to above measures. In addition nitroglycerin has documented efficacy, and aspirin and heparin seem reasonable. Rarely, in the setting of coronary infarction, thrombolytic therapy has had favorable use. Pending the development of specific antidotal therapy, evidence supports an approach that emphasizes sedation and rapid cooling for patients with acute cocaine intoxication. Rarely, adjunctive vasodilatory agents can be used.

28 NONINVASIVE MEASUREMENT OF HEMODYNAMIC PARAMETERS IN MILD-MODERATE ACUTE COCAINE INTOXICATION

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Background: Cocaine intoxication is known to have variable effects on the cardiovascular system. It is widely believed that mild-moderate cocaine intoxication produces hemodynamic effects primarily via central nervous system stimulation of the autonomic nervous system, resulting in high total peripheral resistance (TPR). Methods: We evaluated observational hemodynamic data obtained from a convenience sample of urban emergency department patients presenting with acute cocaine intoxication. Eight patients (mean age = 28 years) with acknowledged cocaine ingestion and drug screens positive for cocaine metabolites were evaluated using a thoracic electrical bioimpedance (TEB) monitor. Two of these patients showed signs of congestive heart failure (CHF) upon presentation. Evaluated hemodynamic parameters include heart rate (HR) in beats/minute, blood pressure BP in mm Hg, mean arterial pressure (MAP) in mm Hg, cardiac output (CO) in liters/minute, and total peripheral resistance (TPR) in dynes sec/cm^5. Results: The results are shown in the Table. Six patients without signs of CHF had relatively high cardiac output and low TPR measurements. Two patients with signs of CHF had relatively low cardiac output and high TPR measurements. Conclusions: This observational study utilized a portable noninvasive hemodynamic monitor to evaluate patients with acute cocaine intoxication in the emergency department. Our limited data indicate that six patients without signs of CHF had relatively high cardiac output and low TPR by TEB measurement. Two patients with signs of CHF had relatively low cardiac output and high TPR by TEB measurement. A prospective study is currently in progress to assess by TEB the hemodynamic parameters of patients with acute cocaine intoxication.

Hemodynamic parameters in patients with cocaine intoxication

Patient	HR beats/min	BP mm Hg	MAP mm Hg	CO L/min	TPR dynes sec/cm^5
1	98	123/57	79	7.9	720
2	142	174/74	107	8.8	960
3	131	144/75	98	7.5	1040
4	78	115/88	97	7.5	960
5	97	123/58	79	6.1	960
6	120	180/91	120	7.5	1280
7†	127	185/95	125	4.1	2400
8†	99	294/170	211	2.8	6000

†*Patients presenting with clinical signs of CHF*

29 GAMMA-HYDROXYBUTYRATE, GAMMA-BUTYROLACTONE, AND BUTANEDIOL: ABUSE AND EFFECTS

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Gamma-hydroxybutyrate (GHB) is a naturally occurring neurotransmitter, which was initially introduced as a general anesthetic but decreased in use due to adverse effects. It has also been utilized for therapy of opiate and ethanol withdrawal, and in the treatment of narcolepsy. Abuse has become widespread due to its purported properties as a growth hormone stimulant, appetite suppressant, euphoriant, sedative, and sexual stimulant. The drug has also been reported to be used for 'date-rape' due to its ability to induce rapid-onset sedation and amnesia. With subsequent restrictions on GHB sale and use, its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are being used as substitutes to produce similar clinical results in abuse. In addition to acute toxicity, physical dependence and a withdrawal syndrome have been described. GHB is synthesized endogenously from gamma-aminobutyric acid (GABA) in brain tissue via the intermediate succinic semialdehyde. GHB is found in greatest concentrations in the substantia nigra, thalamus, and hippocampus. It is known to affect several neurotransmitter systems and receptor sites. GHB is thought to bind to GABA–B receptor sites in the brain, and to specific GHB-receptors. At high doses of GHB, increased levels of acetylcholine and 5-hydroxytryptamine have been found. Dopamine release appears to be affected in a biphasic fashion by GHB, with low doses inhibiting and high doses stimulating release. GHB also stimulates growth hormone release, leading to its use as a body builder, yet there is no solid evidence of enhanced muscle growth. GHB is manufactured illicitly from gamma-butyrolactone, which is heated and dissolved in sodium hydroxide. The street drug may be contaminated with this caustic. One teaspoon of the liquid street preparation contains approximately 1 gram of GHB. Sleep induction occurs with doses of 25–50 mg/kg, and toxic effects can occur at doses greater than 60 mg/kg, or 4–5 grams in an adult. Therapeutic doses are 100 mg and 50 mg orally for narcolepsy and alcohol withdrawal respectively. However, up to 20 to 30 grams have been ingested without serious effects. GHB can be measured in plasma and urine by gas chromatography. Doses of 75 mg/kg to induce sleep result in peak concentrations of approximately 1 mmol/L, and coma occurs from higher doses at levels greater than 2.5 mmol/L (260 mg/L). GBL is an industrial solvent, and a constituent of paint, nail polish and glue removers. It is also marketed as a dietary supplement and abused as a GHB substitute. When ingested, it is endogenously converted to GHB. It has greater bioavailability then GHB, and therefore increased clinical effects. The United States FDA has asked manufacturers to recall GBL-containing products, but they remain readily available. BD is an aliphatic alcohol, which is also a GHB precursor, and is used in manufacturing processes of polyurethane and polymers. Although it may have direct neurologic effects, its primary effects are through its conversion to GHB. Interestingly, ethanol inhibits the degradation of BD to GHB, presumably by competing for alcohol dehydrogenase. Therefore, co-ingestion of alcohol may delay or reduce the toxicity of BD. GHB initially induces a hypnotic state, and causes an unusual absence-type seizure activity on the EEG. However, epileptic form activity has not been demonstrated. In narcoleptic patients, GHB diminishes the frequency of night-time awakenings, cataplexy, and sleep paralysis. The toxic effects of GHB, GBL and BD are essentially identical. The typical presentation is that of decreased mental status, including deep coma in over one half of cases. Milder neurologic effects with lower doses include ataxia, nystagmus, somnolence, and disinhibition. Respiratory depression and loss of the gag reflex often are associated, and are in direct proportion to the depth of coma. Hypothermia and bradycardia occur in more prolonged or severe cases. In one large series, hypotension occurred in 10% of cases but only when co-ingestants such as alcohol or another drug was involved. Although seizures have been reported, these likely represent clonic activity consistent with that seen in GHB anesthesia induction. With stimulation or during emergence, myoclonic jerks, confusion, aggressive behavior, and combativeness often occur. Recovery and awakening typically occur rapidly, within 5 hours of exposure in most cases. Autonomic effects include diaphoresis, emesis, and bladder or bowel incontinence, consistent with enhanced acetylcholine release. Therapy is primarily supportive, with particular attention to airway protection and respiratory support. Intubation is necessary for only the most severe cases and often precipitates violent combativeness. Therefore, a conservative approach to intubation is recommended. Atropine may be needed for symptomatic bradycardia, and intravenous fluid boluses for hypotension. The GABA antagonist flumazenil has been shown to decrease GHB-induced growth hormone secretion, but has not reversed clinical effects. Likewise, naloxone blocks some biochemical effects of GHB but does not reverse GHB-induced coma.

30 EVOLVING ABUSE OF GHB IN CALIFORNIA: BODYBUILDING DRUG TO DATE-RAPE DRUG

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Introduction: Gamma hydroxybutyrate (GHB) was synthesized in France over 40 years ago and used primarily as an adjunct to anesthesia. Its appearance in California's health-food stores in 1990 began a phase in which GHB use has evolved rapidly. Initially GHB was marketed to bodybuilders for its presumed anabolic effects associated with stimulated growth hormone release. This use quickly revealed its acute toxic effects: coma, myoclonus and bradycardia, but also led to the recognition of the mood altering effects, disinhibition, euphoria and dissociation. GHB acquired considerable status as a recreational drug of abuse for euphoria following a 1993 death in Hollywood that focused attention on GHB use in the club scene. The novelty of GHB and its disinhibiting effects without a hangover, motivated its use as a sex-enhancing drug. Unfortunately, GHB use followed a pattern of abuse seen with flunitrazepam, and in 1996 GHB began to be used to facilitate sexual assault. Fatalities: It was not until 1995 that toxicology tests for GHB in bodily fluids became available. The Federal Drug Enforcement Administration has since documented more than 58 GHB related fatalities in the United States. Death occurs from abrupt loss of consciousness leading to accident or injury, apnea, positional asphyxia or pulmonary aspiration of gastric contents. Death has also occurred from the combined effects of ethanol or other depressants with GHB. GHB and precursors: California added GHB to its Controlled Substance Act in 1997. Alternative use of the precursors, gamma butyrolactone and 1,4-butanediol is promoted to avoid the criminal penalties associated with GHB. Not only is gamma butyrolactone easily converted *in vitro* to GHB by base hydrolysis of the lactone ring, but it is also converted *in vivo* by a peripheral lactonase to GHB with a conversion half-life of less than one minute The *in vivo* conversion of 1,4 butanediol is also rapid via oxidation by alcohol dehydrogenase to gamma butyraldehyde then aldehyde dehydrogenase to GHB. Formulations: These products are easily and cheaply available over-the-counter, through the Internet and by mail order. They may be powders, capsules, gels of various concentrations, colors and flavors. Exposures in California: The California Poison Control System covering a population base of 32 million people was consulted on 232 cases of adverse effects with GHB or the precursors in 1998 and 356 exposures in 1999. Among this group were patients experiencing withdrawal symptoms after compulsively frequent use. The withdrawal symptoms include central nervous system stimulation and autonomic instability. GHB-dependant patients reported frequent ingestion of GHB, every 1–3 hours around-the-clock with nighttime awakening for doses to prevent the symptoms of withdrawal. The duration of GHB use is typically greater than two months. In 3 cases the product used was obtained and analyzed allowing estimation of the daily dose that ranged from 43–144 g/day. The onset of withdrawal symptoms, insomnia, tremor and confusion begins rapidly within 1–6 hours after the last dose of GHB. Patients experience central nervous system symptoms of tremor, auditory and visual hallucinations and delirium requiring restraints. Autonomic stimulation with tachycardia and hypertension occurs. The duration of symptoms ranges from 5–15 days. Treatment is supportive with sedation to avoid escalation of symptoms resulting in hyperthermia, rhabdomyolysis or seizures. Benzodiazepines and barbiturates have been used although high doses may be required. An overdose fatality occurred in a patient attempting home management of GHB withdrawal symptoms using hydrocodone. Information calls to the California Poison Centers reveal drug facilitated assault as an insidious problem that is often unrecognized in a community until education increases awareness and improves the timeliness of toxicology testing. Recognizing the rapid elimination of some sedatives such as GHB, urine has become the analytic specimen of choice due to the longer duration of detection for most sedatives. The assault cases often involve serial predators whose method of drug facilitation and location of the crime result in a pattern apparent only after multiple reports. Attention to the symptoms and time course of intoxication can focus the investigation and direct analysis to include drugs such as flunitrazepam and GHB that are missed in routine screens. In the past few years many types of sedatives have been detected in the urine of suspected victims. In addition to flunitrazepam and GHB, analysis detected ethanol, various benzodiazepines, opiates, phenothiazines, barbiturates, ketamine, carisprodol, cyclobenzaprine, meprobamate, diphenhydramine and the historical Mickey Finn, chloral hydrate. Suspicion is aroused when victims report unexplained memory loss, loss of consciousness, an inability to move, nausea, vomiting, incontinence, persistent dizziness or drowsiness after a sexual assault.

31 GHB INTOXICATIONS IN SWEDEN

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Objective: Gamma-hydroxybutyrate (GHB) has become increasingly popular as a recreational drug among young people in certain parts of Sweden. This retrospective study was undertaken to survey the epidemiology of the abuse of GHB and to evaluate the symptomatology. GHB is not registered for medical use in Sweden. Case series: From 1998 to October 1999, the Swedish Poisons Centre received 61 discharge summaries concerning patients hospitalized because of GHB intoxication throughout Sweden. During the same period the Poisons Centre answered 271 telephone calls about GHB poisoning. Results: The majority of the 61 patients reported on in the discharge summaries were found unconscious (81%) and had an uneventful recovery in the hospital within a few hours. Men predominated (73%) and most of them were older than 20 years of age. Many patients had co-ingested alcohol. Generalized convulsions occurred in 10% and bradycardia was registered in 25% of the cases. One patient with a head injury illustrates the risk of trauma when rapid unconsciousness and collapse supervene. Disturbances of the respiratory pattern were seen in 13% of the patients. Abnormal pupil reactions were observed in 16% and miosis was somewhat more common than mydriasis. Circulatory parameters were within the normal ranges in all cases but one. This patient developed a junctional rhythm followed by an atrioventricular block requiring treatment with a temporary transvenous pacemaker. The cases were not evenly distributed over the country. A clear predominance was noted for the Gothenburg area and another city area on the northern Baltic coast. The number of telephone inquiries about GHB is steadily increasing. Approximately 20% of the questions concern teenagers. In one telephone consultation signs of GHB abstinence were evident in a man who admitted daily use of GHB for the last few years. In the study material there were no deaths but two fatalities have previously been reported in Sweden. Both victims were found dead outside hospital and also had high blood levels of ethanol. Another fatal case, presumably caused by GHB is presently under investigation. Conclusion: Despite the risks of serious effects, especially in the case of an overdose, GHB is increasingly abused as a recreational drug and a stimulator of growth hormone release. Rapid loss of consciousness is common and these patients may constitute a challenging diagnostic problem on admission to hospital. The acute symptoms normally vanish within a few hours and for patients treated in hospital the prognosis is good.

32 ELECTROENCEPHALOGRAPHIC EFFECTS AND PHARMACOKINETICS OF GAMMA-HYDROXYBUTYRATE IN THE RAT

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Objectives: Gamma-hydroxybutyrate (GHB) is an older anesthetic and recently emerged as a recreational drug leading to cases of abuse. Little is known about the central nervous system (CNS) effects of GHB in relation to its plasma concentrations. In order to gain better insight into the CNS pharmacodynamics of GHB we studied the link between the GHB induced electroencephalographic (EEG) changes and its plasma concentrations in an animal model. Methods: Male Wistar rats ($n = 7$) were instrumented with EEG electrodes. GHB was administered intravenously in a continuous infusion (450 mg/kg within 10 min). One control animal received an equimolar saline solution. Blood pressure and heart rate were continuously monitored. A 6 lead EEG was continuously recorded and subjected to off-line quantification using aperiodic analysis which determines the EEG amplitude on a wave by wave basis. After screening for a suitable EEG parameter, the GHB-induced EEG changes were quantified using the total amplitudes for 2.5–4.5 Hz and 15.5–30 Hz frequency range. Blood samples were taken over 6 hrs and plasma concentrations of GHB were determined by GC-MS. Results: Saline infusion did not alter the EEG signal. Following the start of GHB infusion, a transient increase in blood pressure was observed with a simultaneous decrease in heart rate. Plasma concentrations of GHB showed Michaelis-Menten elimination kinetics with a distribution phase. For the frequency band 2.5–4.5 Hz, the EEG amplitude versus plasma concentration relationship exhibited a biphasic pattern with profound hysteresis due to a delay in distribution between plasma and biophase. This hysteresis was minimized using a hysteresis minimization program incorporating an effect compartment. This procedure yielded a first order-rate equilibration constant of 0.13 ± 0.02 min^{-1} describing the transfer of drug from the central compartment to the effect compartment. For the frequency band 15.5–30 Hz, the EEG amplitude versus plasma concentration relationship showed a monophasic inhibitory pattern, also displaying hysteresis. The EEG amplitude for this frequency range was related to the plasma concentrations of GHB with the use of an

effect compartment with an inhibitory sigmoid E_{max} pharmacodynamic model. This resulted in an equilibration rate constant of 0.12 ± 0.02 min^{-1} and the following pharmacodynamic parameters: E_0 = 711 ± 71 μV/s, E_{max} = 445 ± 45 μV/s, EC_{50} = 295 ± 37 μg/mL, Hill factor = 5.6 ± 1.3. Conclusion: GHB produces EEG changes in the lower frequency range analogous to other general anesthetics, but also changes in the higher frequency range. Linking of these effects with the plasma concentrations is feasible and may contribute to a better understanding of the CNS effects observed in anesthesia and overdose.

33 PITFALLS AND PARADOXES IN THE ASSESSMENT OF SEROTONERGIC DRUG NEUROTOXICITY-LESSONS LEARNED FROM MDMA

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Serotonergic drugs neurotoxicity (SDN) refers to drug induced toxic effects on serotonergic neurons. Many drugs have serotonergic effects, some have been implicated as causing SDN. The assessment of SDN is a daunting task because of the challenges implicit in determining adverse effects on the serotonergic nervous system. Among those agents implicated in causing SDN is the serotonergic substituted phenylethylamine (3,4-methylenedioxymethamphetamine, MDMA). MDMA has emerged as a model for the study of SDN and in this role serves to illustrate the challenges associated with the assessment of this phenomenon. Ideally, conclusions on toxicologic effects should be based on prospective controlled studies. None exists regarding MDMA. Alternatively, epidemiologic studies can be most helpful. However, the few that exist are marred by the large number of confounding variables implicit in this kind of research. A less desirable alternative to human studies is animal studies. Although primates are better models for human disease than are rodents, the limitations implicit in using primates, and the better characterization of rodents render the latter more commonly studied. This is illustrated in the study of MDMA SDN in which most of the publications use the rat model. Animal neurotoxicology experiments typically use one of the following: (i) Morphologic evaluations, (ii) Biochemical markers, (iii) Integrity of high affinity uptake pumps, (iv) Functional studies. An evaluation of a potential neurotoxicant should selectively utilize all of these approaches. Only the first three have been utilized regarding MDMA SDN. A fundamental consideration in the use of animals is the appropriate dose. To be relevant to human toxicology the dose in animal studies should be aimed at achieving a tissue or blood concentration similar to that obtained in humans. However, often doses used in animal studies are significantly in excess of those used by humans, in order to magnify the likelihood of an effect. Because of these high doses it is often difficult to reach conclusions about what may happen at lower, more therapeutically relevant doses. For example, virtually all of the rodent studies on MDMA SDN derive from a model[1] showing that extremely high doses of the MDMA analog MDA had a dramatic depleting effect on brain serotonin (5-HT) levels. These doses (20–80 mg/kg) are in excess of those used by humans. Thus, effects observed are questionably related to what may occur with standard human use of MDMA. Morphologic studies are considered the 'Gold Standard': The generally considered 'gold standard' in neurotoxicology are morphological studies which typically involve general microscopic techniques, or immunocytochemical evaluations looking at particular cell populations or components of cells. Using the Ricaurte regimen for example, it has been shown that MDMA preferentially causes axonopathy of serotonergic neurons without significant effects on adrenergic axons or cell bodies. A morphologic characteristic of axonal injury is reactive astrogliosis, which is normally determined by finding increased levels of glial fibrillary acidic protein[2] have demonstrated reactive gliosis in rodents following MDMA administration. However, the MDMA studies show that morphologic evaluation of SDN is fraught with potential pitfalls. Multiple studies, (for example Scanzello et al.[3]) have demonstrated that MDMA in large doses can cause immunohistochemical indications of loss of serotonergic axons. However many of these changes may be reversible. Thus, in the absence of frank morphological evidence of unequivocal cell death, it may be difficult to distinguish between temporary axonal loss and permanent effects. Biochemical markers of neuronal cell function are a common measure of neurotoxic effects: For SDN common markers are levels of either tryptophan hydroxylase, 5-HT, or its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA), either in brain regions or in the cerebral spinal fluid (CSF). The value of the latter is that sampling can relatively easily be done in humans. Studies with MDMA illustrate that conclusions utilizing these biochemical markers must be cautiously interpreted. For example, some serotonergic drugs (such as MDMA) cause serotonin release from cells. Therefore the finding of decreased 5-HT or 5-HIAA in a brain region may be an expected trivial observation. Thus it is difficult to distinguish between primary physiologic effects and subsequent undesirable events. For example, it is possible to deplete 5-HT levels in multiple regions of the brain following a large dose of MDMA, however, subsequent analysis may show 5-HT reconstitution. In addition, the time course for this analysis can be quite important

as there can be an initial phase of serotonin release followed only later by an adverse effect on the cell, which may or may not be reversible. Several studies have demonstrated that human MDMA abusers have decreased CSF HIAA without any effect on biochemical markers of andrenergic function. However, this can occur without any clear alterations in serotonergic function, including sleep, mood, or appetite. Thus, the significance of these findings is unknown, and of questionable significance. High affinity uptake pumps as a measure of terminal integrity: Damage to a nerve terminal may be assessed by determining the quantitative integrity of its uptake pumps. Those can be assessed in animals by evaluating the binding of specific agonists. For example, the serotonin transporter can be evaluated by the binding of agents paroxetine or fluoxetine. PET studies can be done in man using the carbon 11-labeled radioligand McN-5652, which appears to be specific for the 5-HT transporter. However, as demonstrated in studies in human MDMA users, there may be multiple confounding factors to this technique. These include a wide range of normal values and a lack of appropriate dose response. Studies evaluating a toxicologic effect should generally be validated by dose response. Although the animal studies appear to demonstrate that high dose MDMA causes a decrease in terminal 5-HT transporter, rodent studies suggest that this normalizes. Thus, at least in the rodent, this may be a reversible effect. The MDMA experience shows us that animal studies in neurotoxicology have limitations. Ultimately, the determination of the existence of a neurotoxic effect relies on human clinical and epidemiologic studies. References: [1]Ricaurte G, Bryan G, Strauss L, Seiden L, Schuster C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science* 1985;**229**:986–988. [2]O'Callaghan JP, Miller MB. Neurotoxicity profiles of substituted amphetamines in the C57BL/6J mouse. *J Pharmacol Exp Ther* 1994;**270**:741–751. [3]Scanzello CR, Hatzidimitriou G, Martello AL, Katz JL, Ricaurte GA. Serotonergic recovery after (+/−) 3,4-(methylenedioxy) methamphetamine injury: Observations in rats. *J Pharmacol Exp Ther* 1993;**264**:1484–1491.

34 METHAMPHETAMINE ABUSE

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Methamphetamine has become one of the most commonly abused substances in the United States. It has also become a major drug of abuse in the Pacific Rim countries particularly Korea, Taiwan and Japan. The United States experienced epidemics of methamphetamine abuse in the 1950s, 1960s and 1970s. The current popularity of this drug began in the San Diego area of Southern California in the early 1980s and recently has spread to other portions of the country. Unlike previous episodes of methamphetamine abuse, which involved diversion of medical supplies of the drug, in the current epidemic clandestine manufacturing of methamphetamine accounts for virtually the entire supply. In addition to the problems associated with abuse of methamphetamine, the illegal laboratories producing the drug are also associated with significant environmental contamination resulting from illegal disposal of unused chemicals or by-products of manufacture. In the 1980s most clandestine laboratories were small and highly mobile and operated by a small group of individuals. More recently, organized crime and gangs are involved in the production resulting in significant ancillary crime activity. In addition, methamphetamine users are frequently involved in violent crime, homicide and suicide. The most commonly used method of manufacture involves the removal of a hydroxyl group from the β position of the ethylamine side chain of ephedrine resulting in methamphetamine. The use of pharmaceutical grade ephedrine results in highly pure and stereospecific methamphetamine. Other processes using phenyl-2-propanone result in a product that may contain significant amounts of contaminants. Methamphetamine has potent CNS stimulant as well as strong peripheral sympathetic activity. The CNS effects of methamphetamine are thought to be due to release of the biogenic amines, norepinephrine, dopamine and serotonin from presynaptic storage sites while the peripheral effects are thought to be caused by release of norepinephrine from sympathetic neurons. Methamphetamine can be ingested, insufflated, smoked or injected. The onset of action is dependent on the route of exposure and the duration of action may be 6 to 8 hours or longer. Users experience CNS stimulation often with euphoria and aggressive behavior. Chronic use rapidly leads to the development of tolerance with anxiety, delirium, hallucinations, paranoia, fatigue and depression. The overdose toxicity is an extension of the pharmacology of the drug with seizures, cardiac dysrhythmias, hypertension, hyperthermia and vasospasm leading to ischemia of the heart, kidneys, brain and other organs. Physical restraint should be avoided if possible and benzodiazepines should be used to control agitation and seizures. Hyperthermia is a frequent and rapidly fatal complication that must be recognized and managed rapidly. Often adequate sedation will lower heart rate and blood pressure but in some cases short acting β adrenergic blocking agents and vasodilators may be needed. As rhabdo-

myolysis leading to acute renal failure frequently occurs following severe agitation and hyperthermia, urinary acidification, which in the past was suggested to enhance elimination, should be avoided.

35 THE FOUR ECSTASYS (HERBAL, CHEMICAL, LIQUID, OTC): PATTERNS OF USE, ABUSE, AND EXPERIMENTATION BY ADOLESCENTS IN A SUBURBAN CLINIC

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Background: Ecstasy (XTC) includes four distinct chemicals of abuse which are capable of causing hallucinations, coma, and death. Liquid ecstasy refers to the central nervous system depressant gamma hydroxybutyrate (GHB). Herbal ecstasy refers to products containing the stimulant Ma Huang or ephedra. Chemical ecstasy refers to 3,4-methylenedioxymethamphetamine (MDMA) containing substances. Associated with all-night dances known as 'Raves', it's considered the most dangerous, and most commonly abused form of XTC. OTC ecstasy refers to the opioid dextromethorphan (DMX). Operators of Raves are becoming aware of the dangers of XTC, but are the adolescents who experiment with these substances so aware? Objective: To evaluate if the risk associated with XTC would affect experimentation or discourage repeat usage? Method: We surveyed 200 patients between the age of 11 and 17 years at a suburban clinic about their experiences and use patterns with any form of XTC. Results: Thirty seven (18.5%) tried a form of XTC at least once (20 females and 14 males). The youngest age of experimentation was 12 years (3 females, 2 males), although most tried XTC for the first time at age 14 years (15 female, 8 male). Thirty-one (15.5%) experimented with MDMA (average 14 years), usually associated with raves or other parties. Three of the 31 (10%) required treatment in a health care facility, and 3 (10%) abused it on a regular basis. Four (2%) claimed to have tried GHB and MDMA (all male, aged 14–17). None claimed to use DMX, although 32 adolescents knew it could cause hallucinations. Four (2%), all male (15–17), used only liquid XTC (GHB), claiming to have done so regularly to build muscle mass. Two (1%) 17-year-old females used Ma Huang for weight reduction over a period $>$ one month. Discussion: Approximately 10% of adolescents surveyed who experimented with MDMA claimed to have repeated the experience. Most respondents expressed concern about the safety of such drugs, and were unlikely to abuse MDMA again, although continued attendance at Raves and parties where MDMA might be available remained likely. Unlike MDMA, respondents who used GHB or Ma Huang did so for a specific outcome—bodybuilding or weight loss, and were more likely to be continuous users. Conclusion: XTC is a dangerous collection of drugs, and the use of these products is unlikely to stop in the near future. Younger adolescents seem particularly vulnerable to MDMA experimentation. Patient education, an active partnership with our patients, and early intervention are essential to slow the use of these drugs.

36 LIFE-THREATENING LEVO-α-ACETYLMETHADOL (LAAM) OVERDOSE

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Objective: Levo-α-acetylmethadol (LAAM) is an opioid agonist with an extremely long half-life and minimal euphoriant effects. Like methadone, it is used as substitution therapy for opioid addiction. In part due to its limited use, there are no published cases describing the clinical effects or pharmacological properties of LAAM overdose. This report describes an unintentional, iatrogenic overdose in a participant in a LAAM maintenance program. Case Report: A 39-year-old man with a history of heroin abuse who had discontinued LAAM therapy 6 months earlier was restarted on therapy five days prior to presentation because of renewed craving for heroin. He received an initial dose of 20 mg orally, followed 3 days prior to admission by the same dose. On the day prior to admission, the treating physician doubled the dose to 40 mg orally. That evening, the patient's spouse noted that the patient was acting 'high' and vomited several times. After having remained immobile for approximately 16 hours while 'sleeping', he was found unresponsive and 'foaming at the mouth'. In the ED, the patient was unresponsive, had constricted pupils, and shallow respirations with an oxygen saturation of 80% by pulse oximetry. Vital signs were: pulse 86/min; BP 140/80 mm Hg; and respiratory rate 18/min. Administration of naloxone (2 mg IV) produced agitation and vomiting. Standard laboratory analyses were normal except for a CPK level of 6778 IU/L (normal $<$40 IU), and urine analysis demonstrating hematuria and proteinuria. Urine toxicology screening for morphine, methadone, methaqualone, propoxyphene, barbiturates, and benzodiazepines was negative. Several hours after arrival, the patient required endotracheal intubation for respiratory distress, and a chest radiograph demonstrated bilateral pulmonary edema without cardiomegaly. He received supportive care, including mechanical ventilation, for 2 days at which time his respiratory status normalized and rhabdomyolysis resolved. The patient denied taking any drug or substance other than LAAM. Serum collected at the time of presentation was analyzed

by gas chromatography/mass spectrometry for LAAM and its metabolites, norLAAM and dinorLAAM. LAAM was below the limit of detection (≤10 ng/dL), norLAAM concentration was 15.8 ng/dL, and dinorLAAM concentration was 11.4 ng/dL. Conclusion: LAAM overdose may produce respiratory failure, non-cardiogenic pulmonary edema, and rhabdomyolysis, which is consistent with other opioids. Due to the prolonged clinical action and half-life of LAAM, overdose may require a longer period of observation or treatment than that needed for overdose of other opioids. Additionally, it is noteworthy that this patient responded to standard dosing of naloxone, suggesting that this dose may be appropriate for treating LAAM intoxication.

37 THE PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT OF ALCOHOL WITHDRAWAL

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Introduction: The Alcohol Withdrawal Reaction has been known and described since antiquity with the term 'Delirium Tremens', coined in 1811 by Thomas Sutton, although the fact that it was due to withdrawal and not to the direct effect of alcohol was only demonstrated recently. Given this length of time, and the great advances made in other fields of medicine, it is remarkable that the traditional teaching on this syndrome has changed very little in the last hundred years. The Alcohol Withdrawal Reaction is still described as a dramatic illness coming on three or four days after admission to hospital and characterized by extreme agitation, delirium, and cardiovascular collapse. Although there is now a considerable body of knowledge about the pathogenesis and management of the condition, this is largely confined to specialist practitioners working in specialized settings whose experience may not be transferable to mainstream situations. Most doctors working in hospitals know little about alcohol withdrawal in spite of the frequency of the problem in general hospitals (8% of our hospital inpatients have some form of alcohol withdrawal) and its long history. Most understanding and practice remains based on folklore and previous practice rather than well designed clinical studies. Pathophysiology: The pathophysiology of alcohol withdrawal involves changes in fluid and electrolyte status, sleep disorders, steroid hormone regulation and other parameters. Recently most interest has been in changes in biogenic amines with particular emphasis on the way in which the adrenergic system is disordered with down regulation of the α-2 receptor. We have studied this phenomenon and found that the down regulation was relatively short, between 24 and 48 hours, and have hypothesized that this period of reduced inhibitory function corresponds to a period of hyperexcitability and heightened vulnerability to stress during which the patient is at risk of developing complications. This hypothesis was tested in a study of the clinical course of 539 episodes of alcohol withdrawal seen in a general hospital. Features: The median time of onset of alcohol withdrawal was five hours post admission and 90% of reactions had begun by 20 hours. Patients whose blood alcohol level was zero were already in withdrawal on arrival. The majority of cases had resolved by the third day, even those complicated by delirium or hallucinations and 90% of all reactions were over by the end of the fifth day in hospital. Seizures had usually occurred either before or on admission and it was rare for them to occur for the first time after admission. Factors increasing the risk of complications included age >70 yrs, assisted ventilation and a variety of clinical factors, but the most significant was failure to detect a case within the first 24 hrs i.e. during the period of correction of α-2 down regulation. Management: From these results the management principles can be formulated. Firstly, a surveillance mechanism which will allow the early identification of cases. This is important in all settings but particularly in hospitals and should consist of a simple checklist and, where possible and relevant, blood alcohol measurements. Secondly, an objective monitoring system to allow tracking of progress and early detection of those patients who will require sedation to avoid delirium or hallucinations. In our series of unwell hospital inpatients only 74% needed sedation which in the majority of cases was diazepam 40 mg or less. The monitoring system we use is based on the CIWA-A system developed by Sellers and colleagues in Toronto[1] which scores autonomic hyperactivity, level of arousal and sensory changes giving a composite continuous variable which can be used as a measure of the risk of complications. Finally, a set of guidelines for the management of alcohol withdrawal which emphasizes the use of supportive nursing measures but also provides indications for the use of sedatives prior to the development of complications. By implementing a hospital wide strategy based on these principles, we have achieved a 90% compliance with treatment guidelines and a reduction from 18% to 11% in the complication rate. Conclusion: The Alcohol Withdrawal Reaction is common in many health care settings, particularly in the wards of general hospitals where it appears to require considerable resources for its management and forms part of the early experience of most young doctors and nurses. It is very responsive however, to competent and intelligent management and there is consider-

able personal and professional satisfaction from looking after this group of patients well. Reference: [1]Shaw JM, Kolesar GS, Sellers EM *et al*. Development of optimal treatment tactics for alcohol withdrawal. Assessment and effectiveness of supportive care. *J Clin Psychopharmacol* 1984;**1**:382–389.

38 DOSE DEPENDENT TOXICITY OF DEXTROMETHORPHAN OVERDOSE

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Objectives: From 1990 to 1998, the number of inquiries to the Swiss Toxicological Information Centre concerning dextromethorphan poisoning increased by 376% as compared to 26% with therapeutic drugs in general. The aim of this study was to investigate the severity of dextromethorphan poisoning and its dose dependent toxicity. Methods: We retrospectively analyzed all feedback reports from physicians on patients with dextromethorphan poisoning between January 1997 and June 1999. Only cases with dextromethorphan monointoxications containing sufficient information regarding ingested dose and severity of symptoms were included. Severity was assessed according to the EAPCCT/EC/IPCS Poisoning Severity Score.[1] Results: 108 patients (59 children and 49 adults) were included in the study. 44 ingestions were suicidal, 33 accidental and 17 abusive. In 14 cases the circumstances were unknown. The most frequent symptoms were somnolence (36%), tachycardia (25%), ataxia (23%), mydriasis (21%), agitation (14%), vomiting (13%), confusion (11%), nystagmus (7%), hypertension (6%) and hallucinations (6%). Ingested doses of dextromethorphan ranged from 1.6 mg/kg to 64.6 mg/kg. There was a large variability of doses within the same degree of severity. The association between increasing doses and the severity of symptoms was statistically significant ($p < 0.05$). Severe symptoms included seizures, coma and hypertension (>160 mm Hg in children). Single seizures were observed at a minimum dose of 10 mg/kg, coma and multiple seizures at 22.5 mg/kg, and hypertension at 5.5 mg/kg. As severe complications one patient developed psychosis at 4.3 mg/kg, another rhabdomyolysis at 64.6 mg/kg. No fatalities were reported in our series. Conclusions: Dextromethorphan poisoning seems to be relatively benign since only a small percentage of patients develop severe symptoms. In our series poisoning with dextromethorphan showed a dose-dependent toxicity, whereas the poisoning severity at comparable doses varied considerably. A genetic polymorphism (CYP2D6) in dextromethorphan metabolism may explain why some patients develop severe symptoms at doses which lead to only minor or even no symptoms in others, with poor metabolizers running a greater risk of serious toxicity. References: [1]Persson HE, Sjöeberg GK, Haines JA, De Garbino JP. Poisoning severity score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998;**36**:205–213.

Severity of symptoms in patients with dextromethorphan poisoning

Symptoms	Patients (n=108)	Dose Range (mg/kg)	Mean Dose ± SD (mg/kg)
None	23 (21.3%)	1.6–16.7	8.7 ± 4.7
Mild	51 (47.2%)	1.9–38.7	9.1 ± 6.8
Moderate	28 (25.9%)	4.2–32.7	10.3 ± 6.5
Severe	6 (5.6%)	4.3–64.6	24.2 ± 24.0

39 CLINICAL CHARACTERISTICS OF MIXED OVERDOSES BY HEROIN AND COCAINE. PROSPECTIVE STUDY OF 30 CASES

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Background: Intravenous overdoses of heroin and cocaine, formerly named ‘speed-ball’, were a very uncommon occurrence in our country. In the last two years there has been an alarming rise in the frequency of this type of overdose, named ‘combi’ by users, as stated by police and forensic opinions and as shown especially by the number of cases treated in Emergency Departments (ED). The combination produces a potentially misleading clinical picture because of the opposing effects of these substances on the CNS and peripheral targets, such as the pupils. Objective: To evaluate

the clinical characteristics of heroin-cocaine overdoses, complication frequency, treatment and evolution. Methods: We have studied prospectively combination overdoses of heroin and cocaine which were analytically confirmed and treated in the ED of the Clinical University Hospital of Zaragoza (Spain) in the last two years to verify the main clinical symptoms and signs, complications, treatment and evolution. Overall, 1892 cases of acute poisoning occurred in this two year period. In 127 cases heroin was suspected as the causal agent, cocaine was suspected as the causal agent in 83 and both substances were found on urine analysis in 30 cases. Results: Males accounted for 93.33% (28) of cases; mean age was 28.83 $\pm$ 5.2 years. Main symptoms were as follows: miosis, 18 cases (60%); mydriasis, 5 cases (16.66%); conscious level: GCS $\leq$ 5, 8 cases (26.66%); GCS $\leq$ 10, 10 cases (33.33%); GCS $>$ 10, 12 cases (40%); respiratory depression, 17 cases (56.66%); O_2 saturation $<$ 90%, 18 cases (60%); respiratory arrest, 6 cases (20%); hypertension, 2 cases (6.6%); sinus tachycardia, 15 cases (50%); agitation 6 cases (20%); convulsions, 2 cases (6.6%). The main complications were bronchoaspiration, 5 cases (16.66%) and rhabdomyolysis, 3 cases (10%). Antidotes were employed in 25 cases (83.33%), naloxone in 24 and flumazenil in 6. Intubation was required in 4 cases (13.33%). RCP was necessary in 6 cases (20%). There were two deaths (6.66%), one due to cerebral hypoxic damage and the other occurred as a sudden death 15 days after admission. Conclusions: The clinical picture observed in combined heroin-cocaine overdose shows CNS depression due to opiates and the presence of cocaine-related effects such as mydriasis, agitation and sinus tachycardia. It must be stressed that the presentation of agitated coma and mydriasis do not exclude the need for naloxone, especially if respiratory depression is present.

40 THE INFLUENCE OF OPIATE WITHDRAWAL AND THE OPIATE ANTAGONIST NALTREXONE ON THYROID FUNCTION

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Objective: Investigating thyroid function during opiate withdrawal under general anesthesia precipitated by an opiate antagonist, we observed a suppression of TSH and a fall in TT_3. Former studies on the influence of opiates on the hypothalamic–pituitary–thyroid gland axis revealed conflicting results. To answer the question if opiate withdrawal or the opiate antagonist suppresses TSH secretion we performed two studies, one in opiate addicts during withdrawal and one in healthy volunteers receiving the opiate-antagonist naltrexone. To differentiate between an effect of naltrexone on the hypothalamic or pituitary level we studied naltrexone alone, naltrexone + dopamine antagonist metoclopramide and performed a TRH-Test with and without medication. Methods: TSH and TT_3 were measured in 20 opiate addicts before, during and after 'cold' withdrawal. 20 healthy volunteers were used as control group. In each of 12 healthy volunteers (informed consent) four different tests were performed: a. Blood was taken at 9:00 and 13:00, 14:30 before and 15:00 after TRH (no medication), b. Same blood sampling as under a. (100 mg naltrexone orally after first blood sampling), c. Same blood sampling as under a. metoclopramide was given IV after 13:00 blood sampling, d. Same blood sampling as under a. naltrexone was given at 9:00 after first blood sampling, metoclopramide was given IV after 13:00 blood sampling. The statistical comparison was calculated by the Wilcoxon Test. Results: during opiate withdrawal TSH levels in serum (μU/mL) fell from 1.53 $\pm$ 0.23 (at admission) to 0.25 $\pm$ 0.19 (height of the withdrawal) and rose again to 1.01 $\pm$ 0.47 (after withdrawal). These were significantly different to the controls ($p < 0.0001$). TT_3 followed the same pattern. In the volunteers TSH fell from (9:00) 1.39 $\pm$ 0.79 to (13:00) 1.20 $\pm$ 0.53 [circadian rhythm (a)]. If naltrexone was given (b) TSH fell from 1.4 $\pm$ 0.73 to (13:00) 0.77 $\pm$ 0.6. If metoclopramide (c) was given and compared to naltrexone (b) at 14:30 TSH was significantly higher [0.67 $\pm$ 0.22 (N) vs 1.11 $\pm$ 0.57 (M)]. In experiment d. the TSH suppression by naltrexone was reversed by metoclopramide, the TRH-Test showed no significant difference in the TSH release (a-d). Conclusion: Opiate withdrawal suppresses TSH secretion naltrexone inhibits TSH secretion. Metoclopramide can reverse the inhibitory effect of naltrexone. Opiate thus inhibits hypothalamic dopamine release. Therefore during opiate withdrawal a lack of endorphins allows hypothalamic dopamine release which suppresses TSH secretion.

41 CHANGE OF PATTERN OF DRUGS ABUSED BY WIDESPREAD USE OF METHADONE FOR OPIATE SUBSTITUTION IN MUNICH

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Background: Methadone as a substitute for opiates became available for nearly all opiate addicts in Munich in 1998. It was hoped by many physicians and most politicians that methadone prescription would lead to a psychosocial stabiliza-

tion of the drug addicts, less intoxications and fewer deaths. Objective: Therefore we tested the hypothesis if drug addicts on methadone perform better during physical withdrawal and if they take lesser risks in their life conduct. Furthermore the aim of the study was a comparison of the drugs taken by the addicted patients before and after the widespread use of methadone. Method: Urine was taken and analyzed for drugs in all patients that were treated as in-patients due to their drug addiction in our Centre. The patients treated in 1995 and 1997 were compared with those treated in 1998 and 1999. 999 patients were included into the study before 1998 (n = 521) and after 1998 (n = 478). Groups were formed: first: Admission due to drug overdose (178 vs 157); second: Admission due to other emergency (115 vs 118); third: Admission due to a planned elective detoxification (228 vs 203). Results: In patients admitted due to a drug overdose, methadone was found in 15% before 1998 and in 48% after 1998. The use of heroin declined from 48% to 22%. The use of dihydrocodeine declined from 47% to 31%. Benzodiazepines were found before 1998 in 71% after 1998 in 82%. The additional use of ethanol rose from 33% to 50%. In drug patients who were admitted to our unit for detoxification or other emergencies we could not find such a rise in the use of benzodiazepines and ethanol. Patients in methadone programs consumed in 1998 more other drugs than those not substituted with methadone (3.5 ± 1.1 vs 2.4 ± 1.2). Patients on methadone treatment more often left our unit before detoxification was finished than those not under methadone prescription (64% vs 41%). Conclusion: The widespread prescription of methadone for drug addicts of the opiate type changed the pattern of polydrug abuse. Those patients on methadone take more drugs additionally than those who are not treated with methadone. Patients in methadone substitution are more often involved in overdoses than patients without methadone. Patients in methadone programs do not finish withdrawal as frequently as patients not treated with methadone.

42 FETAL EFFECTS OF MATERNAL ALCOHOL EXPOSURE

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Objectives: Many studies have been carried out in the last 20 years to try to identify the effects of ethanol in pregnancy and to establish intake levels at which these effects occur. There are conflicting definitions as to what constitutes heavy, moderate and low drinking levels. However, the full spectrum of physical and mental handicaps known as Fetal Alcohol Syndrome (FAS) is only seen in the children of alcoholic women. It has proven more difficult to define the risk associated with binge drinking and moderate drinking during pregnancy. Genetic polymorphism exists at the alcohol dehydrogenase and acetaldehyde dehydrogenase gene loci, the two principle enzymes involved in ethanol metabolism. Oxidation by cytochrome p450 2E1 is considered to be a minor route. Because of this genetic variation some women and fetuses will metabolize ethanol and/or acetaldehyde faster than others. This may partly explain the variability in adverse pregnancy outcomes seen with similar maternal alcohol intakes. In April 1994, the UK Government established an interdepartmental group to review the Government's 'sensible drinking message' in the light of the evidence that alcohol might give protection from coronary heart disease. This report was published in December 1995. Methods: A major problem in interpreting the human studies is the large number of confounding factors, including poor nutrition, licit and illicit drug intake, smoking, socioeconomic factors, maternal parity and other demographic characteristics, each of which can have adverse effects on pregnancy. There is also difficulty in verifying alcohol intake and in controlling for cultural differences in patterns of consumption. In post-natal developmental studies, environmental factors are also critically important. There are conflicting opinions as to the fetotoxic effects of paternal alcohol exposure. Results: There is general agreement from prospective studies involving over 57,000 subjects that a high concentration of alcohol has the potential to induce the FAS in genetically susceptible children. Adverse effects can be induced at all stages of pregnancy. The main clinical features of FAS are CNS dysfunction including mental retardation, a distinctive pattern of facial features (short palpebral fissures, hypoplastic philtrum, flattened maxilla), major organ system malformations, prenatal and postnatal growth deficiency, and behavioral abnormalities. FAS is likely to occur in the children of 30 to 45% of women who drink at least 5 ounces of absolute alcohol (equivalent to 150 g = 15 glasses of wine) daily. As children with FAS age, the facial features become less distinctive, but short stature, microcephaly, intellectual deficits and behavioral abnormalities persist. Regular maternal alcohol use has been associated with an increased risk of congenital heart disease, and cleft lip, with or without cleft palate. Most studies agree that 2 drinks per day and above may be associated with reduced birth weight, which is one of the most sensitive parameters. There is some evidence that stopping, or greatly reducing alcohol intake before 20 weeks of pregnancy has a beneficial effect on the final birth weight. Some studies have reported adverse effects on cognitive and behavioral development in children of women

with lower alcohol intakes, but most have not. A number of reports have suggested that the risk of miscarriage is twice the normal rate in women who drink 1 ounce of absolute alcohol (equivalent to 30 g = 3 glasses of wine) two times per week. The difficulty of accurately monitoring dose and exposure of such a widely available toxicant undermines the strength of many observations describing the adverse effects of moderate alcohol consumption during pregnancy. However, there is no good evidence that 1 or 2 drinks per week has any adverse effects. Human data indicate that binge drinking, defined as five or more drinks on one occasion, can also produce fetotoxicity. There is limited evidence that alcohol may also impair reproductive function in men and fertility in women. However, this evidence is inadequate in so far as the identification of the intakes at which these effects are induced. Maternal alcohol abuse during pregnancy has also been associated with an increase in childhood leukemia, particularly with late pregnancy exposures. However, there was no association with paternal alcohol use or with parental smoking. Elevated fetal erythropoietin levels have also been reported, but it is unclear whether this is a direct effect of alcohol exposure or due to the toxic effects of alcohol on the placenta, producing fetal hypoxemia. It has been suggested that beer drinkers are at greater risk than consumers of other alcoholic beverages for having children with fetal alcohol damage. Six beers are equivalent to about 3 ounces of absolute alcohol, and such a daily dose has been associated in some studies with birth weight reduction and malformations. Such effects may be related to malnutrition often associated with high beer intakes. Several mechanisms have been suggested e.g. hyponatremia produced by the elevated fluid intake and the adverse effects of the subsequent hyponatremia on neural myelination. Women who drink heavily may experience an inhibited milk-ejection reflex. Alcohol is excreted into breast milk in similar concentrations to those found in maternal blood. There have been a number of adverse effects reported in children exposed to alcohol during lactation, but most of these studies have been criticized on methodological grounds. It is not known whether alcohol changes the taste of breast milk. Conclusion: The full spectrum of physical and mental handicaps known as FAS is only seen in genetically susceptible children of alcoholic women. The risks associated with binge drinking and moderate drinking during pregnancy are more difficult to define. Fetal toxicity is likely to be associated with the severity of the maternal toxicity. Data indicate that in order to minimize risk to the developing fetus, women who wish to become pregnant, or are at any stage of pregnancy, should not drink more than 1 or 2 units of alcohol once or twice a week. Episodes of intoxication should be avoided.

43 FETAL AND NEONATAL EFFECTS OF INHALANT ABUSE

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Introduction: Inhalant abuse, also known as volatile substance abuse, solvent abuse, sniffing or huffing is a worldwide practice. It is the favored type of recreational substance abuse of the young. Onset can be as early as the seventh or eighth year of life, with peak prevalence during adolescence only to decline during the latter portion of the second decade of life. However some users continue into their adult years. Approximately 15–20% of children have tried inhalants. However, in many countries, this practice is endemic in localized populations. Prevalence of regular use greater than 50% has been reported. Typical features of these populations are poverty and social dysfunction. The volatile hydrocarbons, both aliphatic and aromatic, are the most commonly used inhalants. There are many chemicals within this broad category hence the potential for differential toxicities. This complicates the assessment for both general and teratogenic adverse effects. Toluene is most commonly used substance. Thus the inhalant abuse literature is dominated by this hydrocarbon. There are countless numbers of consumer products that can be used as inhalants. It is their availability and relative low cost that are the basis for inhalant abuse being the favored recreational substance abuse of the young. However, because this practice continues into the child bearing years, there is the potential for deleterious effects upon the fetus and the newborn. The literature regarding fetal and neonatal effects is very scant. It concentrates upon a so-called fetal solvent syndrome with phenotypic features very similar to the fetal alcohol syndrome. However this literature is entirely descriptive and suffers from referral bias and lack of maternal alcohol exposure as an exclusion criterion. Review of personal studies: I shall review our studies that describe neonatal acidosis and neonatal withdrawal from inhalants. I shall also review our case-control study designed to address the question whether *in utero* exposure to inhalants results in a recognizable physical phenotype. Metabolic acidosis is a known complication of inhalant abuse particularly associated with toluene. In the literature there is brief anecdotal mention of 3 neonates born of inhalant abusing mothers who developed this complication. We have described metabolic acidosis in 22 of a series of 36 newborns of mothers who abused inhalants. Withdrawal symptoms have been described in chronic solvent abusers especially following binge sniffing. In a series of 48 newborns studied over a four year period we described neonatal withdrawal from inhalants and probable benefit of phenobarbital pharmacotherapy. The clinical features of neonatal inhalant with-

drawal include: excessive and high pitched cry, sleeplessness, tremors, hypertonia and poor feeding. A fetal solvent syndrome consisting of a group of clinical features not unlike the fetal alcohol syndrome has been described. The literature description is confined to case reports and case series. However, *in utero* exposure to alcohol was not an exclusion criterion in this literature. We performed a case control study in 27 children who were heavily exposed to inhalants *in utero*. An experienced dysmorphologist blindly assessed cases and controls and no significant dysmorphic features were found in children with a history of exposure to inhalants *in utero* without exposure to alcohol. Conclusion: Neonates exposed to inhalants *in utero* are at risk for neonatal acidosis and neonatal withdrawal. However our data do not support the existence of a fetal solvent syndrome physical phenotype.

44 FETAL EFFECTS OF SUBSTANCES OF ABUSE

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Objective: Substance abuse causes serious health problems. The number of people with problems related to drug misuse has increased over the past 2 years. Nationally 22% of all misusers are females of childbearing age (15–39 years). Overall, 91% misuse heroin, methadone or other opiates, 35% misuse stimulants and other substances such as cannabis (25%), benzodiazepines (22%) and hallucinogens (7%). At least 25% use more than one drug and 38% inject their main drug. Drug use in pregnancy is one of the most difficult and emotive of all drug safety issues that raises concern regarding both maternal and fetal toxicity. This often presents parents and clinicians with ethical, medico-legal and emotional dilemmas as to whether the pregnancy should continue. This paper will exclude discussion on the effects of alcohol, volatile substances, tobacco and caffeine. Methods: Epidemiological studies of addicted mothers are extremely difficult to perform and it is even more difficult to establish causal relationships of drug intake and adverse effects. The majority of studies have raised more questions than answers. Potential confounding factors, like the difficulty of selecting suitable control groups (drug users vs non-drug users), the dose and purity of the substance, other drug use (including alcohol or smoking, caffeine), excessive dropouts, infections (STD, HIV), ill-defined nutritional status, insufficient antenatal care and obstetric and neonatal risk factors, must be addressed, but are difficult to control and to evaluate. Results: Drugs of abuse may cause fetotoxicity at any stage of pregnancy. Little is known about the fetotoxicity of substances such as ketamine, GHB, psilocybine and phencyclidine. Data on heroin misuse provide no convincing evidence for an increased risk of malformations, but the study population is small. Heroin is unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk. In some pregnancies, methadone substitution seems to reduce pregnancy risks. There are a few case reports of malformations in children exposed to methadone *in utero*. Data from large scale systematic studies of malformations in mother-child pairs exposed to methadone are lacking. Most investigations provide only limited information regarding the duration of treatment, and timing of exposure. Cumulative data from several uncontrolled case series and cohort studies on infants (2,500) born to narcotic-addicted women treated with methadone during pregnancy indicate that the incidence of malformations was no greater than expected. Exposure to cocaine and its derivatives, e.g. crack, is connected with clear drug induced effects; an increased incidence of abruptio placentae, maternal and neonatal intracranial hemorrhage, and possibly urogenital defects. Amphetamines and related stimulants have been associated with an increased risk of structural malformations including the heart and great vessels in animals. In human pregnancy there is no conclusive evidence of an increase in the overall malformation rate, or of any specific type of malformation. Chronic use of amphetamines has been associated with an increased risk of spontaneous abortion. The illicit use of ecstasy (methylenedioxymethamphetamine, MDMA) has increased over the past decade and there is growing concern about its potential toxicity. The age group of users means that exposure to the compound in early pregnancy is likely. Few data exist on the potential fetotoxicity of ecstasy. NTIS has collected prospective follow up data on the outcome of 136 ecstasy exposed pregnancies in the UK. The data indicate that ecstasy may be associated with a significant increased risk of congenital defects overall (15.4%, 95% CI 8.2-25.4). Cardiovascular (26:1000, [95% CI 3-90]) and musculoskeletal anomalies (38:1000, [95% CI 8-109]) were predominant. Delta-9 tetrahydrocannabinol is thought to be the primary active agent of cannabis. There are isolated case reports of malformations following cannabis (smoking or inhalation) use in pregnancy, but there is no conclusive evidence to suggest an increased incidence of malformations. Cannabis use is strongly associated with the use of tobacco and alcohol. Although there are isolated reports of malformations (CNS, eyes, limbs) in infants born to women taking LSD, there is no epidemiological evidence of a causal relationship. Equivocal evidence exists of an increase in spontaneous abortions. No increased incidence of abnormal birth weight babies was reported in a small number of women who received LSD therapeutically. However, a small risk of fetal toxicity cannot be excluded. Current data do not indicate any persistent reproductive toxicity from LSD. There is no clear evidence that the misuse of benzodiazepines is associ-

ated with an increased risk of malformations. Chronic use, especially near term has been associated with the 'floppy infant' syndrome. Intrauterine growth retardation, reduced birth weight and head circumference, meconium stained fluids, prematurity, and an increased incidence of neonatal death are common in infants born to drug misusers. In most cases it is not clear whether this is a direct drug effect or due to deficits in socioeconomic lifestyle and postnatal care. There are conflicting reports on whether drugs of abuse, particularly methadone are associated with a higher risk of sudden infant death syndrome (SIDS). In cocaine exposed infants, SIDS is possibly due to abnormal sleep patterns and impaired hypoxia arousal. Neonatal withdrawal symptoms, which may last up to several weeks, occur in a high proportion of babies. The features are variable and include tremor, hypertonicity, irritability, diarrhea, vomiting, abnormal sleep patterns and altered visual response patterns to light stimulus. There are limited and inconsistent data on the possible adverse effects of drugs of abuse on postnatal development. Conclusion: Maternal exposure to drugs of abuse has been associated with fetal and neonatal toxicity. In most cases it is not clear whether this is a direct drug effect or due to deficits in socioeconomic lifestyle. Evidence concerning fetotoxicity from paternal exposure is lacking. Drug-dependent mothers and their babies may represent a unique group, and if variables are to be identified which may affect pregnancy outcome, perhaps intra-group as well as inter-group comparison should be made. Comparison of infants of drug-dependent mothers with a good outcome with those with a poor outcome might be an effective approach.

45 IS EXPOSURE TO AMPHETAMINE-LIKE DRUGS IN PREGNANCY ASSOCIATED WITH MALFORMATIONS?

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Objectives: NTIS provides a 24-hour service on all aspects of toxicity of drugs and chemicals in pregnancy. Its main objectives are healthcare provision (risk assessment), and research (prospective follow up of selected enquiries). Data are lacking in human pregnancy on the reproductive toxicity of amphetamine-like drugs including ecstasy. Although amphetamine is associated with cardiac malformations in animals, the data in man are ambiguous. Methods: NTIS prospectively followed 281 enquiries concerning amphetamine-like drugs. Follow-up occurred at the time of the enquiry, and 4 weeks post-delivery. There were 4 groups (195 pregnancies) of drug misusers and 1 group (86 pregnancies) who took amphetamine-like anorectics therapeutically. Group 1, amphetamine; Group 2, amphetamine + other drugs of abuse (excluding ecstasy); Group 3, ecstasy; Group 4, ecstasy + other drugs of abuse (including amphetamines); Group 5, anorectics mainly phentermine (77). Results: The data are shown in the Table. There were 272 (96%) first trimester exposures (7 women abused amphetamines throughout pregnancy).

Outcome in 281 enquiries to the NTIS concerning amphetamine-like drugs

Group	Number of Women	Normal Term Baby	Normal Preterm Baby	Outcome			
				SA[1]	SB/ND[2]	ETOP[3]	Anomaly
1	41	22	5	1	−1	10	2
2	18	6	1	2	—	6	3
3	74	35	3	3	—	27[4]	6
4	62	22[5]	5	8	1	21	6
Sub-total	195	85	14	14	2	64	21[6]
5	86	54	9	7	—	10[7]	6

Key: [1]Spontaneous abortion; [2]stillborn/neonatal death; [3]elective termination of pregnancy; [4]1 fetus-multiple malformations; [5]1 pair of twins; [6]includes 3 congenital heart disease (CHD), and 9 musculoskeletal defects; [7]1 fetus-multiple malformations.

The live birth malformation rate was increased in groups1–4, (108/1000) and in group 5 (69/1000) vs expected 20–30/1000. In groups 1–4, there was a high incidence of musculoskeletal defects 75/1000 and the risk of CHD was also increased (25/1000 vs expected 5–10/1000). No pattern of malformations was observed in group 5. The incidence of preterm deliveries was similar 11.6% (groups 1–4) and 10.5% (group 5) The spontaneous abortion rate, 7% (groups 1–4) and 8% (group 5) is within the expected range (10–20%), but the ETOP rate in misusers was greater than expected

(33% vs 22%). No adverse effects were observed on birth weights of term infants in any group. Conclusion: Therapeutic use of anorectics was not associated with any pattern of malformations, whereas misuse of amphetamine-like drugs, especially ecstasy, appears to be associated with an increased risk of malformations overall, with cardiovascular and musculoskeletal abnormalities being predominant. Although this small case series has insufficient statistical power to confirm cause-effect relationships, this signal is important, and indicates that further data are required.

46 INFLUENCE OF DRUGS ON DRIVING

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Objectives: to give an overview of the existing evidence concerning the influence of drugs on driving. Methods: A complete understanding of the problem of drugs (both illicit drugs and medicines) and driving will only be achieved in two complementary approaches: experimentation and epidemiology. Information on the influence of drugs on driving performance and the risk of being involved in an accident comes from different types of studies: (1) *experimental controlled studies*, where the drug (in different dosages, compared to placebo and a positive control) is given to volunteers and their psychomotor performance and/or driving ability is measured (in the laboratory, in driving simulators and/or on the road); (2) *surveys of drivers*, in which biological samples (blood, urine, saliva, sweat, . . .) are taken and analyzed for drugs. These studies can be categorized into several groups, according to the subjects that are studied: (a) roadside surveys, where a representative sample of the driving population is analyzed; (b) studies in injured drivers or other road users; (c) studies in fatally injured drivers or other road users; (d) studies in drivers suspected of driving under the influence of drugs (DUID) and/or alcohol; (e) re-analysis studies (analysis of drugs in blood samples taken for the determination of alcohol). Another possibility is to use an interview or a questionnaire (asking drivers which drugs they have taken) instead of the analysis of biological samples, but there is a high risk of underreporting. A further subdivision can be made if all drivers or only the drivers who are responsible for the accident are included. These types of studies are mostly descriptive and give information on the percentage of drivers in the studied population that has been exposed to a drug. However, a comparison of the percentages in roadside surveys and injured/killed drivers can show an overrepresentation of drivers who are positive for drugs and thus suggest a causal role. Another approach is responsibility analysis, a comparison of the percentage of drivers in whom drugs were detected in responsible (for the accident) and non responsible drivers; (3) *pharmaco-epidemiological studies*, where the incidence of traffic accidents in people who take drugs is compared to a control population. Results: Several hundreds or thousands of experimental studies exist for medicinal drugs. Many different tests, doses, subjects (normal volunteers or patients), have been investigated, which sometimes leads to contradictory results. There are some experimental studies for cannabis, and other studies are currently being performed with MDMA (ecstasy) and heroin. Many epidemiological surveys of the different types have been performed in most EU countries. We compared 52 epidemiological studies that were performed at least partly in the nineties in 18 different European countries. There were 3 roadside surveys (one was limited to weekend nights), 10 studies in injured drivers, 9 studies in killed drivers, 20 studies in drivers suspected to be under the influence, 6 reanalysis studies and 4 studies in miscellaneous populations. For each group of studies, the median percentage of drivers positive for drugs was calculated. The median percentage of positive samples was 2.6% in roadside surveys, 19% in injured drivers or other road users, 16.3% in killed drivers or other road users, 82.2% in suspected of being under the influence and 11% in reanalysis studies. The most frequently found drugs were cannabis and benzodiazepines. Drivers who were positive for drugs were overrepresented by a factor of 6.8 in injured or killed drivers compared to roadside studies, which is comparable to alcohol (factor 5.7). Two responsibility analysis studies (one from the USA and one from Australia) were performed. In the Australian study that involved over 2500 fatally injured drivers, data on relative risk (assessed by odds ratio analysis) show a significant risk for drivers consuming alcohol, alcohol and any drug, cannabis (if only the drivers positive for tetrahydrocannabinol (THC) were considered), other psychoactive drugs (sedating anti-depressants, sedating antihistamines, anticonvulsants etc), and any combination of two or more psychoactive drugs. Of the 34 drivers positive for THC (and no other drug or alcohol), 82% were culpable. The odds ratio to control drivers was calculated as 2.0. If THC concentrations below 5 ng/mL were ignored the odds ratio increases to 2.8. The relative risk of THC-involvement in crashes is in the range of blood alcohol concentrations of 0.5–1 g/L, which corresponds to the experimental studies (100–300 μg THC/kg caused ‘weaving’ similar to blood alcohol concentrations of 0.3–0.7 g/L). For medicines, the pharmaco-epidemiological studies give valuable information despite some limitations. Benzodiazepines: with only one exception, all pharmaco-epidemiological studies show an increased accident risk in benzodiazepine users. The highest risk is observed in the first weeks of treatment (in one study a tenfold increased

risk of crash was observed), with long-acting benzodiazepines and in young male subjects. In the two responsibility analysis studies, drivers who were positive for both benzodiazepines and alcohol had a very high risk of being responsible for the accident. Antidepressants: some, but not all pharmaco-epidemiological studies have shown that there is a dose-dependent increased risk for injurious crash. Newer antidepressants seem to be less impairing. Narcotics and opioid analgesics: pharmaco-epidemiological studies yield contradictory results, one out of two having found an increased accident risk in users of opioids. Antihistamines: out of 3 studies, none found an association between antihistamine use and increased accident risk. This could be explained by the fact that most older antihistamines that are impairing are available over the counter and pharmaco-epidemiological studies measure prescribed drugs. Several authors have tried to estimate the number of crashes that are caused by medicines: the estimations vary from 3.5 to 10%. In this discussion, one should not forget that some diseases and conditions do impair driving ability and that for some types of medication, the consequences of not taking the medication and then driving could be worse than the problems of driving with medication. Some efforts are being made to use the results of the different types of studies to categorize the drugs in different classes according to their impairing effect on driving performance. This classification system could be further used to add a pictogram on the package or for prescription guidelines (e.g. professional drivers are not allowed to drive for a certain period after intake of the most impairing class of drugs). Conclusion: The evidence that some drugs (illicit and therapeutic) impair driving performance is growing stronger. There is a need for more information (e.g. clearer package inserts) and prevention campaigns directed to the general public, the dispensing pharmacists and the prescribing physicians. Some countries have changed (or are considering changing) their legislation on driving under the influence of drugs, adding 'per se'-type (or 'analytical') legislation to their impairment laws.

47 INTERPRETING THE RESULTS OF MEDICO-LEGAL ANALYSES IN CASES OF SUBSTANCE ABUSE

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Introduction: Is this an intoxication case, a suicide attempt or a criminal poisoning? How was the drug administered? How long was the survival time? Had the drug an influence on the behavior of the subject? Was ethanol present? What about other drugs? Was the subject a chronic abuser? These are some of the questions frequently asked both by the clinician and the coroner. The role of the analytical toxicologist is to answer these questions according to the biological specimens available, the analytical equipment, the reference material (of both parent drug and metabolites) and his toxicological knowledge. Specimen collection: Adequate collection of postmortem samples at autopsy time is of prime importance for the subsequent toxicological investigations. Peripheral blood (antidepressants, chloroquine, digoxin, meprobamate, chloralose), bile (buprenorphine, colchicine), vitreous humor (ethanol), hair (chronic exposure) and lung (volatiles) must be collected along with cardiac blood, urine and gastric contents. In the clinical setting, the simultaneous collection of blood, urine (to perform the toxicological screening) and hair (to demonstrate repetitive abuse) are prerequisite for the interpretation of the analytical results. These specimens do not need to be tested in each case, but, at least, should be collected if potential forensic consequences are suspected. Hair is a useful specimen to document the pattern of drug use. In the case of attempts at chemical submission, such as spiking drinks or pastry, with short-acting benzodiazepines, ecstasy, cannabis or GHB, the collection of such specimens allow unambiguous conclusions to be drawn. Analytical methods: Over the past few years, great improvements in the capabilities of drug identification have been realized. Current techniques used in forensic toxicology are sophisticated and diverse, yielding faster, higher resolution and more specific analyses. LC/DAD and GC/MS represent the prerequisite for forensic toxicology. Headspace-GC/MS (volatiles, cyanide, anesthetics, CO), ICP/MS (metals), and LC/MS (thermal sensitive drugs, polar compounds, plant material) are useful additional techniques to target specific analytes. Immunochemistry results, based on FPIA or EMIT assays, are not acceptable for cases dealing with drugs of abuse. A positive opiate result, obtained by immunoassay, does not indicate heroin abuse. Only the identification by GC/MS of 6-acetylmorphine, the heroin primary metabolite, can be considered as conclusive. Drugs: Some markers such as anhydroecgonine methylester, the specific analyte that is formed when crack is smoked, are daily used in forensic toxicology and should also be used in clinical toxicology. When dealing with drugs of abuse, European toxicologists should not only be focused to the NIDA 5 (opiates, cocaine, cannabis, phencyclidine, amphetamine and methamphetamine) that are currently tested in the United States. Most of the immunoassays have poor cross-reactivity with the designer drugs, such as MDEA, MBDB or 2C-B, and, therefore, in most cases these drugs are not screened. Several other drugs should be added to the list of 'classic' drugs of abuse, especially, benzodiazepines (particularly the short-acting compounds, such as flunitrazepam), neuroleptics (cyamema-

zine, alimemazine), LSD (in combination with ethanol and ecstasy) and the anabolic androgenic steroids (testosterone esters enhance aggressiveness). Interpretation: The toxicologist must take in account the postmortem redistribution of drugs, the influence of storage conditions of the biological material, the delay between specimen collection and analysis, as these factors influence the interpretation of the analytical results. Because at present most drug abuses are polydrug abuses, analytical procedures are more complicated and correlation with clinical data may be difficult. Moreover, the local epidemiology must also been considered given that the situation in one country does not necessarily apply to another. For instance, 4-MTA, a new amphetamine analogue, largely used in the Netherlands, has never been detected in the area of Strasbourg. Other examples of medico-legal aspects of substance abuse are chemical submissions with benzodiazepines or neuroleptics for sexual attempts, child abuse or to swindle elderly people, psychosis from amphetamine derivatives, psychiatric diseases due to the use of anabolic steroids or the misuse of serotonin uptake inhibitors (fluoxetine). Conclusion: The availability of drugs in the general population has created new aspects of dependence. The definitive characterization and interpretation of these abuses needs a sophisticated combination of the sampling of specific specimens, including hair, a range of analytical equipment and a wide scientific background. In consequence, high level analytical toxicology is expensive and cannot be used for each case. The clinician should be aware of these aspects in order to select the cases for which medico-legal implications are expected.

48 ANALYTICAL CHALLENGES IN THE DIAGNOSIS OF SUBSTANCE ABUSE

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Objective: On the basis of ‘drug of abuse testing’ medical or legal decisions are made. Already one false negative or false positive result can diminish the efficiency of misuse programs and have severe forensic or legal consequences. Considering that the number of contemporary abused substances involves smart drugs, hard drugs, recreational drugs, stimulants and different herbal drugs, the diagnosis of substance abuse needs the reliable analytical detection of all the substances that might be involved. In many cases, however, laboratories perform a so called ‘screening’ that lacks precise definition and is often limited to a panel of commercially available immunoassays in urine which can only check the sample for the presence of amphetamines, cocaine, cannabis, opiates, methadone, benzodiazepines and probably ethanol. When this test panel is offered as a ‘full drug screen’ from the laboratory, a less experienced recipient of a negative report may conclude from this ‘negative drug screen’ that the diagnosis of substance abuse can be excluded. However, the spectrum of contemporary drug abuse is much broader than the panel of the ‘immuno-screening’ drugs and beyond that, the drugs of abuse pattern may rapidly change. This description and discussion of analytical strategies using modern methods as well as guidelines for the composition of a stringent report shall therefore explain why the exclusive use of simple analytical techniques may be misleading in a medico-legal sense. Strategies: A general agreement requires that positive results from a preliminary screening procedure have to be confirmed by a more sensitive and specific chromatographic technique. For the purpose of confirming positive test results the abused substances should be accurately identified. Therefore suitable sample extraction, appropriate derivatization, proper gas or liquid chromatographic separation of peaks and suitable detection by mass spectrometry or scanning UV spectrometry are essential. In contrast, until now no guidelines have been established in Europe that recommend the panel of preliminary tests and the specificity and sensitivity of these tests for distinct substances. Therefore, many screening procedures do not detect commonly abused substances like carbamazepine, clomethiazole, doxepine, gamma-hydroxybutyrate (liquid ecstasy), ketamine, or diuretics, as can be seen from recently performed ring tests. In addition, indications of substance of abuse testing are of many types, for example the tests can be legally ordered in association with crimes or traffic control, or in clinical cases of acute intoxication, or in psychosomatic medicine, or for the aim of work-place testing. To use the right strategy, the choice of analytical methods should primarily depend on case-related aspects. Therefore personal communication between the requesting person and the well trained laboratory staff may be essential already in the preanalytical phase. Of course the analytical possibilities of the laboratory and economical aspects have to be considered, but may not limit the adequate examination of the samples in a case-related sense. Two short case reports will illustrate the necessity of personal communication, confirmation assays and looking for substances in addition to the immuno-screening positives. In the first case serum and urine from a 40-year-old male were sent from the laboratory of another hospital with the request to confirm positive immunoassay results for barbiturates, cocaine, methadone and opiates. The case information from the clinician, however, suggested that these results might be due to a false positive. The patient was found comatose at home and his blood chemistry was indicative of end stage liver disease with a

persistent ammonia concentration higher than 200 μmol/L under ICU therapy. Indeed the immunoassay results except methadone could not be confirmed. Because of the exclusion of heterophilic antibodies or other cross-reacting exogenous substances, we concluded that the immunoassays were disturbed by unusual liver metabolites. In the second case a young male imprisoned for drug addiction had to be resuscitated and drug overdosage was suspected. With a simple GC-MS screen high amounts of clomethiazole could be detected in urine with no other drugs present. Reports: To diminish misleading interpretations a written report should be transferred as fast as possible to the clinician. Today modern networks in the hospital can be used for this aim. The report should give clearly information on which tests have been performed, which substances were identified by the confirmation procedure and which decision limits have been used and should clearly mention all analytical and preanalytical limitations. The involvement of a computer based expert system that automatically produces explanatory hints depending on the results of the performed laboratory tests may be helpful. Conclusion: The diagnosis or exclusion of substance abuse is not a simple 'screening procedure' but on the contrary needs precise communication, case related advanced laboratory methods and a clear and interpretative laboratory report.

49 COMMUNICATING WITH ENQUIRERS: I TOLD YOU–DO YOU UNDERSTAND?

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Objective: People call a poisons center to get information that will help them make a decision. The caller has recognized or defined a problem, has embarked on a search for information, and believes that the poisons center is the best place to get the information they think they need. What the caller wants is information which will dispel at least some of what the caller perceives to be risk. The information the poisons center provides is what the information specialist thinks the caller needs. Similarly, what the caller decides to do after the call depends, in part, on the caller's perception or understanding of what the poisons center said. Optimal communication requires that both sides be sure that each understands what the other is saying. How do we do that, how do we ensure understanding? These questions are particularly important because the amount and complexity of information about the evaluation and management of poisoning exposures has increased exponentially. While it is important for both the caller and the poisons center that the information provided be complete, accurate, and appropriate, it is arguably more important that it be useful and that it be understood. Methods: Poisons centers are in the information or knowledge business; their central function is the reception and provision of information using telecommunications technology. In simpler terms, poisons centers exchange or communicate information with callers over the telephone. Communication between two people is a very complex process heavily influenced by preconceptions and perceptions. There are, to be sure, many barriers or pitfalls in the communication process. For example, attention or information overload may confuse the intended meaning of the messages, and the use of unfamiliar words may hinder the interpretation. People, especially healthcare professionals, tend to be solution-oriented: they want to solve a problem. Given what they perceive to be a 'common sense' problem, they start to think of solutions without listening to or considering the entire problem; sometimes the solution is reached before the other person has finished talking. This rush may be due to many factors, such as work overload leading to the need to be 'efficient'. However, a premature jump to a solution relies on tacit assumptions about the nature of the problem and results in solutions that are familiar or comfortable but which may not be the best. Results: Do we really understand what the caller is telling us? Does the caller really understand what we tell them? What does it mean to 'understand' something and how do we assess that over the telephone? In the day-to-day operation of a poisons center, there may be little effort on either the caller's part or the poisons center's part to ensure that the other truly understands what was said. We too often assume understanding (particularly if the caller is articulate and sounds like us); sometimes we actually ask the caller if she or he 'understands'. When the caller answers affirmatively, we are reassured–but we are wrong, we shouldn't be. The concept of 'understanding' is a complex one and asking if the caller 'understands' is an inappropriate and unreliable way of judging understanding. As with everything else, it is important to define the terms carefully and explicitly. 'Information' is a fact or a collection of facts. Providing information alone to callers will not change their behavior. 'Knowledge' is information 'on tap'; a person knows something when the relevant information can be brought forth on demand. Having knowledge is a prerequisite to understanding, it is not the same as understanding. 'Understanding' is not simply remembering and reciting information or correctly following stipulated procedures. The term 'understanding' means the ability to use one's knowledge; to be able to extend, synthesize, apply, explain, generalize, interpret, or otherwise use what one knows in creative or novel ways. The relevance to poisons centers is that specialists should consider that they have three tasks: (1) to provide the caller with 'information', (2) to

ensure that the caller 'knows' the facts, and (3) to make sure they 'understand' what the facts mean. In order for specialists to ensure understanding by the caller, the specialist must first identify what are the relatively few important things that need to be understood by the caller. It is important not to overwhelm the caller with too many facts because people stop 'listening' after a while. Once the specialist has demonstrated his or her knowledge (by pouring forth the appropriate information), the specialist must then make sure that the caller has received the information and understands what has been said. Asking callers to repeat what the specialist told them is a way of judging a short-term gain in knowledge, but it does not measure callers' understanding. In order to do this, the caller should be asked to answer questions that reflect understanding. There are various ways of doing this. For example, as mentioned above, verbs or actions or concepts such as 'explain', 'interpret', 'analyze', 'relate', 'compare', or 'make analogies' reflect understanding. But how do we do this in the real world? Conclusion: This seemingly complex activity can be simplified into practical steps for specialists: 1. The specialist should re-phrase or re-state the caller's concerns and the information the caller provided, asking the caller if what the specialist understands the caller to have said is correct. This feedback ensures that both parties in the communication agree that the message received by the specialist reflects the message that was sent by the caller. 2. Once the specialist has provided the appropriate information, the specialist should ask the caller to re-phrase or re-state important information that the specialist said. This is a way of judging the new knowledge acquired by the caller. 3. The specialist should then ask the caller to answer a 'what if' question. This helps to convince the specialist that the caller does, in fact, understand what the information means. 4. Finally, the specialist should document the methods used to ensure the caller's understanding. Poisons center directors also need to be involved in the 'understanding' process. Not only do they need to help their staff develop their skills but they need to monitor their performance. In order to do this, they need to develop and use an evaluation tool that lists the desired criteria for call documentation and that specifies gradations of quality for each criterion. Ensuring understanding is a critically important part of a poisons center's activities–both the poisons center specialist and the caller must understand what the other has said. If there is no understanding by the poisons center specialist, inappropriate advice will be given; if there is no understanding by the caller, even the best advice will not be followed. Do you understand? References: Perkins DN. Thinking frames. *Educational Leadership* 1986;**43**:4–10. Perkins DN. What is understanding? In*: Teaching for Understanding: Linking Research with Practice.* Wiske MS, ed., San Francisco, CA, Jossey-Bass: 1998:39–57. Wiske MS. What is teaching for understanding. In: *Teaching for Understanding: Linking Research with Practice.* Wiske MS, ed., San Francisco, CA; Jossey-Bass: 1998:61–86. Blythe T. Understanding understanding. In: *The Teaching for Understanding Guide*. San Francisco, CA, Jossey-Bass; 1998:9–16.

50 FUNDING OF POISON CENTERS–REALLY A LACK OF RESOURCES OR A LACK OF QUALITY?

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Objective: Recent discussions in different countries about the lack of resources for poison centers have focused on the amount of work and the number of calls per capita of the population served. Quality assessment has been concentrated on whether the information given to the callers was timely and correct due to internal or external guidelines (procedural quality). The implementation of ISO 9000 standards has further contributed to this way of thinking and has reduced the discussion on poison center funding to proposals about optimizing computer systems. More important will be the answer to the basic questions, whether or not the information given had been necessary at all and its price therefore justified. The aim of poison information work within the complex health care systems has to be defined in terms of patient outcome data and the real impact and contribution of poison centers work within this system of adequate care (quality of results). We must shift our attention from how we achieve our goals and how we get money for it to the more important questions of what our goals really are and whether we do achieve them. Furthermore we have to imply a more science-oriented view on financing and support it by different epidemiologic methods. Methods: In the period 1996 to 1997 we prospectively collected patient outcome data on all childhood poisonings (age group 1 to 4 years) in the Greater Berlin area (3.4 million inhabitants), the sources being all 11 childrens hospitals, all 310 pediatric practices and all phone consults to the Berlin Poison Center (outcome data were missing in approximately 1.5% of cases). In addition, we undertook an intervention cohort study from July 1995 to June 1996 to evaluate lay persons ability to react more promptly and correctly at home in case of a possible childhood poisoning (24,000 toddlers being the intervention group). Results: Hitherto only estimates as to the epidemiology and health care impact of accidental childhood poisonings existed in Germany. Our data showed a 50% lower incidence rate (16/1000 age-related) than previously

suspected, a similar incidence rate for mild and moderate poisonings (2.8/1000 age-related) and no severe or fatal poisonings during the study period (0/1000 age-related) compared to the estimated risk of 0.3/1000 age-related for the whole country. The money to conduct this epidemiologic study (approx. 250,000 Euro) could have financed about three additional staff members at the Berlin Poison Center during the study period, but with the excellent level of patient outcome already achieved it is improbable that these additional staff members would have contributed to a better outcome, although in the long run factors concerning the procedural quality of our work might favor additional staff. The study data on the other hand help to set the high standard and focus health care providers to look into means to keep these standards by way of cooperation of all institutions involved (pediatric practices, rescue teams, hospitals emergency care, the poison center) and lay people. In fact our parallel cohort intervention study showed that lay people reacted more promptly and acted more appropriately to our medical recommendations if they had received a so-called pediatric emergency kit containing activated charcoal as a method of anticipated guidance prior to an accident. Conclusions: It is not possible to apply simple cost: benefit calculations to the positive effect of poison centers work because confounding and contributing factors exist within the complex health care systems; therefore an integrated public health approach renders more convincing data in the way of cost: effectiveness. Besides the integrated view helps poison centers to find partners in their strive for excellence and funding, based on patient outcome data and the best knowledge available. The integrated public health approach might lead to a redefinition of poison centers tasks as well: identification of frequently occurring nontoxic exposures has to be transferred into community based prevention programs as does further support of the concept of anticipated guidance in the first aid treatment of childhood poisonings by lay people. This might lead to a reduction of calls to poison centers, but at the same time strengthen their role in toxicovigilance by contributing data and knowledge to this process. The focus on calls per capita of population served counteracts further improvements and might turn into an obstacle, if support in funding from insurance companies etc. is asked. This approach might likewise lead to new cooperation structures within the field of emergency medicine or to a reduction in the number of poison centers for a country, or to differently trained staff members in the future. Scientific evaluation e.g. concerning the role of information brokerage in health care and repetitive data on the epidemiology of poisonings have to accompany poison centers work continuously. Funding of poison centers, that takes into account these developments and looks forward to an integrated role in a complex evidence-based public health care system, offers a systematic, reliable and scientific base for the sound financing of these institutions.

51 RISK ASSESSMENT OF CHILDREN EXPOSED TO ENVIRONMENTAL POLLUTANTS

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Pediatric environmental health has been labeled as one of the most important issues in 'millennium health', that is public health in the next century. The specialty, which is the overlapping practice of clinical toxicology, occupational/environmental medicine and pediatrics, has grown rapidly in recent years and has begun to exert considerable influence on health care policy and research. In the US, children's environmental health has been made a health care priority as a result of a 1997 Presidential Executive Order. In a conceptual framework, appreciation of issues in pediatric environmental health first requires the recognition that children, like adults, are exposed to a host of environmental pollutants on a regular basis. These exposures occur through all possible environmental media: air (both outdoor and indoor), water, soil and food. However, children have unique exposure patterns and unique vulnerabilities when exposed to many environmental toxins. For example, the oral habits of young children and their unique diet (ingesting 7-15x more fruits, vegetables and water than adults) magnify their exposure to certain agents. Unique vulnerabilities are related to factors including an immature renal system, an under-developed blood brain barrier and a limited ability to metabolize many xenobiotic agents. Pharmacokinetically children are significantly less able to perform certain Phase I biotransformations, resulting in delayed elimination of toxins. Finally, because children have a longer life span, toxins with effects having a long latency (e.g., certain carcinogens) or cumulative toxicity pose a greater risk of harm to the young. There are several existing paradigms which exemplify the concept of pediatric environmental health. Lead, polychlorinated biphenyls (PCB) and mercury are environmental toxins that have been shown to affect children more than adults. Scientific data demonstrating this exaggerated toxicity have been robust and reproducible. Less clear, but of equal concern are the effects caused by agents including environmental endocrine disrupters, and pesticides. The practicing clinician is increasingly being asked to translate these principles into practice by being asked to evaluate a child with known or suspected exposure to an environmental toxin. Examples include: (1) an infant who has been chronically exposed to carbon monoxide from a malfunctioning heating system, (2) a child who has been playing in an area later

discovered to contain a variety of toxic wastes, (3) a school-age child who presents with evidence of building-related illness, appearing only when he/she is in school, (4) children found to be chronically exposed to radon from the home, tetrachloroethylene from a nearby laundry or arsenic from the water. Assessment and management of such children requires a physician with expertise in clinical toxicology (in order to understand the potential toxicities of the exposure), pediatrics (in order to understand key principles in pediatric medicine), and occupational/environmental medicine (because for many of these toxins, considerable adult experience exists). Also needed by clinicians treating these children is expertise in treatment (when necessary) and risk communication. It was the growing demand for pediatric environmental health clinical sites that led the US Agency for Toxic Substances and Disease Registry (ATSDR) to begin establishing a network of Pediatric Environmental Health Specialty Units (PEHSU) in 1998. Currently 4 such centers exist with a tentative plan to double this number in the next year. The Pediatric Environmental Health Center at Children's Hospital Boston remains the most active service to date. Summary data from the Boston PEHSU as well as a review of the Unit's model of assessment/management will be provided. In summary, pediatric environmental health is rapidly moving towards establishment as a defined specialty existing within three clinical domains: medical toxicology, pediatrics and occupational/environmental medicine. The priority of this specialty is research to further define the unique effects that environmental toxins have on the child. Research will further guide policy (e.g., amendments to the Clean Air Act, the Clean Water Act and other protective federal regulations). The need for clinicians to evaluate such children can also be expected to increase.

52 RISK ASSESSMENT IN CHEMICAL INCIDENTS: THE VALUE OF A NATIONAL ASSESSMENT TEAM

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Introduction: In order to be better prepared for chemical disaster relief a national multidisciplinary assessment team for chemical incidents (in Dutch: BOTMI) has been installed. This risk assessment team has to advise regional, provincial or national authorities on the adverse effects and necessary actions required in chemical incidents with the intention to reduce the number of human casualties and the size of environmental pollution. Methods: In the Netherlands the Ministry of Housing, Spatial Planning and the Environment (in Dutch: Ministry of VROM) has a specific section that deals with environmental and nuclear incidents: the Crisis Management Department. This department has a 24 hour call centre and activates (depending on the severity of the reported incident) another centre, the Departmental Coordination Centre. In case of chemical incidents this Centre can activate the national assessment team. This team is composed of members of several large institutions, who can fall back on their institutes for further expertise. Among these institutions are other Ministeries, the National Institute of Public Health and the Environment, Institutes on Meteorology, Water management and Agriculture. The risk assessment team has broad advisory capabilities related to health effects, the environment, food, and water. In this framework the National Poisons Control Centre has advisory obligations with regard to acute and chronic health effects in humans caused by chemical exposure, advice on treatment of intoxicated patients, and the medical coordination of mass casualties. Results: In the past three years all members of the various Institutions have come to know each other thoroughly. The tasks and necessary knowledge and capabilities of all members have been defined. The working methods in all stages of the incident (alarmphase, collection of information, data management, interpretation, coordination, advise, deactivation, and evaluation) are described. Apart from handling chemical incidents several exercises were held. A process of continuing education is installed by discussing relevant minor incidents in this risk assessment group. Conclusions: Risk assessment in chemical incidents is a true challenge. By means of integrating data from various relevant Institutions the best possible balance between the need for accuracy of risk estimation and a rapid disaster relief can be achieved.

53 SILDENAFIL (VIAGRA®) . . . NOT YOUR TYPICAL SUBSTANCE OF ABUSE!

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Introduction: The traditional profile of a substance of abuse is one that is available, cheap and mood-altering. However, a variety of natural products and pharmaceuticals are used recreationally, but not necessarily for their psychoactive effects. Body-building hormonal agents are legend for their misuse. Nutritional supplements and natural products are

the focus of significant contemporary misuse. Women and men alike have been the victims of surreptitious aphrodisiac misuse for centuries. Not surprisingly, a new trend is the recreational use of sildenafil (Viagra®). Cloaked in embellished folklore, the misuse exists because of the misperception that sildenafil produces enhanced sexual prowess and performance. Discussion: Sildenafil is indicated for the treatment of male erectile dysfunction, with growing use among women as well. Sildenafil has no inherent pharmacological properties that stimulate sexual response or arousal. To the contrary, sildenafil facilitates penile tumescence through a cascade of events that must be initiated by sexual stimulation.[1–11] In healthy males, sexual stimulation results in the release of nitric oxide from nonadrenergic and noncholinergic nerves and endothelial cells in the corpora cavernosa. Nitric acid catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Cyclic GMP produces smooth muscle relaxation within the corpora cavernosa that permits arterial blood flow into the penis. The increased blood flow increases cavernosal pressure and results in tumescence. Sildenafil inhibits cGMP specific phosphodiesterase (PDE) type 5 from metabolizing cGMP resulting in maintained tumescence. When erectile dysfunction is secondary to impaired neural and/or hemodynamic response to sexual stimulation, sildenafil has been used successfully to remediate those problems. While sildenafil has helped to resolve this malady, it has changed the focus of erectile dysfunction from a medical condition to a lifestyle issue that minimizes inappropriately the medical significance of the problem. When lifestyle enhancement is desired, substances that purportedly affect lifestyle are often abused or misused—sildenafil is no exception. Sildenafil is a prescription medication in most countries. However, it is available quite readily via unauthorized or liberal prescription refills, on the Internet, in newspaper advertisements, over-the-counter without a prescription in some countries, under-the-counter in nightclubs, through illegal imports, etc.[12–17] The ubiquitous nature of sildenafil and the perception of its safety have led to significant recreational misuse and abuse. Creative users have attempted to capitalize on the fact that some easily obtained pharmaceuticals (cimetidine, etc) inhibit the metabolism of sildenafil (cytochrome P450 3A4) and increase the serum concentration of sildenafil and produce enhanced effects. Others seeking enhanced performance have fallen victim to the concurrent use of sildenafil and amyl nitrite poppers. The restricted use and failure to authorize health insurance payment for sildenafil prescriptions has fueled the underground sale in some countries. A survey of 77 U.S. Web sites that sold sildenafil directly to consumers revealed that 45% failed to provide medication information, only 35% noted that a physician would review the patient medical questionnaire, only half actually queried the patient about the presence of erectile dysfunction and only 44% required information about the concurrent use of nitrates.[18] The average cost of a 50 mg tablet was $12.50. Conclusions: Sildenafil is being misused and is obtained easily, bypassing the conventional prescription process and subjecting users to risk. While this misuse may not fit the classic definition of drug abuse for psychoactive purposes, sildenafil is clearly being abused in a multitude of ways. References:
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54 MEASURING PLASMA PARACETAMOL CONCENTRATIONS IN ALL PATIENTS WITH DRUG OVERDOSE OR ALTERED CONSCIOUSNESS: DOES IT ALTER OUTCOME?

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Background: Many clinicians take a blood sample for plasma paracetamol concentration in all patients presenting after drug overdose regardless of the history. There have been a few systematic studies performed to evaluate this common practice in the USA, Hong Kong and Australia but none in Europe where the prevalence of paracetamol poisoning is much higher. Objective: Our aim was to assess whether measuring plasma paracetamol concentrations in all patients with drug overdose or collapse/altered consciousness alters outcome. Methods: We performed a retrospective survey of all patients attending the Accident and Emergency department at Guy's Hospital, London over a 12 month period (July 1997–June 1998) who had plasma paracetamol concentrations measured. It is hospital policy that all patients presenting after a possible drug overdose or with a collapse/altered consciousness and a suspicion of drug overdose have a plasma paracetamol concentration routinely estimated. The chemical pathology computer was used to identify the patients and their hospital records were traced and reviewed by one author (SL) using a standard evaluation form. Results: Of the 42000 patients attending the A&E department over this time period we identified a total of 440 patients who had plasma paracetamol concentrations measured, of whom 411 were eligible for the study. 115 (26%) patients presented after a collapse/altered consciousness and paracetamol was detected in 4 of these. Of the 296 cases presenting after a drug overdose, 160 (54%) gave a history of overdose with a paracetamol containing product and 136 (46%) denied overdose with a paracetamol containing product. None of the 136 patients who denied overdose with paracetamol had paracetamol detected, giving a negative predictive value of 100%. Of the 160 patients with a positive history for overdose with paracetamol, 122 presented within 24 hours and 94 had detectable paracetamol levels with 16 cases above the relevant treatment line. 12 presented more than 24 hours after ingestion and 26 presented with a staggered overdose. One patient died as a result of a staggered paracetamol overdose. Conclusions: Taking blood samples for plasma paracetamol estimation in London in patients who deny taking paracetamol is of little clinical value. However, amongst patients presenting with altered consciousness, there is the potential for missed paracetamol poisoning and because the consequences of missing this diagnosis are potentially life threatening, screening for paracetamol poisoning is clinically justified in such patients. Such an approach can only be justified in a country in which paracetamol poisoning is prevalent such as the United Kingdom.

55 DATURA SPECIES—NATURAL HALLUCINOGENS

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The datura species of the Solanaceae family have been used since antiquity for their toxic, hallucinogenic and herbal properties. Included are *Datura stramonium, D. sauveolens, D. innoxia, D. metel, D. fastuosa,* and *D. tabula*. Historical references include Homer's Odyssey, Cleopatra's use to woo Caesar, the poisoning of Mark Antony's troops, and use by European witches and Mexican Indians for religious, sexual, and hallucinogenic purposes. In the United States the first documented use was in 1676 in Jamestown by British troops, hence the abbreviated name 'Jimson Weed'. Abuse became particularly widespread in the 1970s by adolescents and others seeking an inexpensive and natural hallucinogen. Current use tends to occur in clusters as a group recreational experience. The datura species contain the tropane alkaloids scopolamine, hyoscyamine, and atropine. These are competitive muscarinic antagonists, which inhibit the actions of acetylcholine at autonomic and smooth muscle sites, but have little or no effect on nicotinic binding sites. Both central and peripheral anticholinergic effects result, with hyoscyamine and scopolamine accounting for the central nervous system toxicity due to their blood-brain barrier penetration. *D. stramonium* (jimson weed, thornapple, locoweed, devil's trumpet) grows wild throughout the United States. Its white, tabular flowers, leaves, roots and seed-containing spiny fruit are all toxic. The 50 to 100 brown–black seeds in the fruit pods each contain about 0.05 to 0.1 mg of atropine. Serious toxicity can thus result from one-half the seeds of a pod. The leaves and seeds are smoked, ingested, or made into a tea. *D. Sauveolens* (angel's trumpet) is native to South America, and now grows throughout the southeastern United States. It also found as an ornamental plant in the US and Europe. It produces a large, pink/white, fragrant

trumpet-shaped flower. The leaves and blossoms are usually steeped in water to yield a 'magic drink', often mixed with alcohol. Each blossom contains about 0.2 mg atropine and 0.65 mg scopolamine. *D. metel* (Yangjinhua, Hindu datura), *D. fastuosa*, *D. innoxi*a, and *D. tabula* are Chinese herbal medications used for treatment of asthma, chronic bronchitis, and for analgesia. Yangjinhua use is most widespread and the plant is found throughout China. The others differ from *D. metel* in place of origin, flower appearance, and alkaloid contents, but have similar uses and effects. They are available as the native plant or as proprietary medicines, and can be taken orally, intravenously, or in cigarettes. Although the intent of use is therapeutic rather then recreational, these represent another natural source of anticholinergic toxicity. Irrespective of the type or route of datura use, the clinical effects are similar except for rate of onset, duration, and severity. Peripheral anticholinergic effects include sinus tachycardia, hyperpyrexia, mydriasis, tachypnea, urinary retention, thirst, and dry mucous membranes. Tachycardia early in the course is a particularly consistent finding, and may be associated with a widened pulse pressure. Hyperpyrexia is much less common, occurring in 18% of cases in one study. The most common central anticholinergic effect is hallucinations, coupled with bizarre and combative behavior. Patients typically are observed flailing and picking at clothing or imaginary objects. Clonus and hyperreflexia are also common. Seizures are rare, occurring in only one of a 73 case series. Likewise, deep coma occurs in only the most severe cases. Symptom onset may be as early as 10 minutes with smoking or tea ingestion, and almost always within 1 hour. Duration of effect in those requiring hospitalization is 1–2 days, but may be as long as six days. Urinary retention and mydriasis are typically the last effects to resolve. Laboratory findings are non-specific, but commonly include leukocytosis and rhabdomyolysis. Drug screens usually do not detect datura plants. Treatment of datura intoxication is that of other anticholinergic toxins: decontamination, sedation, and selective use of the antidote physostigmine. The first intervention should be sedation with benzodiazepines. Adequate doses to calm and control the patient are necessary, rather than physical restraints, which aggravate the CNS effects. Datura toxicity rarely requires intubation, even with high-dose benzodiazepine therapy. Gastric lavage to remove plant parts has been anecdotally reported, but is of questionable efficacy, and introduces stimulation which aggravates the delirium and agitation. Decontamination with activated charcoal was associated with shortened lengths of stays in one series, and may be effective for hours after ingestion due to the potentially slow absorption of these agents. Physostigmine salicylate is an anticholinesterase with a tertiary amine, allowing it to cross the blood-brain barrier and reverse both the peripheral and central effects. Although case reports suggest the potential for serious adverse cholinergic effects, several series show it to be a safe and effective antidote. Indications include persistent agitation or hallucinations, or the rare seizure or symptomatic tachycardia. It has also been shown to aid diagnosis and facilitate decontamination.

56 EVIDENCE FOR RED-BACK SPIDER ANTIVENOM EFFICACY IN THE PREVENTION OF ENVENOMATION BY OTHER WIDOW-SPIDERS (GENUS *LATRODECTUS*)

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Background: Widow spiders of the genus *Latrodectus* are found world-wide. All produce a similar clinical envenomation syndrome. Species-specific antivenoms (AV) are available in a number of countries but in some regions of the world no antivenom exists to treat envenomation. Some AV preparations may have a relatively higher incidence of allergic reactions following administration than other products resulting in physician anxiety in their use for treatment of widow-spider envenomation. Red-back spider (RBS) AV is an effective and safe treatment for envenomation by the RBS (*L. hasselti*) in Australia with an extremely low incidence of allergic reactions. It has been anecdotally reported to reverse envenomation by *L. tredecimguttatus* in one case and is used to treat envenomation by the *L. katipo* in New Zealand. Presently there exists little controlled data assessing the cross-reactivity of AVs raised against specific widow-spiders with the venom from other widow-spiders. Methods: (1) The binding of RBS-AV to α-latrotoxin and various *Latrodectus* venoms (*L. mactans, L. hesperus, L. lugubris, L. tredecimguttatus, L. hasselti*) was assayed using Western blotting. (2) Prevention of *in vitro* toxicity to α-latrotoxin and the above venoms was tested in triplicate by pre-treating an isolated chick biventer cervicis nerve-muscle preparation with 100 to 200 Units of RBS-AV. (3) Five male Balb/c mice per group were administered one of the above widow spider venoms sc ($2.5–5 \times LD_{50}$) or α-latrotoxin ($10 \times LD_{50}$) with either saline or pre-incubated for 30 min with 100 Units of RBS-AV and observed for evidence of envenomation. Results: (1) Western blotting revealed that RBS-AV bound with both pure α-latrotoxin and similar venom proteins in all venoms tested. (2) Antivenom prevented the typical muscle contracture and loss of twitch tension seen with α-latrotoxin and the widow-spider venoms tested on the nerve-muscle preparation. (3) All mice administered venom or

α-latrotoxin alone developed severe signs of envenomation (piloerection, rapid breathing, immobility, priapism, hind-leg paralysis) within 2 hours and 5 hours of administration respectively. Mice administered antivenom plus venom or α-latrotoxin were observed for 72 hrs and remained free of signs of envenomation. Conclusions: RBS-AV binds with α-latrotoxin and widow-spider venoms suggesting a degree of antigenic similarity with protein fractions found in RBS venom. Antivenom prevented development of both *in vitro* venom toxicity and the *in vivo* envenomation syndrome in mice. These data suggest that RBS-AV may be effective in the treatment of envenomation resulting from the bite of widow-spiders from various continents.

57 SCOMBROID FISH POISONING: ELEVATED PLASMA HISTAMINE IN INTOXICATED PATIENTS CAN CONFIRM THE DIAGNOSIS

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Background: Scombroid poisoning is a form of ichthyosarcotoxism caused by eating 'spoilt' fish mainly of the scombroid family (tunas, bonitos). Histidine contained in their flesh can be decarboxylated to histamine by enterobacteria during inappropriate storage. Histamine poisoning mimics IgE-mediated food allergy: nausea, vomiting, diarrhea, hives, itching, rash, and/or hypotension appear within minutes to a few hours, lasting up to 24 h. Case reports: Ten to 90 minutes after a common meal including cooked tuna, nine persons complained of faintness, headache, generalized urticaria, angioedema and tachycardia. Because the symptoms suggested an allergic reaction, a physician gave them dexamethasone 4 mg and cetirizine one tablet. Five were hospitalized within 4 hours, with a warm urticaria mainly on the face, the trunk and the root of the upper limbs, headache, abdominal pain (2 patients) with diarrhea (1) or vomiting (1), and upper limb paresthesia (2). There was no sign of hemodynamic or respiratory failure. A sixth patient came in at the sixth hour, after symptom resolution. Symptoms resolved within 4 to 6 hours in three patients, but persisted at 24 hours in 2 with past history of allergy. Quantitative plasma histamine determination was performed with the Immunotech Radioimmunoassay kit, a routine technique. The results are reported in the table. Two tuna pieces were sent for toxin analysis: a piece of tail did not show histamine, but another piece had toxic concentrations, above 100 mg/100 g flesh. The tuna weighed 6 kg, had not been gutted, had been stored in a room at 8°C and was eaten 4 days after being fished. Discussion: The association of symptoms of histamine poisoning and a previous collective fish meal should alert physicians to the possibility of scombroid fish poisoning. Tissue histamine concentration is a good indicator of fish spoiling, and a key to the diagnosis. Most of the histamine is produced in the flesh around the intestines and then diffuses into the tissues, so that distant tissue can have misleadingly low concentrations. Increased patient plasma histamine soon after the contaminant meal (<4h) confirms the origin of the intoxication, as shown in animals. Elevated urinary excretion of histamine was also described in 3 victims of scombroid poisoning, but false urinary positives are possible, as in women with interstitial cystitis. Steroids and H1 and H2 antihistamines are effective on the symptoms. This histamine being exogenous, patients will be able to eat the same (fresher) fish later on.

Evolution of plasma histamine concentrations in six patients with tuna ichtyosarcotoxism

Patients	Past History of Allergy	Sampling Delay	Plasma Histamine Level on Admission (N < 10.8 mmol/L)	Plasma Histamine Level at 24 Hours (N < 10.8 mmol/L)	Outcome at 24 Hours
F 19	Asthma, rhinitis	3 h	21.5	2.5	Flush, headache
M 37	—	3 h	24.5	4.1	Resolved
M 41	Rhinitis	3 h	34.9	2.7	Erythema, abdominal pain
M 47	—	4 h	30.6	2.5	Resolved
M 48	—	4 h	47.8	3.6	Resolved
M 39	—	6 h 30	6	1.8	Resolved

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58 KINETIC-DYNAMIC RELATIONSHIP—PRINCIPLES

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The kinetic-dynamic relationship in the poisoned patient depends on several factors: the mechanism of action of the poison, the type of relationship between the dose or concentration and the symptoms, the factors which may modify this relationship. Mechanisms of action of poisons: Most poisons act by an interaction with macromolecular components (receptors) which results in biochemical and physiological changes that are characteristic of the toxicity. Receptors are mostly proteins: enzymes (e.g. organophosphates–acetylcholinesterase), proteins involved in transport processes (e.g. digoxin–Na^+K^+ATPase), structural proteins (e.g. colchicine–tubulin). An interaction with physiological receptors may result in an agonist or antagonist effect. The target organs depend on the localization of the receptors specific to the poison. The magnitude of toxicity depends on the poison concentration at the receptors. The action of the poison may be due to a direct effect on the receptor, an effect mediated by a second messenger (e.g. cAMP) or a modification of the permeability of ion membrane channels. In fact, 3 major aspects should be taken in account: (1) Has the poison a local effect (limited to one organ) or a systemic effect? (2) Is the toxicity reversible or not? (3) Has the poison a primary effect dependent on the presence of the poison at the target organ or a secondary effect which may persist even if the poison has disappeared from the organ? The global effect results from 3 factors: the type of action, the magnitude of the effect and the duration. Classification: Poisons can be classified into 3 types according to the mechanism of action. (1) Functional poisons impair the function of one or several organs. The toxicity is directly related to the concentration at the target organ or receptor. (2) Lesional poisons induce cellular or organ damage. The severity depends on the maximal concentration which has been (or will be) reached at the target organ. (3) Poisons which act by both mechanisms. Toxicodynamics: Some poisons have an 'all or nothing' effect with a precise threshold level for toxicity (e.g. carcinogens). For other poisons the effect is linearly dependent on the dose or concentration. However, in most cases toxicity appears after a given threshold level, increases with the dose and reach a maximum if all the receptors are saturated. The relation has the typical aspect of a sigmoidal log dose-effect curve. The two important parts of the curve are the slope of the median part and the position of the dose-toxicity curve in comparison with the dose-therapeutic effect curve and the dose-mortality curve. In practice, the slope of the curve is an important parameter to estimate the dose of an antidote which should be administered or the amount of poison which should be removed in order to reverse a toxic effect. The position of the different curves is important to determine the therapeutic margin of a drug and the toxic-mortality margin of a poison. Applications of kinetic-dynamic relationship in the poisoned patient: (1) Assessment of severity and prognosis criteria. For functional poisons (e.g. barbiturates, meprobamate, ethanol, theophylline), toxicity is usually well related to the plasma concentration. For lesional poisons (e.g. metals, paraquat, paracetamol), the toxicity depends on the maximal dose or concentration reached at the target organ. For poisons acting by both mechanisms (e.g. methanol, ethylene glycol, carbon monoxide), the relation has to take in account the dose or concentration, the delay and the secondary effects of the poison or the toxic metabolites. (2) Variations of the kinetic-dynamic relationship. Numerous factors may influence the kinetic-dynamic relationship. The dose ingested may change the bioavailability, the protein binding, or the hepatic metabolism with a possible switch from a first order kinetic to a zero order kinetic (e.g. theophylline, salicylate). The delay ingestion-analysis is important because the potential severity of the poisoning cannot be evaluated until the plasma peak concentration has been reached (e.g. paracetamol). High initial concentrations may not be related to symptoms if the phase of tissue distribution is not completed (e.g. acute lithium poisoning). With identical plasma concentrations, the symptomatology may vary according to the type of poisoning. For theophylline, lithium and digoxin symptoms are more severe in chronic than in acute poisonings. Toxicity may be age dependent: for instance, in chronic theophylline overdose, symptoms and prognosis are more severe in elderly patients. Underlying diseases or toxic symptoms such as hypoxemia and shock may strongly modify the kinetics (e.g. theophylline and congestive heart failure). Epileptic patients are at higher risk for developing convulsions in poisonings with convulsant drugs. The toxicity of cardiotropic drugs is increased in patients with chronic heart diseases. A concurrent ingestion of other drugs may prolong the absorption (anticholinergic effect) or decrease the elimination by interfering with the hepatic metabolism. A tolerance may be due to kinetic changes (e.g. enzyme induction by alcohol or barbiturates) or to dynamic changes (tolerance to opiates). If the parent compound is metabolized into active metabolites, all the active compounds must be taken in account for the kinetic-dynamic relationship (e.g. benzodiazepines, tricyclic antidepressants). (3) Evaluation of treatment. The evaluation of elimination techniques and antidotes should be based on kinetic and dynamic parameters: decrease of plasma concentrations and half-life, amounts removed, correction or prevention

of toxic symptoms. Conclusion: Kinetic investigations in clinical toxicology have contributed to the progress in many fields such as the indications of toxicological analyses, the assessment of kinetic-dynamic relationships, of severity and prognosis criteria, the evaluation and indications of decontamination or elimination procedures and antidotal treatments. Therapeutic strategies should always take in account the kinetic-dynamic relationships.

59 DYNETICS—A NEW CONCEPT IN TOXICOLOGY

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Background: Acute toxicity is the expression of dose-effect relationships, toxicokinetics, toxicodynamics, and their interactions. Some compounds (benzodiazepines) appear to involve single mechanism toxicity. Others (paraquat, ethylene glycol) induce toxic effects through multistage mechanisms. We propose 'dynetics' as a general term to describe the chronology of toxic effects, their individual duration and magnitude, and the dependence of one effect on another. In other words, dynetics represents the kinetics of dynamic events. Attention to dynetics may allow the refinement of our understanding of the contribution of individual mechanisms of toxicity demonstrated in experimental studies to the clinical presentation of poisoning in humans. The medical interests of such a concept are manifold. In acetaminophen poisoning, the diagnosis and prognosis within the first 24 h rest on serum acetaminophen concentrations, while late in the course of poisoning they depend on serum ASAT and ALAT. Obtaining the right diagnostic test depends on an understanding of dynetics. Specific treatments (antidotes, extracorporeal elimination) cannot be adequately evaluated without considering this concept. Experimental and clinical data show that fomepizole can prevent life threatening intoxication at a time when plasma ethylene glycol concentrations are high and glycolate concentrations are low. Fomepizole appears to be devoid of any therapeutic value, however, when plasma glycolate and oxalate concentrations are high and plasma ethylene glycol concentrations are low. The efficacy of many antidotes will be strongly dependent on the dynetic phase at which they are administered. Dynetics demands that we classify patients in clinical trials according to the dynetic phase of the poisoning in order to more precisely assess treatment efficiency. Conclusion: Dynetics belongs to the area of integrated physiological systems. Dynetics attempts to integrate the mechanisms of toxicity in order to explain the pathophysiology of a poisoning and the corresponding signs and symptoms observed throughout its course. The consequence of this approach is to assess more precisely the efficacy of specific treatments.

60 CLINICAL IMPLICATIONS OF THE PHARMACOKINETIC AND PHARMACODYNAMIC RELATIONSHIPS BETWEEN THERAPEUTIC IMMUNOGLOBULINS AND THEIR TARGETS

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Background: Therapeutic immunoglobulin (Ig) antibodies have been developed against a wide variety of poisons: Botulinum toxin, venoms of various snakes, scorpions and spiders, digoxin, PCP, colchicine, paraquat, amanitin, and tricyclic antidepressants (TCA). In the recipient, target-specific Ig binds to and neutralizes poisons with an affinity in the range of 10^8 to 10^{10} M^{-1}, much higher than most poisons' affinity for binding sites in the body. Initial therapeutic Igs were minimally purified equine IgG. More recently, affinity-purified $F(ab')_2$, Fab′ and recombinant single chain (sFv) fragments of IgG have been developed in a variety of animals and cell lines. Kinetics/dynamics: Ig pharmacokinetic parameters generally follow a 2–compartment model. Molecular weight (MW) is the greatest determinant of Ig kinetics, with the MW of IgG, $F(ab')_2$, Fab′ and sFv approximately 150,000, 100,000, 50,000 and 25,000 Daltons, respectively. Ig kinetics are source-, recipient- and target-dependent, making extrapolation from animal studies difficult and giving each therapeutic Ig a relatively unique kinetic and dynamic profile. Kinetics are stable over a wide dose range but may be affected by such factors as ionic charge, non-specific binding, analytic methods and study design. For example, an Ig will display different kinetics depending on whether it is evaluated in the presence or absence of its specific target. The kinetics of targets are also affected by interaction with an Ig. For example, PCP exhibits decreased volume of distribution (V_d), clearance (Cl) and metabolites in the presence of PCP-specific Fab′. Pharmacodynamic factors—target specificity and affinity, Ig molecular stability, anti-idiotypic antibodies and concentration at the site(s) of action, as well as dynamic alterations caused by Ig and target interactions—further help to determine an Igs clinical efficacy. In general, IgG has the smallest V_d, poorest tissue penetration, longest distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively), slowest Cl, longest mean retention time (MRT), is primarily eliminated by the reticuloendothelial system (RES) and produces the greatest hypersensitivity reactions. $F(ab')_2$, Fab′ and sFv have progressively larger V_d, increasing tissue penetration, shorter $t_{1/2\alpha}$ and $t_{1/2\beta}$, faster Cl, shorter MRT, increasing percentage of renal elimination and decreasing antigenicity. In humans, equine crotaline-specific IgG distributes to a space approximating vascular

volume (~90 mL/kg), has a $t_{1/2\beta}$ of 61 to 194 hours and is eliminated predominantly by the RES, whereas crotaline-specific ovine Fab′ distributes to a volume approximating the extracellular space (~400 mL/kg), has more rapid distribution and elimination ($t_{1/2\beta}$ 2.5 hrs; $t_{1/2\beta}$ ~15 − 25 hrs) than IgG or $F(ab')_2$ and has over 50% renal elimination. E. coli-derived sFv in mice has very rapid distribution and elimination compared with other Igs (sFv $t_{1/2\alpha}$ = 3.7 min vs. 9.1, 26, and 39 min and sFv $t_{1/2\beta}$ = 1.5 hrs vs. 1.5, 12, and 113 hrs for Fab′, $F(ab')_2$, and IgG, respectively). Also, sFv does not accumulate in the kidney as do $F(ab')_2$ and Fab′, suggesting that sFv may be less nephrotoxic at very high doses. Clinical implications: Kinetic and dynamic mismatches between an Ig and its target may result in undesired effects. For example, a phenomenon of recurrent toxicity following initially successful Ig therapy has been observed. That is, the initial dose of an Ig neutralizes all of the available poison, with a clinically efficacious result, but there remains a depot of un-neutralized poison in the body. When circulating concentrations of Ig fall below protective levels, recurrent toxicity may be seen. The greater the clearance of the Ig in relation to the clearance of the poison, the greater and earlier the likelihood of recurrent toxicity when such a depot exists. Two such recurrence phenomena, for example, have been observed in crotaline envenomations. Recurrence of local effects is seen in up to 50% of ovine Fab′-treated patients during the first 24 hours following initial control. Also, over 50% of crotaline envenomations with early coagulopathy treated with ovine Fab′ will develop recurrent venom antigenemia and coagulopathy 2 to 7 days following initial control. A dynamic mismatch occurs because venom-induced local tissue injury prevents Ig from initially reaching and neutralizing all of the venom. Fab′ and IgG given intravenously are equivalent in neutralizing venom at the bite site, suggesting that improved tissue penetration is not the answer to correcting this dynamic mismatch. The very rapid clearance of Fab′ in comparison to venom components (which may remain in the body for greater than 2 weeks), is a kinetic mismatch. Recurrent venom antigenemia and coagulopathy is not only a phenomenon of Fab′ therapy, however, having been documented in $F(ab')_2$- and IgG-treated patients as well. And a similar recurrence phenomenon occurs in ovine digoxin-specific Fab′-treated patients, as un-neutralized digoxin redistributes from tissue stores after unbound Fab′ elimination or consumption. Other kinetic and dynamic mismatches are possible. TCAs, for example, are present in the body in very large quantities following overdose. An equimolar neutralizing dose of Fab′ may be impracticably high because of renal toxicity concerns. Poisons with an extremely large V_d, very high tissue affinities or other properties may also result in kinetic or dynamic mismatches and undesired effects. Possible solutions: Modifying the dose regimen and route of administration may allow IgG kinetics to more closely match those of target poisons. In crotaline envenomations, repeat dosing of ovine Fab′ in the first 18 hours prevented local recurrence. And theoretical work suggests that a continuous intravenous infusion or an intramuscular preparation of Fab′ following initial control of coagulopathy may prevent coagulopathic recurrence. Imparting anionic charges or complexing Fab′ with molecules such as dextran or glycolate to reduce renal clearance may also improve the relevant kinetics. With TCA toxicity, animal studies and preliminary human trials suggest that partial neutralization by TCA-specific Fab′ may still be clinically effective. Thus, such mismatches need not preclude Ig use. Conclusions: Developing target-specific Igs pose a variety of kinetic and dynamic challenges. Understanding the kinetic and dynamic relationships between Igs and their targets will aid in developing appropriate target-specific Igs and optimizing treatment regimens.

61 THE TOXICOKINETICS OF ETHANOL

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Ethanol is widely available, a cause of serious illness and of great legal importance. Considerable uncertainty remains about many aspects of ethanol pharmacokinetics. Measurement of ethanol concentration is itself controversial, since the ratio of values in breath to those in blood is only stable after absorption is complete, and varies considerably between one healthy individual and another and may differ by a factor of two.[1] Infrared breath ethanol measuring devices are not entirely specific and other volatile organic compounds interfere. Ingested ethanol is absorbed much more rapidly from the small intestine than from the stomach or esophagus, so that overall absorption depends largely on the rate of stomach emptying, which is very variable. The proportion of ethanol lost by pre-systemic elimination by alcohol dehydrogenase in the gastric wall is probably small. Ethanol is distributed in total body water, whose individual value can be estimated from simple anthropometric measures with reasonable accuracy.[2] Methods based on body weight alone are much less accurate. Ethanol is largely metabolized by alcohol dehydrogenase to acetaldehyde. The enzyme is easily saturable, and so for most toxicological and legal purposes, the rate of disappearance is independent of ethanol concentration (the kinetics are ‘zero-order’), as described by Widmark in the 1930s. However, the absolute rate of ethanol disappearance differs substantially between subjects. A reasonable range, derived from Holford’s review (1987)[3], is between

12.5 and 25 milligrams per 100 milliliters per hour. Even these rates are too high at low ethanol concentrations and may be too low in exceptional subjects. Clinical toxicologists may be asked to consider legal problems such as back-extrapolation, the hip-flask defense, and the lacing defense. It is best to consider a range of possible values for each of the pharmacokinetic parameters required for such calculations; the range of results may be so wide as to be unhelpful to the lawyers, but at least it is likely to contain the true value. References: [1]Dubowski KM. Recent developments in alcohol analysis. *Alcohol Drug Driving* 1986;**2**:13–46. [2]Watson PE. Total body water and blood alcohol levels: Updating the fundamentals. In: Crow KE, Batt RD, eds., *Human Metabolism of Alcohol*, Vol. 1. Boca Raton: CRC Press, 1988: 41–55. [3]Holford NH. Clinical pharmacokinetics of ethanol. *Clin Pharmacokinet* 1987;**13**:273–292.

62 TOXICOKINETIC-TOXICODYNAMIC RELATIONSHIPS IN HUMAN MEPROBAMATE POISONINGS

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Introduction: The value of PK-PD relationships in clinical pharmacology is now well recognized. However, the potential interest of Toxicodynamic-Toxicokinetic (TK-TD) relationships in medical toxicology has been poorly investigated. The aim of this study was to correlate the depth of coma with plasma meprobamate concentrations. Materials and Methods: Plasma meprobamate concentrations were measured using a colorimetric assay. The depth of coma was assessed using the Glasgow coma scale (GCS). Non-linear regression was used for modeling TK-TD relationships. Results: TK-TD relationships were studied in 7 acute meprobamate poisonings. Three patients were previously treated with meprobamate. Previous treatment was unknown in 2 patients. Mixed drug poisoning was noted in the 7 patients. The mean GCS at the time of hospital admission was 4 ±1, the mean plasma meprobamate concentration was 1054 ± 318 μmol/L. The mean plasma meprobamate concentration associated with a GCS of 3 was 714.6 ± 277.7 μmol/L (95% CI: 546.8-882.4). The TK-TD relationship was well fitted with the sigmoidal Emax model. In the 7 patients, the mean Hill coefficient (m ± SD) was 6.9 ± 4.0 (95% CI: 3.2-10.7), the mean C_{50} was 487.9 ± 318.8 μmol/L (95% CI: 193.0-782.7). Two patients exhibited tolerance to the sedative effect of meprobamate. In the 5 non-tolerant patients, the mean Hill coefficient (m ± SD) was 8.0 ± 4.4 (95% CI: 2.5-13.4), the mean C_{50} was 315.8 ± 148.9 μmol/L (95% CI: 130.9-500.7). Discussion: A maximal toxic effect, i.e.: GCS of 3, was associated with a wide range of plasma concentrations. During the course of acute human meprobamate poisoning, the relationship between the depth of coma and the corresponding plasma concentrations is of a sigmoidal shape. The high value of the Hill coefficient in non-tolerant patients showed that a small decrease in plasma meprobamate concentrations near the C_{50} was associated with a dramatic improvement in their level of consciousness. In non-tolerant patients, the mean C_{50} was close to the upper limit of the therapeutic plasma concentration of meprobamate given by our toxicological laboratory (≤200 μmol/L).

63 COMPARISON OF THE PHARMACOKINETICS AND TOXICOKINETICS OF CARBAMAZEPINE

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Objective: Before considering problems in the field of toxicokinetics we must first define what we mean by this concept. In the context of research into new drugs, toxicokinetics should be understood as kinetic studies aimed at assessing risk from drugs through toxicological trials on animals (pre-clinical trials). Some researchers, who wish to avoid using the term pharmacokinetics when referring to absorption and disposition studies concerning xenobiotics which are not medicines, use the term toxicokinetics. Clinical toxicologists in turn use this term to refer to studies of the kinetics of medicines/xenobiotics in acute poisoning cases. If we accept this definition we should ponder where the data for toxicological elaborating/modeling come from. Only in a few cases can the data originate from planned clinical studies involving volunteers; furthermore only relatively non-toxic compounds and relatively small doses can be applied. Most papers on kinetics are based on xenobiotics determinations in physiological fluids carried out for diagnostic purposes, sometimes ‘enriched’ in terms of numbers of determinations (having in mind future scientific papers). The aim of this presentation is an attempt to answer the question: ‘Can results of routine diagnostic studies be applied to kinetic studies/toxicokinetic modeling, and not just to the calculation of basic pharmacokinetic parameters?’ A fundamental problem

encountered when applying such results in toxicokinetic modeling is uncertainty as the future dose and the time of its taking. Attempts to solve this problem are presented in this paper: the application of pharmacokinetic models, population pharmacokinetic and neuronal networks. Material and methods: The pharmacokinetics of carbamazepine were studied using data from routine toxicological analysis of 57 poisoned patients and of 20 patients who were administered carbamazepine in therapeutic doses (3×200 mg) for the first time in their life, so carbamazepine monitoring was done for toxicological diagnosis or for drug therapy monitoring. Patients were given carbamazepine at 6 a.m., 12 p.m., and 6 p.m. The blood samples were collected at 3 and 6 p.m. just before administration a new dose of the drug. Basic information on amount and time of ingestion in acutely poisoned patients were known from interview and laboratory determinations. The basic pharmacokinetic parameters of carbamazepine in patients treated with carbamazepine were calculated using the one-compartment model. The data from poisoned patients were analyzed using the non-linear mixed effects model (NONMEM) program designed for population pharmacokinetic parameters. Also the neuronal network was applied for pharmacokinetic calculation in poisoned patients. Results: The pharmacokinetic parameters of carbamazepine in patients treated with this drug were: $t_{1/2} = 27.7 \pm 8.7$ h; Cl $= 0.0681 \pm 0.0281$ L/h/kg, $V_d = 4.0 \pm 1.8$ L/kg and for carbamazepine poisoned patients respectively: $t_{1/2} = 39.3 \pm 17.2$ h; Cl $= 0.08 \pm 0.0171$ L/h/kg, $V_d = 2.9 \pm 0.5$ L/kg. Conclusion: The simple compartment models can be used for pharmacokinetic calculation after administration of drug in therapeutic doses however the population pharmacokinetics and neuronal network are well fitted in toxic concentrations.

64 TOXICOKINETICS OF SALICYLATE POISONING

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Objective: A grasp of the toxicokinetics of salicylate poisoning has utility if it aids understanding the natural history of the poisoning and predicts those patients who are likely to develop significant morbidity. The association of serum salicylate concentrations, with morbidity and mortality, is not close. However, a close relation between CSF salicylate concentration and morbidity has been demonstrated in both man and animals. The objective of this paper is to determine to what extent readily available measurements such as the salicylate concentration and time since ingestion can be used to predict CSF salicylate concentration. Database: Absorption of salicylate following overdose is highly variable and can vary between 0.5 hours and 24 hours. Distribution of salicylate into CSF occurs at a fairly constant rate and takes approximately 12 hours to reach equilibrium. Elimination of salicylate is complex. At therapeutic concentrations, 95% of salicylate is eliminated by metabolism. At least two pathways (those producing salicyluric acid and salicyl phenolic glucuronide) are saturated at high therapeutic concentrations of salicylate. Other pathways involving the production of acyl glucuronides and gentisic acid are first order processes as is renal elimination of salicylic acid. At toxic concentrations of salicylate up to 70% of ingested drug is eliminated as salicylic acid in the urine. The terminal slope of plasma salicylic concentration is, however, log-linear so the toxicokinetics of elimination can be collapsed into a single first order process yielding a half-life of 18–32 hours in untreated poisoned patients. Prediction of CSF concentrations reduces to solving an equation which contains three first order variables: rate of absorption, rate of distribution, and rate of elimination. Unfortunately, rate of absorption varies greatly between each poisoning so it is impossible to provide one solution (as in the case of paracetamol poisoning) for prediction of morbidity. Furthermore, that solution can only be obtained if the time of ingestion and serial concentrations of salicylate are available. Therapeutic interventions have a reproducible effect on plasma salicylate concentrations. Alkalinization of urine reduces the plasma half-life of salicylic acid to about one third of untreated subjects and the half-life on dialysis can be as low as 1.6 hours depending on the technique used. Conclusion: Understanding the toxicokinetics of salicylate poisoning gives insight into the natural history. However, variability in the various rate ‘constants’ makes it unrealistic to use this approach with finesse. Clinical surrogates for CSF salicylate concentrations such as disturbance in level of consciousness, and gross toxicokinetic measurements such as time to peak, and peak salicylate concentration remain the order of the day.

65 PHARMACOKINETICS AND PHARMACODYNAMICS OF NICOTINE, COCAINE AND HEROIN

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Background: The psychoactive substances nicotine, cocaine and heroin all are associated with important health problems. Nicotine is generally consumed legally by cigarette smoking and the number of ingested cigarettes is dependent on

serum nicotine concentrations.[1] In contrast, heroin and cocaine are illegal drugs. Heroin and cocaine are sometimes also smoked, but more commonly injected intravenously. All three substances are highly addictive.[2] The aim of this presentation is to discuss and compare the pharmacokinetic and pharmacodynamic properties of nicotine, cocaine and heroin. Drug disposition: All three drugs exhibit short half-lives. Heroin has a half-life of 2 to 3min. and cocaine of ~10 min. Nicotine has an initial half-life of ~6 min and a terminal half-life of ~2 h.[3] All three compounds also have high hepatic clearances. Drug absorption: After oral cocaine dosing, cocaine input into the systemic circulation increases slowly and peaks around 45 minutes after ingestion. The systemic bioavailability after oral dosing is ~35%. After nasal dosing, drug input is substantial even in the first minutes and shows two peaks at 10 and 45 minutes after ingestion. The second peak probably occurs, because part of the dose is swallowed and absorbed gastrointestinally. The fraction reaching systemic circulation after nasal application is only slightly higher (~47%) than the oral bioavailability. However, in contrast to oral dosing, nasal dosing leads to a very rapid initial increase of cocaine serum concentrations, which probably enhances its pharmacological effects. Heroin is generally not ingested orally, because of its bad taste and because neither heroin (diacetylmorphine) nor its primary metabolite monoacetylmorphine reach the systemic circulation.[4] Orally ingested heroin is completely metabolized to morphine. For nicotine, non-inhalative administrations are only used for withdrawal therapy. Tolerance: For nicotine, one generally distinguishes between acute and chronic tolerance. Acute tolerance to various effects of nicotine (increases in heart rate, blood pressure, plasma epinephrine and energy expenditure) occurs within the range of nicotine plasma concentrations found in smokers.[3] However, the rate of tolerance development varies considerably. The half-lives of tolerance range from 3.5 min for the increase in energy expenditure to 70 min for systolic blood pressure. There is no apparent tolerance to the effects on free fatty acid concentrations which reflects lipolysis.[3] These differences in the pharmacodynamics of tolerance may reflect differences in the rate of desensitization of various subtypes of nicotinic receptors and/or differences in mechanisms of tolerance for various nicotinic effects. The pharmacodynamics of tolerance development are less well studied for the other drugs. However, the high daily heroin doses of 400 to 600 mg required in heroin substitution programs for severely addicted patients clearly show that, in the case of heroin, chronic tolerance development is a major issue. Arterio-venous concentration differences: Nicotine[5] and cocaine[6] exhibit major arterio-venous concentration differences, which can however only explain a part of the tolerance observed.[5] Also after intravenous heroin administration, considerable arterio-venous concentration differences are observed for heroin and for the primary metabolite monoacetylmorphine. For diacetylmorphine, and monacetylmorphine, the area under the concentration time curve obtained from arterial concentration data is about twice the area obtained from venous concentrations. Heroin-derived morphine, in contrast, generally exhibits larger venous AUC estimates as compared to arterial ones. These data suggest that diacetylmorphine and monacetylmorphine are efficiently metabolized to morphine intravascularly and perhaps additionally in peripheral tissues. Conclusions: Heroin, cocaine and nicotine have many pharmacokinetic and pharmacodynamic properties in common: (1) a short half-life (2) a high hepatic clearance and therefore a low bioavailability (3) considerable arterio-venous concentration differences shortly after intravenous or nasal dosing and (4) rapid tolerance development. Rapid tolerance development requires that all three compounds are consumed by routes leading to rapidly rising plasma concentrations and might contribute to their high addictive potential. References: [1]Bergen AW, Caporaso N. Cigarette smoking. *J Natl Cancer Inst* 1999;**91**:1365–1375. [2]Henningfield JE, Benowitz NL, Slade J, Houston TP, Davis RM, Deitchman SD. Reducing the addictiveness of cigarettes. 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66 THERAPEUTIC IMPLICATIONS OF THE TOXICOKINETICS AND TOXICODYNAMICS IN CYANIDE POISONING

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Background: The proper choice of therapeutic measures in cyanide poisoning requires familiarity with the intricate toxicokinetic behavior of the poison and the pharmacokinetic peculiarities of the antidotes. This overview may help to

optimize the therapeutic strategy in the emergency situation. The onset of symptoms in cyanide poisoning depends on dose, route, and duration of exposure. Inhalation of small amounts of HCN induces hyperventilation, resulting from direct stimulation of chemoreceptors in the carotid and aortic bodies. Cyanide also stimulates the nociceptors, which is characterized by a brief sensation of dryness and burning in the nose and throat, retrosternal pain, and itching of the conjunctivae. These events are short-lived and may rapidly disappear by sequestration or metabolic elimination if small amounts of cyanide have been inhaled. This kind of poisoning does not require antidotal treatment. On exposure to high inhalative doses, the first breath is immediately followed by hyperpnea, sometimes associated with a brief outcry; apnea, a few gasps, collapse, and convulsions occur in less than a minute, often together with cardiovascular failure. This kind of poisoning is usually fatal if antidotal treatment is not instituted immediately. Mechanism of toxicity: Cyanide exerts its acute toxic actions mainly by binding to the cytochrome oxidase complex, thereby inhibiting the final step of oxidative phosphorylation in the respiratory chain. As a result, the most effective ATP regeneration and the removal of catabolically formed hydrogen are impeded. Extensive anaerobic glycolysis cannot compensate for the rapid loss in energy-rich phosphates, particularly in the brain, but leads to massive lactic acidosis. Because oxygen is hardly consumed, the venous blood contains high proportions of oxyhemoglobin and the skin acquires a rose-colored hue. This phenomenon, however, is not consistently found in fatal cases of acute cyanide poisoning due to slow oxygen-consuming processes that are not inhibited by cyanide (cyanide-insensitive autoxidation reactions). After oral ingestion of cyanide salts, rapid intoxication is observed as long as gastric acid is available for protonation of cyanide to form the readily diffusible HCN. There are some cases in which even patients with rapid loss of consciousness, late arrival at the hospital, and ingestion of several lethal doses of KCN survived. Analysis of the gastric juice showed an alkaline reaction with copious unabsorbed cyanide. Hence it appears that the energy-dependent proton pump in the gastric mucosa is also quickly inhibited by cyanide. Mild intoxications are usually survived without any remaining ailment. Recovery from more severe intoxication, however, may not be complete due to hypoxic brain damage similar to that seen after carbon monoxide poisoning. Recent findings indicate that cyanide interacts with the glutamate transmitter system by activating the NMDA receptor with ensuing Ca^{2+} overload, leading to oxidative stress and neuronal cytotoxicity. Chronic exposure to cyanide occurs under conditions of low-temperature combustion of vegetable matter, e.g. tobacco smoke, and low birth weight and sterility have been associated with the cyanide intake of heavy smokers. Other sources are found in the diet upon intake of large amounts of cyanogenic food. The degree of chronic cyanide intoxication largely depends on cyanide detoxication, which may be inadequate due to inborn metabolic errors or to a dietary deficiency. Thus, low protein and vitamin B_{12} intake are important nutritional factors. Typical diseases are tobacco amblyopia, tropical ataxic neuropathy (konzo, mantekassa, West Indian neuropathy, lathyrism), and tropical goiter. Leber's hereditary optic atrophy results from an inborn error of thiocyanate formation. One of the common pathophysiological endpoints of increased cyanide load is a shift of hydroxocobalamin to cyanocobalamin, which is more readily lost via the kidneys than the former. In fact, hydroxocobalamin infusion ameliorates most sequelae due to chronic cyanide intoxication. Therapeutic measures: The therapy of acute cyanide intoxication pursues three strategies: 1. Detoxication of cyanide via the formation of thiocyanate, which is by two orders of magnitude less toxic. 2. Complexation of cyanide outside of cyanide-sensitive cells. 3. Symptomatic measures that should be instituted as early as possible. Detoxication of cyanide: Thiocyanate formation is drastically increased upon the administration of a sulfane sulfur donor, mostly thiosulfate. Thereby, the biotransformation of cyanide into thiocyanate increases markedly. Nonetheless, the plasma-cyanide concentration decreases only slowly because it is distributed into the central compartment from body stores such as erythrocytes. Moreover, thiosulfate and the metabolizing enzyme rhodanase are located in different compartments separated by a virtually impermeable barrier, the mitochondrial double-membrane. Thus, pharmacokinetic obstacles hinder the otherwise highly effective detoxication. Complexation of cyanide: Cobalt(II) salts and dicobalt-EDTA form stable cyanide complexes that are excreted with the urine. Unfortunately, cobalt compounds are quite toxic by themselves. In fact, there is a mutual antagonism in the toxicity of dicobalt-EDTA and cyanide. Hence, dicobalt-EDTA should only be used, if at all, in unequivocally cyanide-poisoned patients with fractional dosing. Hydroxocobalamin is a non-toxic cobalt compound that has been shown to be highly effective in human cyanide poisoning. It is able to penetrate into cyanide-loaded cells and to complex cyanide to the non-toxic cyanocobalamin, which is easily excreted by the kidneys. A certain disadvantage of this elegant therapeutic concept is the high molecular weight of the antidote, which can only bind 1/50 of cyanide on a weight basis. To detoxify one lethal dose of cyanide approx. 5 g of hydroxocobalamin are needed, which have to be dissolved in 200 ml of saline. These features indicate that hydroxocobalamin may be suitable in intoxications from moderate doses of cyanide such as in fires. Another possibly more versatile

method to complex cyanide makes use of limited methemoglobin formation by 20 to 30%. Methemoglobin binds cyanide with an affinity similar to cytochrome oxidase. Because of the much larger pool of methemoglobin, cyanide is rapidly sequestered in the red blood cells. An amount of 30% methemoglobin (about 13 mmol in adults) binds about five lethal doses of cyanide. The particular advantages of 4-dimethylaminophenol over other methemoglobin-forming agents are its fast onset of action (15% methemoglobin within 1 min), the quick termination of methemoglobin formation (30 to 35%, T_{max} 15 min), and the lack of influence on respiration, blood pressure, and heart rate. In contrast, methemoglobin formation by sodium nitrite, which is the standard in the United States, proceeds much more slowly. Thus, 6% methemoglobin is formed within 30 min after 4 mg/kg IV. This dose lowers the blood pressure by 20%, resulting in orthostatic dysregulation. Nevertheless, sodium nitrite in conjunction with sodium thiosulfate is effective in cyanide poisoning. It is unclear whether the vasodilating effects of nitrites are of value during cyanide intoxication. It has been suggested that NO liberated from nitrite or amyl nitrite, another cyanide antidote, which is practically inefficient in producing methemoglobin, may be responsible for the antidotal activity. At present, intravenous injection of 4-dimethylaminophenol and sodium thiosulfate is probably the fastest-acting measure to safely detoxify cyanide. Symptomatic therapeutic measures: The presence and intensity of lactic acidosis indicate the severity of acute cyanide poisoning and can be taken as a prognostic indicator of the ultimate outcome. Infusion of sodium bicarbonate is essential if the blood pH has fallen below 7.2. Concomitantly, oxygen should be administered. At first glance, this recommendation appears strange, because oxygen consumption is reduced and venous blood is oxygenated above normal. Many experiments, however, have shown that the toxicity of cyanide is reduced when the animals are allowed to breathe pure oxygen; moreover, thiosulfate appears to be more effective in the presence of high oxygen partial pressure. Conclusion: Peracute cyanide poisoning, whether by inhalation or oral ingestion, requires rapidly acting antidotes at the scene. Of these, 4-dimethylaminophenol followed by thiosulfate is the most potent one, which can be safely administered. Less florid poisoning with lower doses may be rapidly antagonized by hydroxocobalamin (quite expensive) or thiosulfate infusion (slowly acting). Both antidotes are suitable in mixed carbon monoxide/cyanide poisoning such as in fires. In this case methemoglobin forming agents would reduce the oxygen-carrying capacity of the blood even more. Sodium bicarbonate is a necessary adjunct to cope with the acidosis. Unfortunately, all of these antidotes have to be administered intravenously. Only oxygen can be administered by paramedics.

67 TOXICODYNAMIC AND TOXICOKINETIC ASPECTS OF THE TREATMENT OF ARSENICAL POISONING

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Background: Arsenic, the 50th most abundant element of the earth crust, is an ubiquitously distributed contaminant of the environment including air, water and soil. Some areas in Argentina, Chile, Taiwan, India and Bangladesh are strongly contaminated leading to chronic arsenic poisoning in the population. Medicinal and homicidal use of arsenicals is known since ancient times. Agricultural (herbicides, rodenticides, pesticides) and industrial (smelters, alloys, glass) uses are declining, but are still an important source of poisoning. A newer source is semiconductor production (gallium arsenide). Arsine, a non-irritant gas with a slight garlic odor can be formed in the processing of metals containing arsenic and is used in gallium arsenide production. Four to six hours after exposure it can cause depletion of glutathione stores in erythrocytes, and hemolysis. The mechanism of effect is not understood and no specific therapy is known. Exchange transfusion and hemodialysis may become necessary in the case of hemolysis.[1] Pentavalent organic and inorganic arsenicals exhibit a much lower toxicity compared to the trivalent compounds. It is proposed that the toxicity of pentavalent arsenicals may be attributed at least partly to their trivalent metabolites.[2] Trivalent arsenicals: The highest toxicological relevance is attributed to organic and inorganic compounds containing trivalent arsenic with at least two reactive binding sites, such as sodium arsenite and the chemical warfare agent chlorovinylarsinedichloride (Lewisite). These compounds form stable rings with molecules bearing adjacent SH groups[3]. The author postulated the pronounced cytotoxicity of these compounds to be based on their reaction with the dihydrolipoyl moiety of pyruvate dehydrogenase, leading to inhibition of carbohydrate metabolism in the citric acid cycle, acetyl coenzyme A depletion, and thereby reduced oxygen consumption and ATP formation. An early consequence of citric acid cycle impairment was shown to be gluconeogenesis inhibition in the main gluconeogenic tissues (hepatocytes and kidney tubules) of rats and mice.[4] In agreement, Berry

and Smythe[5] showed complete carbohydrate depletion (glycogen and glucose) in mice dying by arsenite poisoning and Reichl et al.[6] demonstrated improved survival after glucose treatment indicating glucose solutions to be useful in arsenic poisoning. In this context it is interesting to note that sodium arsenite as well as Lewisite only poorly penetrate the blood-brain barrier, the concentration of arsenic in the brain being much lower as compared to the tissues, especially liver and kidney[7]. This is not well in agreement with signs of CNS damage (seizures) caused directly by arsenic, indicating secondary effects are involved i.e. capillary (endothelial) damage or hypoglycemia. Treatment: Peters[3] and Whittaker[8] recognized early that the five-membered ring of dithiols with arsenic is more stable than the six-membered with dihydrolipoic acid and introduced 2,3-dimercapto-1-propanol (dimercaprol; BAL) in the treatment of arsenical poisoning to mobilize the poison from the tissues and increase renal elimination. The relatively high toxicity of BAL with local and systemic side-effects and only the IM route for treatment soon stimulated a search for more adequate compounds. At present the best investigated compounds are 2,3-dimercapto-1-propane sulfonate (DMPS) and 2,3-dimercaptosuccinic acid (DMSA).[9,10] DMSA is an approved drug in the USA (p.o.) and DMPS in Germany (p.o., IM, IV). A serious disadvantage with BAL is the finding of increased arsenic content in the brain of treated animals not observed with DMPS and DMSA.[10,11] The significance of this finding has not yet been elucidated but in patients treated with BAL polyneuropathy is not uncommon and progression of neurological complications during therapy has been reported.[12] In contrast, in severe cases of arsenic poisoning treated with DMPS,[13] polyneuropathy was not found and recovery following IV DMPS treatment was reported in a patient with polyneuropathy requiring ventilatory support.[14] As oral DMSA given before was ineffective, the route of treatment might have been decisive in this patient. In the Toxicology Department of the Technical University in Munich, 6 patients with arsenic poisoning were treated with BAL since 1984, 4 survived, one developed neuropathy. Three patients were treated with DMPS, all survived and none developed neuropathy. Interestingly, the patient with neuropathy (treated with BAL) showed much lower serum arsenic concentrations (0.55 mg/L at admission) than the patient with the highest serum level treated with DMPS (2.24 mg/L at admission). The time of initiating BAL treatment relative to the end of exposure to arsenicals is important for its efficacy.[15] Oral DMSA had no effect on arsenic elimination in subjects terminating the exposure 1 to 5 months before treatment[16] These findings indicate that irreversible tissue changes or mechanisms not primarily based on reactions with adjacent SH groups were involved. Extracorporeal elimination techniques (EET): In two patients with arsenic poisoning (see above), one with BAL the other with DMPS treatment[17] hemodialysis-hemoperfusion or hemodialysis and CAVHDF was assessed. In both patients kidney function was not impaired and the arsenic portion removed by EET was negligible. The results are in agreement with the findings and conclusions of Vaziri et al.[18] Elimination enhancement: Arsenic is mainly eliminated by the kidney, but treatment with DMPS increases biliary excretion. Experimental data in guinea pigs show that by inhibiting enterohepatic circulation, i.e. by i.p. and p.o. treatment with DMPS the latter combined with oral cholestyramine, fecal arsenic excretion could be increased from 6 to 18.5% of the dose administered, the increase in renal excretion by i.p. and p.o. DMPS (14 to 33.4%) remaining unchanged.[19] Hypotension: Vomiting, diarrhea, capillary leak, myocardial dysfunction, and decreased peripheral resistance may lead to severe hypotension and shock needing careful attention to electrolyte and fluid balance. Conclusions: Besides arsine and the organic trivalent irritants, the main risk from arsenicals is due to trivalent compounds with two reactive binding sites. Hypoglycemia by gluconeogenesis inhibition may become a serious problem, masked by stress-induced hyperglycemia. Elimination enhancement by chelating dithiols is the main specific and effective treatment in arsenic poisoning, DMPS and DMSA are similarly effective, both being superior and safer than BAL in arsenic poisoning. DMPS has the advantage of IV injection. Extracorporeal elimination enhancement procedures are useful only in patients with impaired renal function. Experimental data in guinea-pigs indicate that a further increase in elimination is possible by enhancement of faecal excretion using oral DMPS with cholestyramine in combination with parenteral DMPS. References: [1]Hall AH. Arsenic and arsine. In: Clinical Management of Poisoning and Drug Overdose. Haddad LM, Shannon MW, Winchester JF, eds., Philadelphia, Pennsylvania: WB Saunders Co. 1988. [2]Vahter M, Marafante E. 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68 POISONING BY ORAL ANTICOAGULANTS

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Although warfarin was synthesized in 1942, it was considered to be too toxic for human use until taken in overdose (>550 mg) in a rodenticide by an American soldier in 1952. His complete recovery and the subsequent successful treatment of President Eisenhower with the drug in 1955 resulted in the widespread introduction of warfarin for treating and preventing thromboembolism. Other oral anticoagulants (e.g. dicoumarol, phenindione, nicoumalone and phenprocoumon) are now much less widely used in man. Some (particularly those with long duration of action such as the 'superwarfarins', bromadiolone, difenacoum or brodifacoum) are used only as rodenticides. All oral anticoagulants produce their pharmacological and principal toxicological effects by inhibiting the vitamin K-dependent carboxylation of the terminal glutamic acid residues of the clotting factor precursors of factors II, VII, IX and X. This prevents their cross-linkage with calcium, and thus coagulation time, (particularly the one-stage prothrombin time) is prolonged. Since oral anticoagulants have no effect on already synthesized vitamin K-dependent clotting factors, the effect of an initial dose is not seen until 12 hours or more when the latter decline in concentration. The one-stage prothrombin time (international normalized ratio or INR) prolongation correlates most closely with the decline in concentration of factor VII, which has a half-life of elimination of 4–8 hours. The risk of bleeding is related to the increase in INR but bleeding is not invariable, even with markedly increased INR values. Bleeding may occur at any site, but carries the worst prognosis when it occurs intracranially. Oral anticoagulants are generally rapidly and completely absorbed after oral administration and gastric emptying is unlikely to be of benefit unless performed within an hour of ingestion. Charcoal and cholestyramine effectively bind several oral anticoagulants. They may also enhance their elimination by interfering with enterohepatic recirculation of the parent compound and/or metabolites.[1] Vitamin K_1 (phytomenadione) antagonizes the effects of oral anticoagulants and should be administered if a large dose of oral anticoagulant has been taken and the INR is rising. Oral vitamin K_1 has variable bioavailability and may also be adsorbed by charcoal or cholestyramine. It should not be given intramuscularly if the INR is greater than 2. Intravenous vitamin K_1 is reliably effective when given intravenously but should be administered slowly. A newer mixed micellar preparation of vitamin K_1 may be safer than previous preparations solubilized in Cremophor EL.[2] Prothrombin complex concentrates (PCC) or fresh frozen plasma (as well as blood replacement) may be necessary in those who are actively bleeding.[3]The half-life of vitamin K_1 in plasma is short (around 2.2 h.) and the body pool of the vitamin is small. It may therefore be necessary to give vitamin K at high dose for considerable periods (sometimes up to a year) after overdose with some of the coumarin rodenticides. References: [1]Shetty HGM, Buss DC, Harry F, Hutchings AD, Routledge PA. The effect of oral cholestyramine on the pharmacokinetics of warfarin enantiomers. *Br J Clin Pharmacol* 1998;**46**:280P. [2]Pereira S, Williams R. Adverse events associated with vitamin K1: Results of a world-wide postmarketing surveillance programme. *Pharmacoepidemiol Drug Saf* 1998;**7**:173–182. [3]Guidelines on oral anticoagulation: third edition. *Br J Haematol* 1998;**101**:374–387.

69 4-DMAP AS CYANIDE ANTIDOTE: ITS EFFICACY AND SIDE EFFECTS IN HUMAN POISONING

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Objective: Suicidal cyanide poisonings are usually fatal. It was shown in animal studies that 4-DMAP forms methemoglobin and can reverse cyanide poisoning which would otherwise be fatal. Little is known about its use in human poisoning. Methods: 4-DMAP was used in 10 patients treated in our unit. In 9 patients it was used for cyanide intoxications; in one case it was used wrongly. Eight patients were given a dose between 250–500 mg, two patients got an overdose of 1250 mg. In all cases cyanide levels (normal—0.15 mg/L), and methemoglobin levels (N: 0–2%) were measured in blood. Thiocyanate was measured in urine (N: 6 mg/L). All patients were in coma when they were found and received immediate life support. Results: 5 patients survived, 4 patients died. The cyanide dose in the survivors ranged from 250–5000 mg. The dose in the non-surviving patients stayed unknown. All the non-survivors showed cardiac arrest before 4-DMAP was administered. In all but one of the non-survivors circulation could be restored. The survivors had cyanide levels in blood between 1.4 and 31 mg/L, those who died between 11 and 34 mg/L. In the survivors thiocyanate levels ranged from 30–60 mg/L, in the fatal cases from 10–54 mg/L. Methemoglobin was formed according to the 4-DMAP dosage: 250 mg up to 19%, 500 mg up to 33.4%, 1250 up to 73%. Signs of hemolysis were found in all patients who had more than 250 mg 4-DMAP. Severe hemolysis with kidney failure was found in one patient after 1250 mg 4-DMAP. In the survivors 4-DMAP was given between 15-60 min after ingestion, and in the fatal cases after 20, 90, 120 and 150 min. Conclusion: 4-DMAP is a very efficient cyanide antidote. If it was administered within one hour after cyanide exposure 80% of the patients could be saved. If the patient was found in cardiac arrest circulation was restored in 75% but brain damage was irreversible and fatal. More than 250 mg of 4-DMAP produces signs of hemolysis. 250 mg 4-DMAP seems to be sufficient for most cases of cyanide poisoning.

70 A ONE-YEAR LONGITUDINAL STUDY OF 563 CARBON MONOXIDE POISONINGS IN NORTH OF FRANCE

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Carbon monoxide (CO) poisoning is known to induce long term manifestations with severe consequences for patients and high socioeconomic cost. However, few studies are available on the incidence of long term effects after acute CO poisoning. Objective: To describe the long term clinical features after CO poisoning and evaluate their incidence. Methods: One year longitudinal prospective follow-up study of all patients hospitalized in the different hospitals of the Nord Pas de Calais region for acute CO poisoning from January 1st through December 31st 1997 who were alive at the time of hospital discharge. All patients were treated by normobaric or hyperbaric oxygen therapy following the recommendations of Mathieu *et al*. [1]Follow-up was done 1, 3, 6 and 12 months after discharge by the Lille Poison Centre Toxicovigilance Unit (LPTV). Information on patient's clinical status was obtained by the LPTV physicians by phone or by questionnaire from the patient himself, his first degree relative or his family physician when the patient was at home or from a hospital physician if the patient was hospitalized. A patient was considered to be symptomatic if any behavioral, neurological or other clinical effects had been observed by his physician or family or if he had any complaints. Results: 563 CO poisoned patients met the above criteria for follow-up. At one month, 56 patients of whom 2 were symptomatic and 54 asymptomatic when discharged from hospital, were lost to follow-up. A complete follow-up over one year was obtained for 507 patients (90%) of whom 27 were symptomatic and 480 were asymptomatic when discharged. Follow-up at 1, 3, 6 and 12 months showed persistent symptoms in 7.8% (41/507), 6.6% (34/507), 4.5% (23/507) and 4.3% (22/507) of patients respectively. Two patients died: an 84-year-old diabetic man, asymptomatic when discharged died 6 weeks later from diabetic decompensation; and an 88-year-old female who suffered from major disability, and whose CT scan showed diffuse leucoencephalopathy. After 8 weeks, she remained disoriented and died 3 months later. The other patients complained of mild subjective symptoms at home: headache, asthenia, mild memory impairment, vertigo. All had returned to their previous occupation at least by 12 months. Conclusion: Following our proposed oxygen therapy, long term manifestations of CO poisoning are of low frequency and induce only mild degree of disability. References: [1]Mathieu D, Nolf M, Durocher A, *et al*. Acute carbon monoxide poisoning. Risk of late sequelae and treatment by hyperbaric oxygen. *J Toxicol Clin Toxicol* 1985;**3**:315–325.

71 COMBUSTION TOXICOLOGY IN A DISASTROUS DISCOTHEQUE FIRE

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Objective: To study the incidence of cyanide poisoning among the dead and the survivors after a disastrous discotheque fire. Sixty-one patients died on the scene and 190 patients were brought to hospital. Two patients died after arrival at hospital. Methods: Patient data in the ICU and post-mortem examinations were evaluated to determine if cyanide poisoning contributed to morbidity and mortality. Cyanide concentrations were only measured among the dead (n = 61). Blood gases and clinical parameters were evaluated among the ICU patients. Results: Smoke inhalation injury, burn injuries and mental trauma were the main injuries. Two patients received treatment with hyperbaric oxygen (HBO) and two received treatment with hydroxocobalamin to prevent eventual cyanide poisoning. Post-mortem analysis determined carbon monoxide poisoning to be the cause of death in almost all victims. Mean COHb levels among the dead were 57% (17–80%). Mean cyanide levels were 0.76 μg/g (0–2.10 μg/g). Laboratory analysis including blood gases and clinical data in the patients treated at the intensive care unit did not indicate cyanide poisoning among the survivors. Conclusions: Carbon monoxide poisoning and smoke inhalation were the major toxicological threats in this indoor discotheque fire. Acute hypoxemia and hypercapnia contributed to deaths. Preventive treatment with hydroxocobalamin to avoid cyanide poisoning did not seem justified in this scenario.

72 4-METHYLPYRAZOLE TREATMENT IN ACUTE METHANOL INTOXICATION

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Objective: Acute methanol poisoning may produce serious clinical events or even be lethal in cases of non-treatment or delayed treatment. Toxicity is due to the enzymatic metabolism of methanol by alcohol dehydrogenase that yields two toxic metabolites, formaldehyde and formic acid. Recognized treatment includes sodium bicarbonate, hemodialysis and ethanol therapy as a competitive inhibitor of methanol metabolism. 4-Methylpyrazole (4-MP) is now an established treatment for ethylene glycol poisoning. The aim of this study was to determine the efficacy and safety of 4-MP in methanol intoxication. Methods: Retrospective data collection from patients (pts) hospitalized in ICU during 1992–1998 for methanol intoxication, confirmed by laboratory assessments and treated with 4-MP; descriptive analysis (median [range]) and report of 4-MP side effects. Results: 11 pts were treated for documented methanol intoxication [cooking alcohol (7 pts), windshield washing fluid (1 pt), antifreeze (1 pt) and undetermined (2 pts)]: 7M/4F; 46 years [18–58]; 5 pts with a past history of chronic alcoholism; 8 suicide attempts and 3 misuses. Six pts were severely and 5 mildly intoxicated. On admission, 6 pts were awake, 1 pt inebriated, 2 pts lethargic and 1 pt comatose requiring mechanical ventilation. Two pts presented bilateral blindness, 2 pts color vision disorder, 2 pts vomiting, 1 pt hypotension and 3 pts tachypnea. Serum methanol level on admission was 51 mg/dL [6–518]. Six pts had co-ingested ethanol with blood concentrations of 14.5 mg/dL [0–35]. Arterial pH was 7.32 [7.10–7.51], serum bicarbonate 17.0 mmol/L [2.5–25.0], $PaCO_2$ 3.6 kPa [1.1–7.2], lactates 2.2 mmol/L [1.1–6.9] and creatinine 83 μmol/L [53–128]. All pts were treated with 4-MP, 9 intravenously and 2 orally, with a loading dose of 700 mg [500–1200], 2 [1–7] multiple doses and a cumulative dose of 1300 mg [500–6000]. Hemodialysis was performed in the 2 pts who presented bilateral blindness. No patient died and all were alive without sequelae, except the 2 blind pts. Three patients received 5, 6 and 7 doses of 4-MP with respectively a total dose of 4000, 6000 and 3100 mg. The main adverse experiences with 4-MP were: nausea and headache in 1 pt, elevation of eosinophil cells, lymphangitis and burning sensation in 1 pt (the one who received 7 doses) and fever in 2 pts (of whom one received 5 doses). Conclusion: 4-MP treatment was an effective and safe therapeutic antidote in preventing or diminishing methanol toxicity in 7 poisoned pts. Hemodialysis was only performed in case of ocular impairment on admission.

73 INGESTION OF OVER-THE-COUNTER WART REMOVER—ESOPHAGEAL BURNS NOT AS BAD AS THEY LOOK?

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Objective: Wart removers are commonly available, especially in families with small children. Usually the active ingredients in these preparations are salicylic acid and lactic acid in a collodion vehicle. Both salicylic acid and lactic acid are weak acids which act as keratolytics. In order to produce their effect they need a prolonged surface contact which

is facilitated by the collodion. Normally, endoscopy is recommended after ingestion of corrosive agents to diagnose any deeper lesions or burns. The aim of this study was to evaluate the diagnostic value of endoscopy after ingestion of collodion wart remover products. Methods: We studied retrospectively all case reports of accidental or suicidal ingestions received by the Poison Centers in Sweden and Finland concerning ingestions of over-the-counter wart remover products in 1982–97. Case reports with ingestion of collodion wart remover products together with a diagnostic endoscopy were included in the study. The case reports were graded using the Poisoning Severity Score scale. Results: The Poison Centers received 16 case reports (12 children) during the study period. An endoscopy was performed in 11 cases (9 children). Out of these 11 cases, 6 (55%) had mild symptoms e.g. irritation, erythema and first degree burns. Four (36%) patients had moderate symptoms e.g. prolonged pain and second degree burns in a restricted area. One patient had severe symptoms e.g. severe dysphagia and widespread second and third degree burns. None of the cases were fatal. Treatment was symptomatic and all patients recovered rapidly without sequelae. White corrosion-like areas in the esophagus were noted in 7 patients. However, the gray or white mucous lesions were not very deep and consisted of the water-resistant film from collodion. As seen in one case this surface layer could easily be removed by suction, showing a red, hemorrhagic area beneath. The wart remover does not seem to penetrate very deep and usually only causes superficial injury. Furthermore, there have been no reports to the Poison Centers or in the literature of perforations or remaining sequelae such as strictures. Conclusion: Although the initial lesions seem to be alarming, these special corrosive ingestions are normally uncomplicated. Based on this study we do not find it necessary to routinely recommend endoscopy in the acute stage to diagnose the injuries.

74 TREATMENT OF VALPROIC ACID OVERDOSE WITH CONTINUOUS ARTERIOVENOUS HEMOFILTRATION

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Objectives: Valproic acid (VPA) is an important anticonvulsant that is rarely associated with fatal overdoses. Matsumoto *et al*.[1] have reported on the efficacy of direct hemoperfusion in case of a massive VPA intoxication. At high blood levels, protein binding of VPA is saturated and free concentrations of >50% may be achieved. We evaluated the efficacy of continuous arteriovenous hemofiltration (CAVH) for treatment of an acute VPA intoxication. Case report: A comatose 15-year-old male was hospitalized 6 hours after intentional ingestion of 30 g of slow release VPA. Glasgow coma score on admission was E4M4V1; the neurological condition of the patient gradually deteriorated. Initial serum VPA level was 711 mg/L with 58% free VPA. Following gastric lavage, repeated charcoal administration and adequate diuresis, serum VPA decreased to 350 mg/L. At that moment, 13 hours after ingestion, CAVH was started and effectively continued for 10 hours over a period of 17 hours. During and after CAVH treatment serial blood, urine and ultrafiltrate samples were taken. Total and free VPA were determined. Plasma VPA was effectively removed by CAVH: the patient's plasma concentration decreased from 350 mg/L to 68 mg/L in 17 hours and the half-life of VPA was calculated as 7.3 hours during CAVH and >300 hours after CAVH. Free VPA decreased from 44% at 350 mg/L to 20% at 68 mg/L. In the collected fractions of urine a total of 145 mg of VPA was recovered. Conclusion: CAVH contributes to an effective clearance of VPA after massive intoxication. CAVH is better than endogenous clearance but less effective than the clearance of hemoperfusion, reported in the literature. Despite a high free drug concentration, only 0.5% of the drug is removed by diuresis. References: [1]Matsumoto J, Ogawa H, Maeyama R *et al*. Successful treatment by direct hemoperfusion of coma possibly resulting from mitochondrial dysfunction in acute valproate intoxication. *Epilepsia* 1997;**38**:950–953.

75 SEVERE HYPERAMMONEMIC ENCEPHALOPATHY SHORTLY AFTER VALPROIC ACID PRESCRIPTION AND RAPID AWAKENING FOLLOWING LEVOCARNITINE ADMINISTRATION

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Objective: To present a case of valproic acid (VPA)-related encephalopathy in the early phase of therapy in an adult and to discuss the benefit of levocarnitine administration. Case report: VPA (10 mg/kg/day) was prescribed for seizure prophylaxis after a neurosurgical procedure in a 51-year-old woman. Ten days later, while the serum VPA concentration

was within the therapeutic range, she presented a rapidly progressive alteration of consciousness (Glasgow coma scale (GCS) 5/15) with bilateral non-reactive dilated pupils. Lumbar puncture and brain CT scan ruled out infectious or hemorrhagic disorders. Aspecific slowing was noted on the first electroencephalogram. The patient was admitted to the ICU. A second electroencephalogram showed triphasic waves consistent with hepatic encephalopathy. There was no evidence of hepatic dysfunction (normal serum transaminase and prothrombin time). We hypothesized the role of VPA-related hyperammonemic encephalopathy. Indeed, blood arterial ammonia concentration was very high (234 μmol/L). Arterial lactate and bicarbonate concentration was within normal range; blood VPA level was 86.2 μg/mL. Blood and urine were sampled for the determination of amino acids and carnitine concentrations. VPA was discontinued and levocarnitine supplement (100 mg/kg) was given intravenously before obtaining the results of serum carnitine concentration. Ammonia concentration decreased extremely rapidly (35 μmol/L 10 hours later). The neurological condition improved within 18 h (GCS 13/15). The electroencephalogram normalized after 24 h, with a complete disappearance of the triphasic waves. VPA concentration was still within the therapeutic range (52.4 μg/mL). The patient was discharged from the ICU the next day. VPA was not re-introduced. The initial serum carnitine concentration was normal (33 nmol/mL; reference value: 32 ± 2). There was no change in the amino acid profile. Conclusion: Hyperammonia is a common side effect in children receiving VPA and is generally not clinically significant. In contrast, hyperammonemic encephalopathy is infrequent in adults receiving therapeutic doses. Serum carnitine concentration may decrease during VPA administration and carnitine deficiency may indirectly cause hyperammonemia, the exact mechanisms of hyperammonemia and hypocarnitinemia remaining speculative. The patients usually do not develop any symptoms of carnitine deficiency. As serum carnitine concentration is not available on a routine basis, the empirical administration of levocarnitine is questionable in patients with serious neurological manifestations. While VPA discontinuation is the first measure, isolated observations in acute VPA intoxication suggest that the neurological condition may rapidly improve with a dramatic resolution of hyperammonemia only a few hours after levocarnitine administration. This was also the case in our patient who had a normal serum carnitine concentration.

76 THE EFFECT OF NITRATE ON THE THYROID GLAND

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Objective: Increased nitrate intake might affect the thyroid gland function in humans, as has been observed in animals. The reason is that the nitrate ion (NO_3^-) inhibits iodide (I^-) transport into the thyroid gland by sharing the same transport mechanism. This may lead to a decrease in thyroid hormone (T_4, T_3) secretion, followed by an increase in thyroid stimulating hormone (TSH). In the end thyroid gland enlargement (goiter) may occur. Our aim was to investigate the effect of nitrate on the thyroid gland function in humans in a four week nitrate exposure study. Methods: Ten volunteers received once daily an oral solution of 15 mg sodium nitrate per kg body weight (three times the allowed daily intake, ADI) in 200 mL distilled water (nitrate group) and ten volunteers received 200 mL distilled water (control group) for 28 days. Both groups followed an iodine restricted and low nitrate diet and this was checked by urinary iodide and plasma nitrate concentration measurement. Before and after the 28 days exposure period the percentage (%) radioiodine (^{131}I) uptake (RAIU) was measured 5 hours and 24 hours after ^{131}I-capsule intake, to investigate the competition of nitrate on iodide transport. Before (nitrate) exposure and two, three and four weeks after the start of the exposure period blood samples were taken to measure the hormones: T_4, T_3, rT_3, TSH to investigate the thyroid gland function. Paired (within groups) t-tests were performed to analyze the data (mean ± SD). Results: Within the nitrate group the 24 hrs RAIU after 28 days of nitrate exposure (30 ± 8%) was significantly higher than the 24 hrs RAIU before exposure (22 ± 9%), $t = -2.39$, $p = 0.041$. Within the control group there was no significant difference in the 24 hrs RAIU before and after the 28 days exposure period, 25 ± 10% and 26 ± 6% respectively. In both the nitrate group and the control group no significant differences were found in the RAIU five hours after ^{131}I capsule intake before and after the 28 days exposure period. Furthermore no significant hormonal changes were seen during nitrate exposure. Conclusions: Since no hormonal changes were found, it seems that the thyroid function is not impaired after four weeks exposure to three times the ADI of nitrate. However the ^{131}I uptake was increased in the nitrate group, so further research is necessary to study the consequences of long-term high nitrate exposure.

77 EVALUATION OF EXPOSURE FROM CONSUMER PRODUCTS USING DICHLOROMETHANE

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Objectives: There is potential health risk from exposure to organic solvents, in the occupational setting as well as for consumers. Risks of consumer exposure are under-investigated. A mathematical model was developed for predicting residential exposure to solvents processed in consumer products. Exposure to and uptake after exposure to DCM (dichloromethane, a paint stripper) were studied, in order to validate and to complete the mathematical model with bioavailability data. Secondly, since CO is a major metabolite of DCM, the HbCO percentages were monitored for 12 hours as an effect parameter. Methods: 9 healthy (non-smoking) volunteers were asked to apply the paint stripper (containing 80% DCM) to a defined surface in an environmentally defined room. Three of them were wearing gas masks and protective clothing to prevent dermal and inhalational exposure, the other 6 wore only protective clothing. Air concentration of DCM inside the test room together with blood DCM concentrations and HbCO percentage were measured. The predicted exposure by the mathematical model is compared to actually measured air DCM concentrations in the room. Results: Maximum air DCM concentrations inside the test room ranged from 550 to 1900 mg/m^3. The mathematical model prediction, assuming readily available DCM, overpredicted air concentrations more than tenfold. Sensitivity analysis of the model parameters for the paint stripper matrix showed that the amount of DCM that is immediately available for evaporation sets the peak air concentration, while the migration rate in the matrix determines whether DCM concentration increases, remains at steady state or decreases after reaching a peak level. The maximum DCM blood concentrations ranged from 0.25 up to 5.13 mg/L and the HbCO percentages from 0.4% up to 2.3% in the 'no mask' group. In the 'mask' group maximum DCM blood concentrations were 0.07, 0.58 and 0.64 mg/L with HbCO percentages of 0–0.2%. No complaints and no clinical effects were observed. Conclusion: The studied situation reflects exposure to DCM after use of the paint stripper and the variability among users. Using sensitivity analysis, this model and the results of the experiment show that the matrix contains little directly available DCM. Further, the migration rate in the matrix only caused slow release of DCM into the air. Restricting the amount DCM available in the mathematical model for direct evaporation fits the model to the data. Other parameters like room size and ventilation can stay at their measured value. In this situation no clinical effects occurred. It is however possible that consumers will expose themselves to even higher air DCM concentrations because of the use of DCM inside smaller rooms, at higher temperatures etc. Furthermore, repeated exposure may lead to HbCO accumulation which may lead to clinical effects. A validation in other exposure circumstances will further optimize the model. The implementation of the bioavailability data derived in this study will complete the model.

78 FOLLOW-UP STUDY OF MCS PATIENTS

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Objective: Multichemical sensitivity is a new disease not well defined. Though the patients believe they are poisoned by chemicals from the environment, biomonitoring rarely ever shows an unusual burden of the accused chemical. Thus it is likely that the disease is more or less psychogenic. Little is known about the long-term course of this disorder. This was the stimulation for us to investigate what had happened to those patients who had been seen in our out-patient department years ago. Methods: In 1997/98 we wrote a letter to all patients (120) who had been seen in our out-patients department between 1987–1996, asking them to come in for another clinical check-up and an interview. They were asked questions about their professional life, about life events, about their activity concerning to improve the environment, about their medical treatment and about the improvement of their complaints. Results: 44% of the patients were male, 56% were female. 29% had given up their professional life in the meantime. 28% had changed their place of work. 12% got a divorce or lived separated from their former partner. 24% of the female patients had their uterus removed. 10% had become members of a self-help group. 26% had thought about suicide. 44% had seen a psychiatrist or psychologist since. 4% had undergone psychopharmacological treatment. 58% of those who had received psychotherapy felt an improvement. 75% had blamed formaldehyde, pentachlorphenol, lindane or amalgam alone or in combination to be responsible for their complaints. 25% had blamed multiple other poisons. Only 39% of the patients were still convinced that the environmental poisons had been responsible for their complaints. 44% had accepted other reasons,

17% had even accepted a psychological origin. 47% felt an improvement, 16% felt completely healthy, 16% felt a deterioration. 70% had their amalgam fillings removed, 82% of these patients did not feel an improvement due to the amalgam removal. 26% had had an ambient biomonitoring. 26% had their homes refurbished. 14% had moved house. 23% felt better after moving or refurbishing. 39% had received 'detoxification' treatment, 32% of these patients felt an improvement in their complaints. Conclusion: About half of the patients with MCS accept some sort of psychotherapy. Improvement does not depend on 'detoxification' or changing their lifestyle. In most patients the belief that they are poisoned disappears with time.

79 IS CHILDHOOD LEAD SCREENING IN THE US COST EFFECTIVE?

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Objective: The past century has seen the initial recognition of clinical lead poisoning in childhood, the initiation of treatment efforts via chelation, the subsequent popularization of 'sub-clinical lead poisoning' in toddlers as a significant cause of mental retardation, attempts to reduce or eliminate exposures to environmental lead by a variety of efforts, and call for 'universal screening' of toddlers throughout the United States in 1991. As the century closes in the U.S., does the yield from current epidemiologic data support continued pursuit of universal screening—or has the purported epidemic of lead poisoning actually disappeared? Methods: Blood lead levels and environmental data have been gathered from the scientific literature and additional data have been developed within the state of Washington to attempt to answer the question posed. Results: In 1976–80, U.S. NHANES data revealed almost 90% of children age 5 years or less had blood lead levels greater than 10 μg/dL. By 1990, however, with the elimination of leaded gasoline, atmospheric lead concentration had fallen to less than 7% of prior levels and only some 9% of comparable children's blood levels exceeded 10 μg/dL. Moreover, recent randomized studies conducted in Washington and in Colorado in 1999 have shown the percentage of elevations of blood lead levels greater than 10 μg/dL to have further declined to less than 0.9%—i.e. a 25-year reduction from 90% to less than 1% elevations. Conclusion: Accepting the cost-benefit modeling strategy as published by Berwick and Komeroff[1] for screening to prove effective, the target population has to have more than 6.7% of its members with elevated blood leads. Clearly, with current blood lead level data almost 10 times below such a frequency, it is clearly no longer justified to continue universal testing of toddlers for sub-clinical lead poisoning. One might even go so far as to accuse proponents of universal screening of championing child abuse for their own gratification—much as has been done in dealing with proponents of routine circumcision by critics of that barbaric procedure. References: [1]Berwick DM, Komaroff AL. Cost effectiveness of lead screening. *N Engl J Med* 1982; **306**:1392–1398.

80 EFFECTS OF DMPS ON KINETICS OF LEAD IN RABBITS

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Introduction: Lead intoxications are normally treated by administration of chelators, e.g. dimercapto-propane-sulfonate (DMPS). In clinical observation reports, the effects of lead can hardly be quantified because of lack of control measurements. After absorption the major part of lead is distributed into deep compartments, in particular the bones and the brain. This may lead to different effects of DMPS in acute or chronic poisoning. Unless its administration leads to an improvement of clinical signs and symptoms of intoxication, there is only limited knowledge on the effects of chelators on the clearance of lead. This study was performed to balance the amounts of lead under the administration of DMPS in rabbits. The study was approved by the animal ethics committee of the Senate of Berlin. Methods: 15 male New Zealand rabbits were treated with an oral daily dose of 15 mg/kg of lead in drinking water over a period of 3 months, 8 of them were treated with a daily IV bolus of DMPS for 5 days: the first time after an initial period of 8 days and a second time after 3 months of giving lead chronically. Lead concentrations were followed according to a fixed schedule in whole blood, urine and feces. Results: Basic lead concentrations were in a range of 20–40 ng/mL, after initiation of lead treatment blood levels attained steady state concentrations after a few days of about 400 ng/mL (medians), with a range between 200 and 1000 ng/mL. There was no difference between control animals and DMPS-treated ones. Half-lives of lead were estimated for the two periods of DMPS treatment. For the acute phase, they were in a range of 140–380 h in controls and 78–200 h in DMPS treated animals. The difference between the two groups was not significant.

After chronic lead administration, a generally prolonged lead half-life was found ranging between 240 and 280 h in controls, and between 140 and 200 h in the DMPS-group. In some animals of the DMPS group, the concentration time curve was biphasic. This can be explained by rebound phenomena, possibly together with a loss of the chelating effect over the time of administration. The amount of lead found in the feces ranged between 50 and >90% of the dose. From these data a volume of distribution of ~25–100 L/kg was estimated. Only microgram amounts of lead (with wide range) were excreted in the urine, with a temporary threefold increase at the first day of initiating DMPS treatment. According to the large variability, this increase was not significant. Conclusions: This study shows that DMPS has only little influence on lead kinetics under the conditions described. Because it is not possible to give a long infusion to rabbits, the efficacy of DMPS could have been reduced due to the short duration of action (IV bolus). Nevertheless, the relative small amount of lead detected in the urine with or without administration of DMPS shows that renal excretion does not contribute extensively to lead clearance rather than distribution, as shown by the large volume of distribution. The therapeutic efficacy should therefore be reconsidered in the light of these findings.

81 ENHANCED IRON EXCRETION DURING SYSTEMIC PHOSPHOROTHIOATE OLIGODEOXYNUCLEOTIDE TREATMENT

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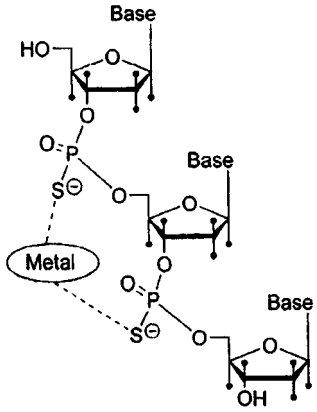
Background: Phosphorothioate oligodeoxynucleotides (PS-ODNs), experimentally synthesized as antisense nucleotides for the possible treatment of malignancies, possess properties that could be utilized in the development of therapeutic heavy metal chelators. As illustrated below, PS-ODNs are modified DNA molecules which have incorporated into the deoxyribose backbone a sulfur replacing one of the non-binding oxygen atoms on the phosphate. This array of sulfur atoms in a DNA backbone creates a poly-anionic molecule that interacts with drugs as well as with other cellular components. *In vitro* analysis reveals that PS-ODNs bind iron as a function of the number of sulfurs present in the backbone with longer molecules capable of chelating more iron than shorter molecules. We estimate that the log of the stability constant of an unsaturated iron-PS-ODN complex is greater than the 14.4 for iron with EDTA. Methods: Iron excretion was measured in 16 patients with relapsed or refractory acute myelogenous leukemia or myelodysplastic syndrome (MDS) participating in studies to test the safety of OL(1)p53, a 20-mer PS-ODN complementary to p53 mRNA. Patients were given OL(1)p53 at doses of 0.05 to 0.25 mg/kg/h for 10 days by continuous intravenous infusion. 24 hour urines were collected prior to and daily during the study and analyzed for Fe, Cu, Zn, and Cd. Results: We found that PS-ODNs have a high affinity for iron as well as several other clinically relevant toxic metals. Analysis of patient urine following administration of OL(1)p53 reveals a 7.5 fold increase in iron excretion at low doses (0.05 mg/kg/h). In a patient with MDS who was regularly transfused with packed red blood cells during the study, urine iron increased 3.7-fold, averaging 1387 ± 177 μg/d following administration of the drug. Conclusions: PS-ODNs, which can be administered safely by slow IV and have a half-life of about 24 h, may have therapeutic potential as heavy metal chelators. Low doses of PS-ODN facilitated the excretion of iron. Renal clearance of iron-PS-ODN complexes most likely involves secretion into proximal tubules.



82 MONITORING OF NEUROMUSCULAR TRANSMISSION DURING ORGANOPHOSPHATE INTOXICATION AND THE INFLUENCE OF OXIME THERAPY

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Objectives: The lethality of acute intoxications with organophosphorus compounds (OP) is still high (approx. 40%). The inactivation of acetylcholinesterase (AChE) during OP poisoning results from phosphorylation of the enzyme, which can be reversed by oximes. For monitoring the oxime effects we determined the erythrocyte AChE (Ery-AChE) status and applied electrophysiologic methods to control the neuromuscular transmission (NT) in order to reveal reactivation of the endplate AChE. Methods: In 9 cases of severe OP pesticide poisoning following suicide attempts, obidoxime was given as an IV bolus (250 mg) followed by continuous infusion of 750 mg/d. In all patients the NT studies were performed before and during oxime therapy. Supramaximal single and repetitive nerve stimulation (RNS; 3–50 Hz) were applied to the ulnaris nerve at the wrist using surface electrodes. The compound muscle action potential (CMAP) was recorded from the M. abductor digiti minimi. Results: In OP poisoning the RNS revealed a decrement or decrement-increment phenomenon, indicating neuromuscular dysfunction due to inactivation of AChE at the motor endplate. The single CMAP showed repetitive discharges. A dramatic electrophysiologic improvement was seen in 4 cases of parathion intoxication after obidoxime. One patient received 250 mg obidoxime initially upon primary care whereas the continuous infusion was started after 85 h; a reactivation was still possible. In 3 cases of intoxication with oxydemeton-methyl an improvement of the neuromuscular block after obidoxime was weak or absent, and reactivation of Ery-AChE was not observed. Conclusions: The efficacy of oximes in AChE reactivation can be determined using electrophysiologic methods. Because of rapid aging of the AChE-OP complex oxime therapy appears inappropriate in oxydemeton-methyl intoxications when given too late. In parathion poisoning even delayed continuous obidoxime infusion (up to 85 h) allowed reactivation up to 40% of normal. A correlation of Ery-AChE activity and NT seems to exist. Ery-AChE levels between 20 and 30% appear predictive for normal NT.

83 TOXICOKINETICS OF GLUFOSINATE—ANALYSES IN 2 PATIENTS WITH ACUTE ORAL BASTA® POISONING

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Objectives: Acute poisoning caused by the suicidal ingestion of the herbicide BASTA®, containing glufosinate ammonium 20%, is increasing in Japan. Symptoms of this poisoning include coma, apnea, and generalized convulsions etc.[1] These signs are considered to be due to the effects of glufosinate on the central nervous system.[2] At present, human toxicokinetics of glufosinate, essential for evaluating the indication for treatments such as forced diuresis and extracorporeal hemopurification, have not been studied except one case report we previously published.[3] Adding a case we experienced recently, we report here 2 cases of acute oral BASTA® poisoning where toxicokinetics of glufosinate were studied. Methods: A 65-year-old male who had ingested about 300 mL of BASTA® (case 1),[3] and a 46-year-old female who had ingested about 200 mL of BASTA® (case 2) were studied. Treatments consisted of gastric lavage, activated charcoal and cathartics, and fluid infusion without diuretics. Extracorporeal hemopurifications were not conducted. Artificial ventilation was necessary for 5 days and 10 days in case 1 and case 2, respectively. Both patients were discharged without any sequelae. Serum obtained from 2 mL blood, drawn every 3-6 hours during the first 2 days, and daily urine collection sampled for 8 days, were used for measurement of glufosinate concentration by HPLC[4]. The toxicokinetics of glufosinate were analyzed by a 2-compartment model. Based on the previous report[3], the absorbed amount of glufosinate was estimated to be the total amount of glufosinate excreted in urine divided by 0.9, the urinary excretion ratio obtained experimentally. Results: The toxicokinetic parameters calculated were as follows in case 1 and case 2, respectively: AUC = 657.6, 1389.7 (h μg/mL), Vd β = 1.44, 1.92 (L/kg), CL_{total} = 0.103, 0.144 (L/kg/hr), $t_{1/2}\alpha$ = 1.84, 1.23 (hr), $t_{1/2}\beta$ = 9.59, 9.22 (hr). In the initial 24 hours, 97% and 98% of total urinary glufosinate was excreted in urine in case 1 and case 2, respectively. Conclusion: The obtained value of Vd of greater than 1 L/kg indicates that glufosinate distributes in tissues more than in the blood. On the other hand, CL_{total} values were at a similar level to creatinine clearance, and over 95% of total urinary glufosinate was excreted in urine within 24 hours after ingestion.

From these characteristics in toxicokinetics of glufosinate, we consider that extracorporeal hemopurification might not be indispensable in the treatment of acute BASTA® poisoning. References: [1]*Oxford Textbook of Critical Care*. Oxford University Press 1999:657–659. [2]Koyami K. Glufosinate and a surfactant: which component produces effects on the central nervous system in acute oral BASTA poisoning? *Vet Hum Toxicol* 1999;**41**:341. [3]Hirose Y, Kobayashi M, Koyama K *et al*. A toxicokinetic analysis in a patient with acute glufosinate poisoning. *Hum Exp Toxicol* 1999;**18**: 305–308. [4]*Bunseki Kagaku* 1997;**46**:66–74.

84 EFFICACY OF LOCAL TEMPERATURE VARIATION IN THE TREATMENT OF MEDITERRANEAN FISH ENVENOMATIONS: EXPERIENCE OF THE MARSEILLES POISON CENTRE DURING SUMMER 1999

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Objectives: Weeverfish (genus *Trachinus*) and scorpionfish (genus *Scorpaena*) are responsible for numerous envenomations on the French Mediterranean coast. Traditional treatment by the Provence fishermen includes local temperature variation with a cigarette. This empirical therapy is described by North European physicians is a barbaric method. Furthermore, the idea of thermal destruction of the venom is not proven. This treatment is still used in emergency units encountering these poisonings in southern France. Actually, the Marseilles Poison Centre advice in such cases is the application of what we call a 'thermic shock' consisting of a sudden local temperature variation (2 minutes of local heat using a cigarette or a hair dryer, then local cold with an ice cube in a tissue). In order to evaluate the efficacy of this treatment, the authors followed the clinical course of bitten patients over 48 hours. Case series: 43 envenomations were collected between 1st June and 30th September 1999. The patients were 31 men and 12 women, with an average age of 34.19 years (min 5, max 73). The fish—weeverfish 72% and scorpion-fish 28%—were responsible for bites during fishing (40% of the cases), swimming (28%), cooking (21%, recently dead fish are able to bite), diving (9%) and selling in fish shops (2%). Clinical signs were local intense pain (100% of the patients), swelling (72%), bleeding (16%), erythema (12%), numbness (12%), paresthesia (7%) and lipothymia (7%). The 'thermic shock' was done for 35 patients (average delay between bite and treatment 42 minutes, (min 3 max 180 minutes). For these patients, intensive pain disappeared after an average time of 25 minutes (min 5, max 120 minutes), and for the patients who presented edema ($n = 22$), the swelling disappeared after 122 minutes (min 15, max 480 minutes). For 8 patients, the 'thermic shock' was not applied, and they presented pain and/or swelling over an average time of 27.6 hours (min 8, max 48 hours). For 5 of them, central pain killers were administered, and for 2 of them, anesthetic blocks were used. Both treatments were described by patients as ineffective remedies. Conclusion: Even though the number of patients not treated by 'thermic shock' was not significant, the values obtained with the two groups are statistically different ($p < 0.02$, *t* test for comparison of 2 average values of small samples). The Marseilles Poison Centre will continue to advise the application of a 'thermic shock' for the treatment of Mediterranean fish envenomations.

85 COCAINE-INDUCED TORSADES DE POINTES

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Objective: We describe a patient who presented various episodes of cardiac arrhythmias in the form of *torsades de pointes* (TP) after consuming cocaine. Case report: A 34-year-old woman with a history of intravenous drug use and chronic alcoholism was attended by the Emergency Service of our hospital complaining of intermittent cephalic instability which had begun after nasal insufflation of cocaine. On arrival the patient was conscious and hemodynamically stable and the physical examination was unremarkable. The ECG showed a sinus bradycardia, a U wave and a prolongation of the QT interval (QTc 0.58 seg). Laboratory tests showed a hypomagnesemia (1.2 mg/dL) with the other biochemical parameters being normal. Toxicological tests were positive for cocaine in the urine. While in the Emergency Department the patient suffered a self-limiting episode of TP, which was initially treated with isoproterenol and magnesium sulfate, and was admitted to our Unit for observation. During the first 24 hours, the patient was asymptomatic, without further episodes of arrhythmia, and it was decided to stop perfusion of isoproterenol after normalization of magnesium levels. A few hours later the patient suffered a further episode of TP which required the placement of an external pacemaker and restarting of isoproterenol perfusion. After 48 hours, when tests showed negative for cocaine and its metabolite benzoylecgonine, medical treatment was ceased, without subsequent re-appearance of TP. Observatory ECG showed

a persisting prolonged QTc and the patient was discharged after 15 days. Examination of the medical history revealed the existence of prolonged QTc (0.50 seg) in previous ECGs during at least the previous year and a half. Conclusions: This patient, with an idiopathic prolonged QT syndrome, presented a TP after adrenergic stimulation which was favored by hypomagnesemia (chronic alcoholism). The most striking feature was that this patient, who had no symptoms of sympathetic hyperactivity at other levels, continued to present TP once the most acute phase of cocaine intoxication was surmounted. For this reason it seems logical to think that as well as the sympathomimetic effect, there must be some toxic effect on the myocardium which contributes to the appearance of TP and which may account for some of the sudden deaths which occur among habitual cocaine users.

86 INTOXICATION WITH GAMMA-HYDROXYBUTYRIC ACID (GHB) IS AN INCREASING SOCIAL AND MEDICAL EMERGENCY IN SWEDEN

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Objective: Gamma-hydroxybutyric acid (GHB) has become a popular new drug of abuse in Sweden. The aim of the study is to present and focus on a new agent of abuse with potential social and medical risks including deaths in overdose. Methods: During a two-year period all cases of poisoning with GHB admitted to Sahlgrenska University Hospital were included in the study. Results: During the early nineties only a few cases presented each year. During 1998, 20 cases were admitted to our hospital and during 1999 that number was more than doubled. Most patients were men in their early twenties; several of them could be described as 'bodybuilders'. Patients presented with drowsiness, nausea, vomiting, myoclonic seizures and coma. Coma normally lasted for 3–5 hours and then the patients suddenly awoke, normally without any sequelae. 10–20% react with mental confusion, agitation and violent acts causing a significant problem for healthcare staff. Respiratory arrest was noted in one patient and 3 patients presented cardiac arrhythmias requiring a pacemaker in one. All arrhythmias were transient and cardiac rhythm was normalized on the next morning. No deaths occurred in the hospital, but during the same period 2 deaths were observed in our city. Conclusion: Intoxication with GHB has dramatically increased in Sweden during the last few years. GHB overdose causes agitation, unconsciousness, respiratory depression and cardiac arrhythmias that may result in deaths.

87 GHB ABUSE IN THE UK: LOCATION AND EFFECT

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Introduction: Enquiries to the London Centre of the UK National Poisons Information Service about cases of gamma hydroxybutyrate (GHB) have shown a marked rise over the last 4 years, a pattern mirrored by other Poison Centres in the UK. GHB abuse has been widely described in the United States but there are few published reports from the UK or the rest of Europe. GHB has the potential to become a serious health risk due to the narrow margin between desired and harmful effects. Possession of GHB is not illegal within the UK. Objective: To assess the usage of GHB in the UK. To collect information on the clinical effects reported following GHB abuse. Method: Clinical effect data was collected from the initial enquiry records and case summaries from the hospital concerned where possible. A search of our in-house database was conducted to provide confirmation. International Programme of Chemical Safety Poison Severity Scores (PSS) were applied to these data. Information on the geographic location of the abuse episode was requested from all UK and Ireland NPIS Centres; these data were processed to show the regional pattern of enquiries in the UK and Ireland. Results: The most commonly reported clinical effects were coma, drowsiness, bradycardia, nausea and vomiting, convulsions, agitation, confusion, and respiratory depression and arrest. The number of enquiries has risen from 134 in 1996 to 202 in 1999 (at the time of writing only 10 months were available). This rise is a rise in absolute numbers and also as a proportion of total enquiry load. PSS scores for the study period are shown in the Table. GHB now represents 0.12% of our total enquiry load and 3.76% of the total drug of abuse enquiry load. Clear regional differences are noted with 27.4% from the N W of England, 21.5% from Wales and 15.6% from London. This disproportionate incidence remains even when population size of these areas is taken into account. Conclusion: GHB abuse, as seen in this study, appears to be centered in specific areas of the UK; London and the North West of England and Wales. However, there is a general spread of GHB abuse to most remaining parts of England, with sporadic cases reported from all other areas throughout the UK and Ireland. The clinical effects seen in these cases are in keeping

with that reported from the USA and elsewhere. The features reported, and the PSS applied indicate 'moderate' poisoning is most commonly observed.

PSS Scores for GHB Enquiries to the UK NPIS 1996–1999

	PSS 0	PSS 1	PSS 2	PSS 3	PSS 4
1999	10	43	51	65	0
1998	10	30	38	84	0
1997	5	27	34	75	0
1996	17	36	19	43	0
TOTAL	42	136	142	267	0

88 A CASE OF GAMMA-BUTYROLACTONE OVERDOSE

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Objectives: gamma-butyrolactone (GBL) is a precursor of gamma-hydroxybutyrate (GHB). As GHB is scheduled in an increasing number of countries, one can expect a shift in usage from GHB to GBL and an increasing number of poisonings with GBL. Only a few cases of GBL overdose have been published in the literature. We describe a case of GBL overdose and measured GBL and GHB concentrations in gastric lavage fluid, urine and serum. Case report: After drinking from a bottle containing an 'unknown' clear liquid, a 23-year-old man collapsed. He was admitted to the emergency department in a comatose state. The patient was known to be a drug user who liked to experiment with new drugs ('innovator'). His temperature, pulse and blood pressure were normal. The patient was transferred to the intensive care unit. Five hours after admission, he was fully conscious again, but did not remember anything. He was further observed and discharged home the next day. Gastric fluid, urine and serum were taken and sent to the laboratory together with the remainder of the liquid. Toxicological analysis included screening by immunoassay and confirmation by gas chromatography-mass spectrometry (GC-MS). The liquid was analyzed by GC-FID and headspace GC-MS and was found to contain 19 g/L methanol, 29.5 g/L ethanol and GBL. The routine toxicological analysis revealed the presence of amphetamine, MDMA, MDA, cocaine and benzoylecgonine. Blood ethanol was negative. GHB was measured by GC-MS after precipitation with acetonitrile and derivatization with BSTFA. The GHB levels were 133, 34 and 79 μg/mL in serum, urine and gastric fluid respectively. GBL was measured by GC-MS after extraction into chloroform. GBL was 355 and 13 μg/mL in gastric lavage fluid and urine respectively. Due to recovery problems with serum, the serum concentration could not be determined with this method. Conclusion: The symptomatology was similar to GHB poisonings: sudden coma and rapid recovery. The GHB concentrations were similar to those observed in GHB overdoses. GHB or GBL are not detected in routine toxicological screenings and should be considered in cases of unexplained coma with rapid recovery.

89 CROSS TOLERANCE OF GAMMA-BUTYROLACTONE (GBL) AND BENZODIAZEPINES

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Objective: GBL is converted *in vivo* to gamma-hydroxybutyrate (GHB), a drug known for multiple adverse health effects. A withdrawal syndrome of insomnia, tremor, and anxiety has been observed in chronic GHB users. We describe a patient with history of benzodiazepine and GBL use who presented with a withdrawal syndrome. The pattern of benzodiazepine and GBL discontinuance and response to therapy suggests a potential for GBL or GHB to treat benzodiazepine withdrawal, or vice-versa. Case Report: A 30-year-old male presented to the ED with 2 days of insomnia, tremor, anxiety, diaphoresis and abdominal cramping. His past medical history was notable for insomnia. He denied use of illicit drugs or alcohol, but reported a three-year history of benzodiazepine use for his insomnia. Additionally, he had a three-month history of using GBL to augment the soporific effects of diazepam, which had lost efficacy. During this time period he concomitantly used diazepam (10 mg PO) and an undetermined but consistent quantity of GBL daily to induce sleep. Seven days prior to presentation, he discontinued diazepam use due to a concern that he was becoming tolerant to the drug. He remained asymptomatic while continuing to use his usual daily dose of GBL.

His symptoms began shortly after he discontinued use of GBL at the urging of the supplier, who warned the patient of potential adverse health effects. In the ED, he had normal vital signs, 5 mm reactive pupils, gross tremor and was diaphoretic. Although he complained of anxiety, the remainder of his physical examination was unremarkable. The patient was treated with diazepam (5 mg IV). Within minutes, his tremor, diaphoresis and anxiety ceased. The patient refused admission, but agreed to an outpatient taper of oral diazepam. Over the following four days, he continued to take diazepam (10–20 mg PO daily) in divided doses, including one dose to induce sleep. One the fifth day he discontinued use of all medications. He remained asymptomatic and free from benzodiazepines and GBL, but noted difficulty falling asleep. Conclusion: Since GBL is converted to GHB *in-vivo*, the similarity between this patient's symptoms and previously reported GHB withdrawal is expected. His abdominal discomfort may be a unique feature of GBL withdrawal. The similarity of GHB, GBL and benzodiazepine withdrawal syndromes suggests a common mechanism, potentially related to GABA. It appears that either this patient's withdrawal from GBL was successfully treated with diazepam or that his GBL use masked symptoms of diazepam withdrawal. Either scenario suggests the potential interchangeability of GBL, GHB, and benzodiazepines for treatment of withdrawal from any of these substances.

90 PREDICTING ECSTASY ABUSE. COLLABORATION BETWEEN THE POISON CENTRE AND THE FORENSIC LABORATORY

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Objective: This study was performed to describe the situation of ecstasy intoxications in Spain and to identify the content of ecstasy tablets confiscated in our country. Methods: The Spanish Poison Control Centre database was searched for the years 1991 to 1998 inclusive. Data collected included gender, age, coingestants, signs and symptoms, and complications. Outcome was scored according to criteria of the IPCS. Data from the Drugs Section of the National Institute of Toxicology included composition of the tablets sold as ecstasy in the street. Samples from penitentiary institutions and workplaces as well as autopsies in the last four-year period were also analyzed. Results: Fifty-eight cases of ecstasy intoxication (47 male, 11 female, mean age 20 years), were reported to our Centre. Ninety-three percent of the patients had a mild clinical picture with symptoms like diaphoresis, disorientation, tachycardia and mydriasis. The rest experienced moderate to major toxicity: hypertension, hyperthermia, renal or hepatic failure, metabolic acidosis, convulsions, or coma. Thirty patients used more than one substance: ethanol, cannabis, cocaine, speed, or mescaline. Comparison of the composition of substances sold in the street showed an increase in the amphetamines and related substances: 4.2% in 1994, 13% in 1995, 18.7% in 1996, 35.3% in 1997 and 18.4% in 1998 and corresponded mainly to amphetamine (up to 88% of product in 1997 contained this drug), MDMA (up to 68% in 1996), and MDEA (21% in 1995). MDA stopped after 1988–1992 but reappeared in 1996 and methamphetamine was detected in 1998. Common adulterants were caffeine and piracetam, but paracetamol, ephedrine, atropine, quinine, isoniazid and methylene blue were found also. Amphetamines and analogues were found as the principal compound in 2% of drug related deaths: amphetamine in 19 cases, PMA in 1 and associated substances (amphetamine, MDMA, MDEA, MBDB) in 9. On 42 occasions they were associated with heroin, cocaine, or ethanol. Results from judges showed an increased detection of amphetamines or analogues: 1.5% in 1995 and 13.7% in 1998, whereas it remained low and constant in the penitentiary institutions (less than 1%) and workplaces (never more than 2.6%). Conclusion: The ecstasy abuse trends as monitored in the Poison Centre showed a poly-drug users pattern which corresponds with the laboratory data. Ecstasy tablets not only contain MDMA but also amphetamine and other analogues which emphasize the importance of the collaboration between the Poison Centre and the forensic laboratory in order to evaluate the patient's clinical situation and the toxicovigilance efforts, such as awareness of new substances and intervention activities in special populations.

91 RELATIVE SAFETY OF HEROIN SUBSTITUTION PRODUCTS IN OPIATE-NAIVE RATS

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Objective: Buprenorphine (BUP) and methadone (MTD) are the most commonly employed substitution products for the treatment of heroin abuse. The safety of these products in overdose, relative to that of heroin, is poorly appreciated. We thus undertook an experimental study to compare the lethality of BUP and MTD in comparison with morphine sulfate (MS), used as a surrogate for heroin. Methods: Opiate-naïve Sprague-Dawley rats of 200–300 grams were

employed. An open-label preliminary study was performed to determine the intravenous median lethal dose (MLD) of the three products. Concentrations were then adjusted to allow for MLDs of approximately equal volume. Animals were then randomized and dosed intravenously in a blinded manner using one of the three products. The rats were observed carefully until death or until 7 days had passed. The MLD was determined for each blinded product in quadruplicate to assure reproducibility, using the up-and-down method of Dixon and Bruce. A mean median lethal dose (xMLD) was then calculated. The results are expressed as mean + SD Maximal therapeutic doses (MTD) in humans were obtained from the product package insert. A safety index (SI) was calculated for each drug, using the formula SI = $xMLD_{(rat)}/MTD_{(human)}$. Assigning a safety factor in overdose of 1 to morphine, a relative safety factor (RSF) was calculated for BUP and MTD using the formula RSF = SI(substitution product x)/SI(morphine). Results: The results are shown in the Table. Conclusions: Buprenorphine appears to be significantly safer in overdose, compared with morphine sulfate and methadone in the opiate-naive rat model, using human maximal therapeutic doses as a reference dose. Methadone appears to have a lower margin of safety than morphine sulfate in the rat. Further studies are needed to determine the relative safety of these substitution products in morphine-dependent rats.

Relative Safety of Opioids

Drug	Mean Median Lethal Dose $xMLD_{(rat)}$	Standard Deviation SD	Maximal Therapeutic Dose $MTD_{(human)}$	Safety Index SI	Relative Safety Factor RSF
Morphine	45.7	10.4	0.28 mg/kg	163	1
Buprenorphine	230.7	49.2	0.22 mg/kg	1048	6.4
Methadone	23.8	5.2	1.43 mg/kg	16.6	0.1

92 INTRODUCTION OF TRICYCLIC ANTIDEPRESSANTS IN THE RAPID OPIOID DETOXIFICATION METHOD INSTEAD OF CLONIDINE

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Objectives: Methods of rapid opioid detoxification (ROD) vary significantly in medications used, time and mode of naltrexone introduction and even in duration of detoxification, but in the majority of cases clonidine remains a key medication for the correction of withdrawal symptoms. We performed a prospective study in order to evaluate the possibility of using tricyclic antidepressants (TCA) in ROD instead of clonidine. This point is supported by the fact that some TCA (amitriptyline) are successfully used in the treatment of sleep disturbances in heroin addicts during the post-detoxification period, on the other hand the cholinolytic effects of TCA could be sufficient to correct gastrointestinal symptoms during the withdrawal period. Method: This was a prospective observational study evaluating patients with an established diagnosis of opioid dependence (according to ICD X). The study was performed at the Vilnius University Emergency Hospital in open in-patient settings with no isolation measures. The treatment protocol included: amitriptyline 50–100 mg/day, parenterally for the first 2–3 days, followed by oral administration; long acting benzodiazepine (clonazepam) 4–8 mg/day; in the case of insufficient correction of withdrawal symptoms carbamazepine was added 200–600 mg/day. No opioid substitution was used. Naltrexone, at full 50 mg/day dose, was administered after 36–48 hours after beginning the therapy. Patients remained in the in-patient department for 5 days, longer if the withdrawal symptoms failed to cease during the time assigned by the protocol. Patients were evaluated according to the duration and completion of detoxification. Patients were observed for adverse reactions to TCA, including cardiotoxicity, on ECG. Results: 30 patients were included in the study, predominantly of male gender—26 (87%) males, 6 females. Age ranged between 16–35, mean 22.9. Duration of opioid abuse was 0.5–8.0 years, mean 2.0. 19 patients were intravenous users (63.3%), 11 non-intravenous users. Mean doses of medications used for detoxification: amitriptyline 84.2 mg/day, clonazepam 5.9 mg/day. 16 patients received additional carbamazepine, mean dose 475 mg/day. Duration of detoxification ranged from 5 to 9 days, mean 5.9. 26 patients completed detoxification, drop-out rate—13%. No TCA adverse effects were observed during the study. Conclusion: TCA are effective and safe enough to be used in ROD. A comparison of clonidine and TCA in ROD has yet to be completed.

93 METHADONE RELATED EMERGENCIES IN HAMBURG

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Objective: Since 1998 it is allowed to prescribe for methadone substituted patients take-home dosages not only for the weekend but for up to 7 days. We were interested to study the prevalence of methadone-related emergencies admitted to hospitals for which we analyze blood specimens in cases of poisoning. Methods: Blood specimens of poisoned patients were drawn as soon as possible after admission and analyzed by immunological and GC or GC/MS methods. Results: The number of methadone-associated emergencies increased from 1997: 15, to 1998: 24, 1999 (I–XI): 33 cases. Among these cases there were 3 children (3, 9 and 24 months, respectively), at least 3 suicide attempts and 1 traffic accident. Table 1 shows the main drugs found in addition to methadone. An evaluation of the main causes of poisoning is shown in Table 2.

Frequency of Drugs Found in the Blood of Poisoned Methadone Consumers Admitted to Hospital

Additional Drug	1997	1998	1999 (I–XI)
Opiate (Heroin)	5	3	5
Cocaine	4	10	11
Benzodiazepine corresponding to diazepam	2	7	15
>0.5 mg/L			
0.1–0.5 mg/L	10	7	6
Alcohol (0.8–1.8%)	3	3	2
Tricyclic antidepressants	3	3	4

Main Causes of Poisoning

	Number of Cases		
Main Causes of Emergency Admission	1997	1998	1999 (I–XI)
Methadone only	4	4	9
Mainly methadone	7	10	14
Mainly heroin	0	2	3
Mainly tricyclic antidepressants	1	3	2
Mainly cocaine	1	2	1
Mixed	2	3	4

Conclusion: The increase of methadone-related emergencies parallels better methadone availability for patients and, as a consequence, the black market.

94 METHADONE OVERDOSES IN THE UK: PATTERNS AND PREVENTION

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Background: Opiate addiction remains a very common problem in the UK and methadone is frequently prescribed as a substitute. However, the safety of such a policy remains under constant review. Objective: To review all patients admitted with methadone poisoning in one year to a teaching hospital to establish precipitants for admission and audit the quality of care. Methods: A retrospective review of all patients admitted in 1998 with a diagnosis of methadone overdose to one teaching hospital acting as a Regional Poisoning Treatment Centre for a population of approx. 350 000 was carried out to evaluate circumstances surrounding admission and quality of care provided. Results: 124 patients (86 M; 38F, mean age 27.1 years) out of a total of approx. 20 000 medical admissions per year were admitted having

taken an average of 122 mL of methadone each. Only 3 (2.4%) were admitted to intensive care, 4% to high dependency care and the remaining 93.6% to the poisons ward. Their mean length of stay was 28.3 h. 3 patients suffered a respiratory arrest and 31 had both substantial depression of respiration (RR $<$ 10/min) and conscious level (GCS $<$ 8). One patient was admitted 4 times, 3 on three occasions and 10 on 2 occasions within the year. 37% of (124) patients had taken their own prescription methadone, 33% street methadone and 28% methadone from an unknown source. There was geographical clustering of admissions from postcodes indicating areas of social deprivation in the city. Conclusions: The number of admissions with methadone overdose and their severity of poisoning represented a significant workload. As prescription or methadone available on the street was often taken, family doctors in deprived social areas should avoid excessive prescriptions. Measures to reduce re-admission need to be considered e.g. pre-discharge planning and patient education.

95 AN UNUSUAL FATALITY DUE TO ABUSE OF ALFENTANIL/MIDAZOLAM MIXTURE

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Objectives: Alfentanil is a very potent opioid analgesic, structurally related to fentanil, capable of causing respiratory depression, hypotension and coma. Midazolam is a potent benzodiazepine hypnotic with a short duration of action which is commonly used in anesthesia, often in combination with alfentanil. This is the first reported case of a death due to the abuse of alfentanil alone, or in combination with midazolam. Case report: A 27-year-old trainee anesthetist was found unconscious without vital signs in a locked hospital toilet; resuscitation was attempted but was unsuccessful. He had last been seen alive some three hours earlier. An empty 5 mL syringe and needle were found next to the body and his left leg was exposed showing 4 injection marks; a belt had been attached to his left leg to act as a tourniquet. A post-mortem examination was carried out 2 days later and no signs of natural disease or trauma was found. The cause of death was reported as acute asphyxia. Toxicological analysis of peri- and post-mortem blood, urine and syringe was carried out using immunoassay (EMIT-Dade) capillary gas chromatography with N-specific detection and liquid chromatography with diode-array UV detection. Alfentanil and midazolam were identified in the syringe residue at a relative proportion of 2:1 (alfentanil:midazolam). The deceased had access to an intravenous formulation containing both these drugs in the course of his clinical duties. Immunoassay screening of post-mortem urine for common drugs of abuse detected the presence of benzodiazepines and cannabinoids; no opiates or other drugs were detected. A peri-mortem blood specimen taken at resuscitation gave a result of 79 μ/L for alfentanil. No midazolam was detected (limit of detection 30 μg/L). Analysis of post-mortem blood specimens for alfentanil by liquid chromatography gave the following results: heart (65 μg/L), left femoral (99 μg/L) and right femoral (67 μg/L). Conclusion: The relatively low concentrations of alfentanil found in blood and the circumstances of the case would suggest that self-administration of these drugs was probably for the purpose of 'misuse' rather than overdosage. The presence of multiple puncture marks on the leg suggested earlier experimentation. The deceased was reported to have a history of cannabis usage, but no mental health problems. Because of the potent nature of alfentanil, with or without combination with midazolam, there is a high risk of toxicity, particularly respiratory failure when used in a non-clinical setting, the potential dangers of abuse of such anesthetics agents by those who have access to their use is highlighted.

96 SCREENING FOR CANNABINOIDS: COMPARISON OF KIMS AND FPIA IMMUNOASSAY

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Objectives: Testing a new cannabinoids immunoassay, based on Kinetic Interaction of Microparticles in Solution (KIMS), by screening urine samples of prison inmates and comparison of the results with another older immunoassay, based on Fluorescence Polarization Immunoassay (FPIA). Methods: The new cannabinoids immunoassay (Roche diagnostics) is based on KIMS. Analyses were performed with the Cobas Integra 700 analyzer (Roche). For comparison we used the FPIA of Abbott on the TdxFlx analyzer. During 3 months 257 urine samples of prison inmates were analyzed with the KIMS immunoassay for cannabinoids. All samples with a result $>$ 25 ng/mL were reanalyzed with FPIA. Results: All results are presented as mean (sd) unless stated otherwise. After analysis with KIMS, concentrations $>$25 ng/mL were found for 53 of the 257 samples. The mean ($\pm$sd) concentration of these 53 samples was 178 (270) ng/mL. After reanalysis with FPIA cannabinoids concentrations were also $>$25 ng/mL in all 53 samples: mean 196 (251) ng/mL. The mean ratio of the concentrations FPIA/ KIMS was: 1.32 (0.37). Ratio was 1 for 1 sample, $<$1

for 10 samples and >1 for 42 samples. For all samples with a concentration measured both by KIMS and FPIA <100 ng/mL (27 samples) the ratio was >1 except for 1 sample. So the concentrations, measured with FPIA, of most samples were higher than those measured with KIMS, especially at lower concentrations. The official cut off for cannabinoids screening is 50 ng/mL. Concentrations below the cut-off were found for 20 samples analyzed with KIMS. However for 10 of these 20 samples, concentrations >50 ng/mL were measured after reanalysis with FPIA. The ratio FPIA/KIMS of these 20 samples was 1.41. On the other hand all samples with concentrations below cut-off, analyzed with FPIA, were also below cut-off with KIMS. The reason for this phenomenon is probably that KIMS is more specific for 11-nor-Δ^9THC-9-carboxylic acid, the major metabolite of cannabis in urine. Higher concentrations are found with FPIA because more metabolites cross-react with FPIA. Conclusion: Because lower cannabinoid concentrations are measured with KIMS than with FPIA, more samples will be below cut-off and declared negative. Lowering the cut-off for KIMS to 35 ng/mL could be considered.

97 ACUTE ALCOHOL INTOXICATION IN ADOLESCENTS. A MULTICENTRE EUROPEAN STUDY

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Background: Alcohol-related pathologies and psychosocial problems are extensively studied in adults, whereas in teenagers the topic has received little attention, until now, in most countries. Aim: To emphasize the role of alcohol intoxication in adolescents, a multicentre study involving Poison Centres (PC) and Pediatric Departments was carried out in 6 European Countries. Methods: Acute alcohol intoxication (AAI) in children aged 10–15 years was retrospectively studied in a 10-year period (1990–1999) in two Poison Information Centres (Athens, Lille) and four hospitals (Glasgow, Helsinki, Lisbon, Trieste). Epidemiological and clinical data as well as associated pathologies have been reviewed. Results: 912 AAI were studied. Most of the cases occurred at 14–15 years of age, as a result of deliberate ingestion, and in few of them alcohol addiction was documented. In general the incidence was higher in boys (62–67%), except at Trieste (52%) and Lille (40%). These differences in gender distribution are explained by associated ingestion of drugs (8.3% at Trieste, 67% at Lille) involved in suicide attempts. There was a 50% increase in telephone inquiries considering AAI in adolescents in Poison Information Centres at Athens and Lille in the 90s. In Finland hospitalization rates (more than 15 hours) due to alcohol intoxication in adolescents increased from 25 to 40 per 100,000 inhabitants aged 10–14 in the 90s. The incidence rate of emergency room (ER) referrals in Trieste was 75/100,000 10–15-year-old residents in 1990, rising to 155/100,000 in 1998. Spirits were the prevalent type of alcoholic beverage ingested, although wine had a special role in Greece (31.5% of the cases) and Trieste (27.4%). Alcohol ingestion occurred on Saturday and Sunday in more than half of the cases in Trieste and Greece. Excluding cases with associated drug ingestion, symptoms showed a positive correlation with blood alcohol concentration (BAC). Measurement of BAC was only carried out in some of the patients. AAI severity according to quantitative scores was in most instances of mild/moderate degree. Alcohol-related trauma occurred in some instances. Underlying psychological/psychiatric problems were not uncommon. Outcome was good in all cases, with no deaths occurring. Conclusions: Despite the decrease in alcohol consumption in Europe in the 90s as compared to the 80s, results from the present study demonstrate an increase in acute alcohol intoxication in adolescents. It has to be stressed that most telephone inquiries to PC or ER referrals concern cases of higher severity, with associated drug ingestion, underlying psychological problems or related trauma. The high incidence of AAI in teenagers reflects poor information on alcohol risks, as also pointed out by questionnaire studies in different countries. Specific prevention, through education, needs to be targeted at the problem. The Working Group will launch a prospective study on the topic in European Countries.

98 PRELIMINARY STUDY ON THE ANTI-RELAPSE EFFICACY OF ACAMPROSATE

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Objective: Alcoholism is a chronic disease with far-reaching effects on individuals and on society and is an important public health problem in Poland. Although a number of different, often expensive, strategies have been implemented

to counter alcohol dependence, relapse rates remain unacceptably high. The aim of this preliminary study was to assess the effectiveness of acamprosate in prolonging abstinence in alcohol-dependent patients. Material and methods: 102 alcohol-dependent patients treated at the Detoxification Unit of Kraków Poison Center in 1999 agreed to receive acamprosate in addition to routine counseling. The group (94 men, 8 women) were aged 23 to 59 years (mean: 42.5 ± 7.72) and the mean duration of alcoholism was 12.33 ± 8.32 years. The control group consisted of 50 alcoholics who did not receive acamprosate (mean age: 41.8 ± 7.8; mean duration of alcoholism: 11.5 ± 7.3). The 10th revision of the International Classification of Diseases was used for the diagnosis and classification of alcohol dependence. Before admission to the study, patients had to be completely abstinent from any alcohol consumption for a minimum of 5 days. This period corresponded with the in-patient detoxification therapy including pharmacotherapy, mainly with benzodiazepines, and psychotherapy. Every week during the consultation visit with the study investigator, patients were asked if there had been a period when they had been completely abstinent. The number of abstinent days was used as an outcome measure. Relapse was defined as lapsing (drinking for 1 day), bingeing (drinking for no more than 2–3 days) or real relapse (starting to drink again continuously), or missing a consultation visit with the study investigator. Results: The acamprosate group contained 102 and the control group contained 50 previously weaned alcoholics. 10 of the acamprosate patients started therapy in October, so they were not included in the statistical evaluation. Five acamprosate patients (5.4%) had no days of complete abstinence missing the first consultation visit. In 29 patients (31.5%) lapsing occurred after 1 month, in 30 patients (32.6%) after 2 to 3 months of therapy and in 30.4% of the acamprosate group the abstinence period was longer than 3 months (4 to 10 months). No patient in the acamprosate group drank for more than 1 day. The mean period of continuous drinking in the control group was 7 days. 13% of the acamprosate group and 2.7% of the control patients were continuously abstinent. Conclusion: Preliminary data suggest that when administered to previously weaned alcoholics, in addition to standard care e.g. psychosocial counseling and behavioral treatment, acamprosate prolonged abstinence, reduced the frequency and shortened the duration of heavy drinking.

99 ACUTE POISONING WITH HALLUCINOGENIC PSILOCYBE MUSHROOMS IN SWITZERLAND

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Objective: The abuse of mushrooms containing the hallucinogenic psilocybin is increasing and serious adverse effects requiring hospitalization are not uncommon. The aim of this study was to analyze the health risk of abusive 'magic mushroom' ingestion between January 1995 and July 1999. Cases and Methods: All cases recorded by the STIC between January 1995 and July 1999 were included in this retrospective study. Cases with written feedback reports of treating physicians and hospitals were analyzed with respect to type and severity of symptoms. Symptom severity was classified according to the Poisoning Severity Score (PSS) of the EAPCCT/EC/IPCS.[1] Results: Within the analyzed period (55 months) 161 acute exposures to psilocybe mushrooms [107 males, 41 females, 13 sex unknown; median age 20 y (range 14–56)] were reported to the STIC. The reported cases increased from 12 in 1995, 13 in 1996, 24 in 1997, 65 in 1998 to 47 until July in 1999. Detailed written follow-up reports were obtained in 67 cases. 26 of these 67 exposures were mixed intoxications (18 (69%) with concomitant cannabis consumption). Symptoms included hallucinations in 29 (43%) and panic attacks in 21 (31%) patients. Additional symptoms were mydriasis, gastrointestinal upset, and tachycardia. Severity was assessed as mild in 23 cases (34%), moderate in 41 cases (61%), and severe in 3 cases (4%). There were no lethal intoxications. Reasons for hospitalization were marked hallucinations, hyperexcitability, panic attacks, coma and convulsions. Concomitant cannabis ingestion did not increase severity. However, concomitant opiate and ethanol ingestion induced coma (GCS 3-4) in one patient, and concomitant LSD consumption resulted in convulsions in another patient. A 19-year-old male jumped from a tree in a while having hallucinations resulting in paraplegia. Delayed reactions (flashbacks) were reported in 3 patients. Conclusions: The data indicate that in Switzerland the number of hallucinogenic mushroom poisoning has increased during the last five years, with a sharp increase in 1998–1999. In most cases magic mushroom ingestion alone results in mild or moderate self-limited psilocybin poisoning. Severe complications can occur with the concomitant ingestion of other substances of abuse such as opioids, ethanol and/or LSD, or following self-inflicted injury due to the nature of the psychedelic effects of psilocybin. References: [1]Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino J. Poisoning Severity Score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998;**36**: 205–213.

100 INGESTION OF NUTMEG (*MYRISTICA FRAGRANS*)

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Objective: In the past the majority of nutmeg abuse was reported by prisoners, college students, and adolescents as a substitute for other drugs. Never before have myristicin concentrations been determined in human specimens. We report a series of seven poisoning cases and one fatal case after ingestion from 1996–1998. In two cases myristicin was measured by means of HPLC. Case series: Except in one case nutmeg powder or seeds were abused. Doses of 20–80 g of powder (approx. 280–1100 mg/kg) were ingested. In one case 19 nutmegs (approx. 133 g) were eaten. CNS disorders, tachycardia, mydriasis, nausea, and vomiting were reported up to 20 hours after ingestion. A myristicin blood level of 2 μg/mL was measured 8 hours after ingestion of 2–3 tablespoonfuls of nutmeg powder (approx. 14–21 g, 280–420 mg/kg, respectively). Life-threatening situations were never observed in these cases and the treatment was always symptomatic. Fatal Case: The cause of death of a 55-year-old woman could not be solved by autopsy, but the stomach content has had a conspicuous nutmeg-like odor. HPLC analysis of postmortem serum revealed a myristicin level of 4 μg/mL. Furthermore flunitrazepam (72 ng/mL) was found. Conclusion: Ingestion of more than 15–20 g nutmeg (both powder and seeds) induces gastrointestinal, cardiovascular and central nervous symptoms after several hours. In such cases myristicin is detectable in the blood. The estimated dose ingested in the fatal case is 560–840 mg/kg (39–59 g/70 kg).

101 TWO CASES OF INGESTION OF HAWAIIAN BABY WOOD ROSE (*ARGYREIA NERVOSA*)

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Objective: Different ergoline alkaloids such as ergine and isoergine are the constituents of *Argyreia nervosa*. Growing in southern California, Florida, and Hawaii the seeds of the plant are consumed by young people for sexual magic rites. We recorded two cases where the drug was ingested to gather recreational self-experiences. Case reports: Case 1: A 19-year-old man was admitted with visual hallucinations, anxiety, restlessness, and a diminished power of concentration 8 hours after ingestion of several small packages (about 4 seeds each). He reported the first symptoms 4–6 hours after ingestion. No other clinical signs occurred. Only moderate leukocytosis was observed in white blood cell count. A test for cannabis in urine was positive. Symptoms disappeared without therapeutic measures and the patient left the hospital well-being 24 hours after ingestion. Case 2: A 21-year-old man was admitted 5 hours after ingestion of 4 seeds with color-visual hallucinations, severe anxiety, and substantial change of self-image. He reported that symptoms started about 2 hours after ingestion. Blood pressure was increased transiently. No other symptoms were observed. Toxicological analysis was not performed. Under low-dose diazepam treatment all symptoms disappeared overnight. As it was known after these two events, both patients purchased the seeds in the same 'Head-Shop'. Conclusion: Ingestion of *Argyreia nervosa* seeds result in psychotic symptoms with a latency of several hours. Transient frightful hallucinations are the predominant clinical signs. The effects wear off without residual symptoms within one day. Only symptomatic treatment is necessary, if at all.

102 REASONS FOR INTOXICATIONS IN DRUG ADDICTS—A PROSPECTIVE STUDY

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Objective: Intoxications are frequent complications in drug users. These overdoses lead to coma or loss of physical control. Within 10 years 50% of all drug addicts have at least one overdose leading to hospitalization. 12% of drug dependent patients die from such an overdose. We therefore conducted a prospective study—still going on—to evaluate the motives and reasons which lead to intoxications in drug addicts. Methods: 20 patients (14 male and 6 female) all polydrug abusers who were admitted to our unit with an overdose were studied. After recovery from the intoxication the patient underwent standardized psychiatric interviews to assess the motives and circumstances that led to the intoxication. 4 questionnaires were used for each patient: Europ ASI (European Addiction Severity Index), AMDP (Arbeitsgemeinschaft für Methodik u. Dokumentation in der Psychiatrie) IPC (Control of Reinforcement) and a test for judgment for potential suicide. The patients were scrutinized if an intentional intoxication seemed likely. Did the patient expect no harm to his health (risky behavior), did he expect to damage himself, did he expect to die? In self-inflicted harm

the conflict that caused this action was looked at. In unintentional overdose it was investigated if the reasons were abstinence, underestimation of the dosage, an unusual combination of drugs or a previous consumption of ethanol. Results: In 12 patients (60%) the intoxication was intentional. In 8 patients (40%) an accidental overdose could be diagnosed. Of the 12 intentional intoxications two were severe suicidal attempts. 5 patients did not mind to die, 5 would not give reasons but were aware of having taken an overdose (risky behavior). In 8 patients the cause was a severe partner conflict (separation or divorce), 2 had general stress and two had other reasons. Of the 8 unintentional intoxications, 6 were under the influence of ethanol and doxepin, 2 took the wrong dose after abstinence. Conclusion: Overdoses in drug users are intentional in about 60%. Psychiatric investigation and intervention is imperative. Unintentional overdoses are due to a combination of substances of unknown interaction for the user. Overdoses after a period of abstinence are also seen.

103 PROLONGED TACHYCARDIA, HYPOKALEMIA, AND HYPOPHOSPHATEMIA AFTER CLENBUTEROL INGESTION: CONFIRMATION BY QUANTITATIVE CLENBUTEROL LEVELS

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Objective: Clenbuterol is a long acting $beta_2$ adrenoreceptor agonist used clinically in the treatment of pulmonary disorders. Due to its unique ability to shunt metabolic energy from lipid production to protein and muscle production, clenbuterol is used illicitly as an anabolic agent in livestock and human bodybuilders. We report a case of clenbuterol toxicity confirmed and correlated with qualitative and quantitative serum clenbuterol assays. Case Report: A 28-year-old healthy female tasted a small amount of clenbuterol powder that belonged to a friend. Two to three hours later she presented to the ED with tremor, palpitations, and vomiting. Vital signs included: pulse 140/min and BP 120/80 mm Hg. A fine hand tremor was noted. An ECG revealed sinus tachycardia, and serum chemistries were remarkable only for hypokalemia (2.4 mmol/L), and hypophosphatemia (0.9 mg/dL). Metoprolol (50 mg PO) was given, and her pulse slowed to 115/min, but returned to 130/min within 30 minutes. Twice subsequently, metoprolol (5mg IV) was administered, with only a transient response each time. Hypokalemia was supplemented with KCl (40 mEq PO and 10 mEq IV). After 10 hours of persistent tremor and tachycardia, she refused further treatment and left against medical advice. She returned seven hours later, still symptomatic. Her pulse was 123/min and a fine hand tremor was again noted. The ECG was unchanged, and hypokalemia (3.3 mmol/L) and hypophosphatemia (2.0 mg/dL) persisted. Metoprolol (50 mg PO) was given, and again she refused further treatment. Qualitative and quantitative serum clenbuterol assays were performed on blood samples taken at each presentation, 3 hours and 20 hours after the clenbuterol ingestion, respectively. The qualitative technique, ELISA, was positive for the first and indeterminate for the second serum sample. Liquid chromatography/mass spectrometry (LC/MS) quantitation revealed a serum clenbuterol concentration of 2.93 mcg/L in the first sample and was undetectable (<1 mcg/L) in the second sample. Conclusion: Clenbuterol toxicity resembles other $beta_2$ adrenoreceptor agonist toxicities. Most reported cases describe patients who ate livestock illicitly treated with clenbuterol. In this case, the clenbuterol belonged to a bodybuilder who used clenbuterol for the purpose of increasing muscle mass and decreasing body fat. Although acute clenbuterol toxicity has been rarely reported following illicit use in humans, this is the first such case to provide confirmatory toxicological analysis. This patient developed sustained tachycardia, hypokalemia and hypophosphatemia after ingesting an apparently small quantity of clenbuterol. It is noteworthy that even at a serum concentration below the limit of detection by LC/MS, the patient remained symptomatic for several hours.

104 HERBAL XTREME: ACUTE TOXICITY ASSOCIATED WITH INTRAVENOUS GUARANA

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Objective: Herbal medicines are often perceived and marketed as being a safe and natural. We report 3 cases of recreational intravenous injection of a herb alleged to be guarana. Case Report: In December 1998 three young adults injected half a teaspoon of 'Herbal Xtreme' one hour prior to presentation. One patient had also swallowed 2 teaspoons of the substance. The market stall owner supplying it had told them it was the herbal 'speed' guarana. Within minutes of the injection all patients felt very ill with severe headache, dyspnea, severe abdominal pain, nausea, vomiting and diarrhea. All were febrile, tachycardic, tachypneic and hypotensive. The patient who injected and swallowed the substance was most severely affected and had evidence of pulmonary shunting lasting 24 hours. On admission arterial blood gases

were pH 7.469, $PaCO_2$ 23.4 mmHg, PaO_2 68.6 mmHg, and HCO_3 16.9 mmol. Full blood counts showed transient leucopenia. Potassium and CPK remained within normal limits. Blood cultures were negative. Caffeine was not detected in 3 blood samples from this patient. Conclusion: Guarana is made from the seeds of *Paullinia cupana*. The main active constituent is up to 5% w/w caffeine. To achieve the potential toxic concentration of 20 mg/L a 70 kg person would require the caffeine content of 17 g of guarana (containing 5% w/w caffeine). Our patients' clinical course is best explained as an acute complement activation and associated pulmonary inflammatory response to the injected matter. This product apparently bypassed Australian regulatory tracking systems for complementary medicine therapeutic goods. It illustrates that good manufacturing practices cannot be guaranteed for all herbal preparations and toxicity may not be predicted from the product's labeled ingredients. This preparation did not appear to contain guarana.

105 LETHAL CONSEQUENCES FOLLOWING ORAL ABUSE OF A FENTANYL TRANSDERMAL PATCH

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Background: Fentanyl is a highly potent synthetic narcotic analgesic typically used as a pre-anesthetic and postoperative medication. There are numerous fatalities reported due to fentanyl and illicitly synthesized fentanyl analogues, however, death associated with orally administered fentanyl has not been well described. We report a death in an adult male following the oral administration of a fentanyl transdermal patch. Case Report: A 43-year-old, 81 kg male, was witnessed to have cut up a Duragesic Transdermal Patch into five pieces and subsequently sucked and chewed on the pieces prior to going to bed for the evening. He apparently had been suffering from chronic back pain and had stolen the patch from his place of employment, a home for disabled adults. His girlfriend found him dead in his bedroom the following morning. The deceased also had a history of chronic diazepam use. Quantitative analysis of serum obtained post mortem from femoral blood revealed the following concentrations: fentanyl 2.5 ng/mL, norfentanyl 4.4 ng/mL, diazepam 560 ng/mL, nordiazepam 1600 ng/mL, oxazepam 67 ng/mL. The remainder of the postmortem exam did not reveal any apparent cause of death, but the deceased did have a possible mitral valve prolapse. Conclusion: Surgical analgesia and respiratory depression are associated with fentanyl serum concentrations of 1 to 5 ng/mL, but with wide interpatient variability. Deaths associated with fentanyl overdose have reported serum fentanyl concentrations ranging from 1.0 to 17.7 ng/mL. The largest available fentanyl dose in the USA for oral/buccal administration is a 1.6 mg lozenge. The Duragesic patch our patient cut up and chewed contained a total of 7.5 mg fentanyl. Our patient's serum diazepam concentration is consistent with chronic daily dosing and is not associated with toxic effects. Furthermore, diazepam overdose and high blood concentrations are generally not life-threatening, nor are they likely to produce respiratory arrest. However, when combined with other CNS depressants, particularly opiate compounds, there is an additive effect on CNS and respiratory depression which, as demonstrated in our case report, may potentially lead to a lethal outcome.

106 WHO SAYS WHAT TO WHOM

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Objective: To determine the concordance between verbal and written poisons center records. Methods: A randomized retrospective selection of 25 poisons center written records of calls from hospitals between 03 October and 03 November 1999 were compared to the voice recording of each call. Factual bits of information related to the case were identified from the voice recording and documented as being present or absent on the written record. In-coming information received by the poisons center from the caller was categorized as 'heard and written', 'heard but not written', and 'written but not heard'. Out-going information provided by the poisons center to the caller was categorized as 'said and written', 'said but not written', or 'written but not said'. The complexity of the case was calculated by multiplying the number of drugs involved by the triage score for the existing clinical condition. Results: The cases were handled by 15 information specialists and were received by the during the following time periods: 0001–0600 = 2 cases, 0601–1200 = 4 cases, 1201–1800 = 8 cases, 1800–2400 = 11 cases. The mean age of the patients was 27.3 years. The average complexity of the cases was 4.6; the mean number of substances involved was 2.4 and the mean triage score was 1.7. For the 25 cases, a total of 1099 in-coming and out-going bits of information (mean = 44) were documented either from the voice recording or the written record; 76.7% of the information bits were heard or said and written; an additional 11.8% were heard or said but not written; 11.5% were not heard or said but were written. Of the 443 bits

of in-coming information, 383 bits (86.5%) were heard and written, 49 (11.1%) were heard but not written, and 11 (2.5%) were written but not heard. Of the 656 bits of out-going information, 460 bits (70.1%) were said and written, 81 (12.4%) were said but not written, and 115 (17.5%) were written but not said. Conclusions: This pilot study suggests that the written records of a poisons centre accurately reflected the telephone conversation 76.7% of the time. Information that was said but not written (11.8%) was expected. An unexpected finding was that 17.5% of out-going information was written but not said. Poisons centres need to evaluate how accurately their written records reflect actual telephone conversations.

107 REASONS AND MOTIVATIONS FOR CALLS TO A POISON INFORMATION CENTRE CONCERNING ENVIRONMENTAL ISSUES

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Objectives: Poison Information Centres serve as a potential source of information on environmental toxicology issues for the public and for medical professionals. The aim of our study was to describe the reasons and motivations of the public and of physicians to call our Poison Information Centre with problems related to environmental toxicology. Methods: All calls to the Swiss Toxicological Information Centre (STIC) in 1997 and 1998 labeled as environmental-related were included in this retrospective study. Environmental exposure was defined as any involuntary exposure to any substance mediated by the inanimate nature (i.e. soil, water, air). This included theoretical requests as well as problems after real exposures. Results: Within the two years the STIC received 588 calls related to environmental problems including 313 theoretical questions (53%), 159 calls regarding chronic exposures (27%) and 116 acute exposures (20%). The exposed individuals were 198 adults, 58 children, 6 without known age, and 8 animals. The substances or substance groups of interest or exposed to are presented in the Table.

Environmentally-Related Calls to the STIC (1997–8)

Substance Class	Exposures		Theoretical Questions
	Acute	Chronic	
Pesticides	27 (23%)	12 (8%)	43 (14%)
Industrial chemicals	12 (10%)	18 (11%)	28 (9%)
Gases and vapors	27 (23%)	10 (6%)	22 (7%)
Metals	3 (3%)	28 (18%)	38 (12%)
Solvents	4 (3%)	18 (11%)	19 (6%)
Materials in buildings and with construction	5 (4%)	28 (18%)	28 (9%)
Unknown	16 (14%)	15 (9%)	26 (8%)
Other	22 (19%)	30 (19%)	114 (36%)
TOTAL	116 (100%)	159 (100%)	313 (100%)

Motivation for calling the STIC (n = 588) were: Interpretation of symptoms 164 (29%), information about a substance or a product 131 (23%), question whether a relevant exposure has taken place 118 (20%), bad smell with or without symptoms 21 (4%) and 39 (7%) respectively, exposure followed by typical symptoms 30 (5%), interpretation of a laboratory result 23 (4%), other 48 (8%). Conclusions: The STIC receives calls regarding environmental toxicology issues on a regular basis, the frequency being approximately one per day. More than half of the calls were theoretical questions without exposure. Pesticides, industrial chemicals and gases/vapors are the most important substance classes. The main motivation to call our Poison Centre for an environmental issue is the interpretation of symptoms suspected to be a result of an environmental exposure and theoretical information about environmental poisons. Calls regarding symptomatic cases after a specific exposure are rare events (5%). Thus Poison Information Centres play an important role with the information of the people, in theoretical risk assessment, and with prevention regarding environmental contaminants.

108 GASTROINTESTINAL DECONTAMINATION FOR ACUTE ENTERIC-COATED ASA OVERDOSE: WHAT TO DO DEPENDS ON WHO YOU ASK

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Objective: To characterize the recommendations for gastrointestinal decontamination issued by North American poison control centers for a hypothetical patient who presents shortly after ingesting a large quantity of enteric-coated aspirin. Methods: Seventy-six poison control centers in North America were contacted by telephone, as were 7 clinical toxicologists who helped formulate the AAPCC/EAPCCT position statements on gastrointestinal decontamination. A structured survey was administered to those who agreed to participate. The hypothetical scenario was that of an asymptomatic 25-year-old man arriving at hospital exactly one hour after a single ingestion of one hundred 325 mg enteric-coated aspirin tablets (500 mg/kg). Results: Most of the poison control centers (99%) and all of the toxicologists (100%) participated in the survey. Four centers (5%) recommended syrup of ipecac and 38 (51%) recommended gastric lavage (with two suggesting both), compared with 0% and 0% of toxicologists, respectively. Seventy-three centers (97%) recommended at least one dose of activated charcoal, compared with 6 toxicologists (86%). Fifty-four of these centers (74%) recommended additional doses of charcoal for a variety of reasons. Most centers recommending charcoal (78%) suggested the use of a cathartic, as did one toxicologist. Twenty-one poison centers (28%) recommended whole bowel irrigation, compared with 3 toxicologists (43%). Fifteen centers (20%) expressed a request for an abdominal radiograph to guide therapy, and 30 centers (40%) used rising salicylate levels to guide some aspect of GI decontamination. In total, respondents at the poison control centers suggested thirty-six different courses of action, excluding a consideration of the use of cathartics. Of their five most frequently issued recommendations, none was that of a single toxicologist. It was also of note that some of the recommendations issued by the poison control centers had the potential to cause harm. Conclusions: Considerable variability exists in the recommendations of North American Poison Control Centers for the GI decontamination of patients with large, acute overdoses of enteric-coated aspirin. Toxicologists with an appreciation of the existing literature on GI decontamination maneuvers also disagree on some aspects of treatment, although to a much lesser extent.

109 CURRENT AWARENESS IN CLINICAL TOXICOLOGY—BALANCING COST, COVERAGE AND TIMELINESS

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Objective: With the increasing emphasis on evidence-based medicine, it is important that clinical toxicologists keep abreast of current literature. Some fifty thousand papers are published in the medical and scientific literature every month, of which several hundred are relevant to toxicologists. Reading even the titles of all the papers published in one week would be a daunting task. *Current Awareness in Clinical Toxicology* (CACT), a monthly publication giving a selected list of references relevant to clinical toxicology, is produced by the NPIS (Birmingham Centre) and funded by the UK Departments of Health as a service for the UK NPIS. It is also circulated by the EAPCCT and AACT to their members worldwide. Producing the list is a compromise between cost, timeliness, and coverage of as many sources as possible. Methods: To produce CACT the Birmingham Centre combines subscriptions to a number of core journals with a subscription to *Reference Update*, a weekly listing of titles from 1261 journals. This is supplemented by monthly profiles run against the *Medline* and *Embase* databases, and searches of *Toxline*. Together these four sources cover over 4,000 journals, but with considerable overlap. The monthly listings are searched by a senior information scientist and the most relevant references in clinical, occupational and environmental toxicology are chosen for inclusion in CACT by a senior clinical toxicologist. Results: The monthly listing of 180–250 citations relevant to clinical toxicologists comes from a wide range of source journals (over 450 different journals were cited in 1999). However, more than one third of the 2803 references in 1999 came from 20 ‘core’ journals and almost half were from only 40 journals. Each month approximately 25 per cent of 375 *Reference Update* citations, 10 per cent of 475 *Medline* citations, 15 per cent of 325 *Embase* citations and 17 per cent of 140 *Toxline* citations are selected prior to editing to remove identical references. The overlap in coverage between the references found from different sources is considerable, even when most of the ‘core’ journals have been eliminated from the *Medline*, *Embase* and *Toxline* searches because they are covered by *Reference Update*. Moreover some references are repeated in more than one update search. To avoid duplication of citations in CACT, all the references are entered into a *Reference Manager* database, keyworded, and classified

into subject groups, and checked against the original papers where possible. The monthly listing is produced by downloading selected citations to a word processing package, followed by extensive editing, reformatting and indexing. Conclusion: Centralized production of CACT, by a clinical toxicologist and an information scientist, results in a selected and classified listing which represents a considerable saving in time and effort for clinical toxicologists in the UK and worldwide. Combining references from several sources increases coverage; use of a bibliographic database program eliminates multiple citations and gives a searchable database.

110 IMPACT OF A NATIONWIDE NURSE'S STRIKE ON TELEPHONE ENQUIRIES TO THE NATIONAL POISONS INFORMATION CENTRE

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Objective: To assess the impact of the general nursing strike on the number of telephone enquiries to the National Poisons Information Centre (NPIC), Dublin. Methods: Telephone enquiries to NPIC were analyzed over a period of 27 consecutive days, 9 days immediately prior to the strike, 9 days during the strike and 9 days after the nurses returned to normal duties, using Mann-Whitney non-parametric statistics. Calls were classified according to caller background. Background: The NPIC provides information to health care professionals, emergency services and members of the public 24 hours a day. Poisons Information Officers answer telephone enquiries between the hours of 8am and 10pm and nursing staff provides the service outside these hours. Industrial action taken by 26,000 nursing professionals resulted in withdrawal of all non-emergency nursing services. The Cardiff Centre of the National Poisons Information Service (United Kingdom) agreed to accept telephone enquiries normally dealt with by nursing staff (from 10pm until 8am the following day). An automatic call direction system allowed telephone enquiries to be diverted to the Cardiff Centre between these hours for the duration of the strike. Results: The NPIC received 376 telephone enquiries in the 9-day period prior to the nurse's strike. 270 (71.81%) calls were received from hospital personnel, 33 (8.78%) calls from general practitioners, 57 (15.16%) calls from members of the public and 16 (4.25%) from others. During the strike a total of 290 calls were received, representing a significant decrease ($p = 0.007$) in the number of enquiries compared to the 9 day period prior to the strike. 200 (68.97%) calls were from hospital personnel, 34 (11.72%) calls from general practitioners, 45 (15.52%) calls from members of the public and 11 (3.79%) calls from others. In the initial 9 days after the strike 370 calls were received, a significant increase ($p = 0.047$) of telephone enquiries compared to the 9-day period of the strike. 277 (74.86%) calls were from hospital personnel, 29 (7.84%) calls from general practitioners, 56 calls (15.14%) from members of the public and 8 (2.16%) from others. Conclusion: Industrial action taken by the nursing profession resulted in a significant decrease of telephone enquiries to the NPIC. Underreporting of poisoning incidents may have occurred if medical personnel were too busy to contact the NPIC. The percentage of calls from members of the public remained constant throughout the period of study. The automated call direction telephone system operated efficiently and enabled collaboration between Poisons Information Centres.

111 WHAT WOULD THE CALLER HAVE DONE, IF THE POISON INFORMATION CENTRE HAD NOT BEEN AVAILABLE?

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Objective: The Finnish Poison Information Centre serves the whole country. In 1998 82.9% of the 35 587 calls came from the public. 26 247 or 73.8% of the calls were related to an acute poisoning exposure in humans, and approximately 75% of these could be managed at home. The financing of the Centre comes from the hospital districts of Finland in relation to their population. The costs of a call in 1998 were 14.2 EUR. To evaluate the need for our service we asked the citizens calling what they had done if the Centre had not been available. A secondary aim was to look at the economics of this part of the service. Methods: All calls to the Centre concerning a case of acute human poisoning exposure, and coming from the general public in May 1998 were eligible for the study. At the end of the call, the callers were interviewed using structured questions. Results: In May 1998 we received 3 096 calls. Of the 2 282 (73.7%) calls concerning a case of acute human poisoning exposure 1 743 (76.4%) came from the general public. The inquiry was performed in 1 326 cases (76.1% of eligible calls). One individual refused to participate. In 966 cases (73.4%) the caller would have phoned somewhere else for information, in 891 cases within the health care system. Self-referral was the choice of 134 callers (10.1%). Only 137 (10.4%) would have tried to manage the situation by themselves, 10 (0.8%) would have done nothing and 46 (3.5%) were not able to tell what they had done. If only calls which were managed at home were included, 79.3% cases would have resulted in some form of contact to the health care system.

The estimated total operational costs of a primary care visit in Finland are 25–50 EUR and of a visit to an Emergency Department 50–150 EUR. It is difficult to estimate the costs of a call for poisoning information to a non-specialized healthcare unit. The person giving information would most likely be a physician busy with other duties, and without the special information available in a Poison Information Centre. The costs would hardly be lower than in our Centre where a specially trained pharmacist answers the calls. Conclusion: The great majority of calls to our Centre would have led to a contact to the health care system. The costs of the Poison Information Centre compare favorably with costs which would have incurred if the Centre had been available.

112 TOXICOKINETICS OF TILMICOSIN IN A CASE OF INTRAMUSCULAR SELF-INJECTION

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Objective: Tilmicosin is a macrolide antibiotic utilized in veterinary medicine in the pharmaceutical form of a 25% propylene-glycol solution (Micotil 300®). This preparation is cardiotoxic and potentially fatal for humans. We describe a case of intentional intramuscular self-injection of Micotil 300®, in which the toxicokinetics of tilmicosin was investigated. Case report: A 41-year-old, 53 kg woman with a history of previous attempted suicides, self-injected 2 mL of Micotil 300® into her left gluteal muscle. Seventy-five minutes later she was admitted to the Emergency Department with vomiting, severe cardiovascular collapse (systolic blood pressure: 40 mmHg) and bradycardia (heart rate: 50/minute) with QT prolongation (0.44 seconds). Immediately transferred to the Critical Care Unit, she was treated with dopamine, dobutamine, oxygen and massive vascular filling according to the value of central venous pressure. Hemodynamic status improved rapidly, but bradycardia and ECG alterations lasted 2 days. After recovery, the patient confirmed the injection of exactly 2 mL of Micotil 300®. Toxicological analysis were performed by high performance liquid chromatography. Tilmicosin concentration was determined in the pharmaceutical solution (296 mg/mL), as well as in blood and urine (sequential samples were taken at 1.5, 3.75, 5.75, 9.75, 13.75, 19.75, 25.75, 33.75, 41.75, 49.75, 73.75 hours after the injection). The estimated total injected amount was 592 mg. The highest tilmicosin serum concentration (2.5 μg/mL) was found at 1.5 hours post-injection. In the following hours, a two phase exponential decay was found according to the following equation: $y(\mu g/mL) = 4.54\ e^{-0.3\times(hours)} + 0.2\ e^{-1.6\times(hours)}$. Tilmicosin serum washout time was 49.75 hours (0.09 μg/mL). The antibiotic was detected in urine until 33.75 hours post-injection. The total amount eliminated in urine was 13.56 mg (2.29% of the injected dose). Tilmicosin was not detected in the gastric aspirate at admission. Conclusion: To our knowledge, this is the first description of tilmicosin toxicokinetics in humans. Clinical examination of the injection site and toxicological investigation confirmed the intramuscular route of poisoning. Additionally, this case shows that an intensive symptomatic treatment is effective to counteract the cardiac failure related to a dose as high as 11 mg/kg.

113 MICRODIALYSIS A NEW TOOL TO OBTAIN INSIGHT INTO PERIPHERAL KINETICS OF COMPOUNDS

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Introduction: Computerized mathematical biokinetic and biodynamic models are used in risk assessment for describing the behavior of xenobiotics in the human body and predicting effects after exposure. These models are developed on the basis of plasma and urine concentrations and lack information about peripheral tissues, while these tissue concentrations generally determine the clinical effects. Microdialysis is a sampling technique, useful for measuring substances *in vivo* in peripheral tissue. To evaluate the suitability of microdialysis for measuring peripheral kinetics a kinetic theophylline model was studied. Methods: Microdialysis catheters were inserted in adipose tissue, muscle tissue and the vena femoralis of 12 anaesthetized rats. Theophylline 20 mg/kg IV was administered and concentrations were determined every 10 minutes. Unbound blood-concentrations, measured using microdialysis, were fitted in a one- and a two-compartment model, using kinetic software ph Edsim®. Thereafter, using the fitted models, a prediction was made of a concentration-time curve in peripheral tissues. A comparison was made between the predicted kinetics by the model and the actually measured peripheral kinetics using microdialysis. Results: The blood curve fitted well in a one-compartment model,

with a correlation coefficient of 0.922. However, the use of a two-compartment model is defensible as well since the correlation coefficient in a bi-exponential curve is 0.937. Using a two-compartment model, the amount of theophylline in the peripheral compartment after the same IV dose was simulated. In a two-compartment model, distribution can be seen as an 'absorption'-phase in the peripheral compartment, since theophylline has to be distributed towards the peripheral tissues. Consequently, the predicted curve showed a gradual increase in tissue concentrations. On the contrary, the measured theophylline concentrations in adipose and muscle tissue followed the plasma-curve. Discussion: In a one-compartment model the compound of interest is distributed fast and equally throughout the body. Therefore concentration-time-profiles in adipose and muscle tissue should follow the plasma-profile, as in this experiment. No proof was found that adipose or muscle tissue acts as a second compartment, although other tissues in the body (intracellular, intracerebral) can still form a second compartment. Although the blood curve fitted a two-compartment model slightly better than a one-compartment model, the concentrations at the side of interest appeared to follow the plasma concentrations. Therefore, in this rat study the effects of theophylline can be predicted using plasma concentrations and one-compartment kinetics. Microdialysis proved to be a useful tool to gain more insight into peripheral kinetics of theophylline. A human study has been planned to study the peripheral kinetics of theophylline under normal and in particular circumstances as in shock.

114 NEUROLOGICAL IMAGING IN A SMOKE INHALATION VICTIM WITH AN ELEVATED BLOOD CYANIDE CONCENTRATION

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Objective: Carbon monoxide and cyanide have the propensity to produce delayed neuroradiological findings and a clinical extrapyramidal syndrome following acute intoxication. In smoke inhalation, where both carbon monoxide and cyanide may be present, the relative contributions of each gas is unknown. We present a case of a smoke inhalation victim with a relatively low blood carbon monoxide and elevated blood cyanide concentrations who developed both characteristic neurological images by MRI and an extrapyramidal syndrome. Case Report: A 74-year-old female was discovered in respiratory arrest in an apartment fire. She was intubated, artificially ventilated with 100% oxygen and immediately given 5 g of hydroxocobalamin. The patient remained in a profound coma, GCS = 3, with reactive and symmetric pupils. On ICU arrival, she remained comatose, GCS = 7, with brisk and symmetric deep tendon reflexes, and a left Babinski sign. She had no cutaneous burns. Blood drawn at the scene revealed a carbon monoxide concentration of 0.99 mmol/L (~11% carboxyhemoglobin) and a blood cyanide concentration of 68 μmol/L (1.77 mg/L) A brain CT on day 2 revealed no edema, ventricles of normal size, and small hypodensities in the head of the caudate nucleus and white matter of both frontal lobes. An MRI on day 8 revealed hypersignals in T2 in both hemispheres in the subcortical and paraventricular regions, of ischemic nature. The neurological course improved, with awakening permitting extubation on day 10. Thereafter, an extrapyramidal syndrome involving all 4 limbs appeared. On day 30, choreoathetotic movements of the upper extremities, head, and trunk appeared in the patient, who remained dysarthric. These movements diminished then disappeared over one month. An extrapyramidal hypertonia of all four limbs persisted. Repeat MRI performed on day 60 showed hypersignals in T1 of both lenticular nuclei, representing hemorrhagic lesions. In the T2 sequence, a hypersignal of the two lenticular nuclei was noted, predominantly at the level of the putamen, as well as nodular hypersignals in T2 of the white matter. Subcortical and cortical atrophy were noted as well. Seen in follow-up 6 months later, the clinical examination revealed no neurological deficit of motor or sensory functions. However, an incapacitating extrapyramidal hypertonia persisted, predominantly of the left upper arm and the face. Repeat MRI revealed a bilateral, but predominantly right hemispheric hypersignal on T2 weighting in the putamen, and a lesser signal in the globus pallidus. Cortical atrophy had increased. Conclusion: Cyanide should be considered as possible etiology for delayed neurological manifestations in smoke inhalation victims.

115 FIREBREATHER'S LUNG: A PULMONARY FINDING IN THE BUTANE INHALANT ABUSER

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Background: The growing popularity of volatile substance abuse, especially in the adolescent population, continues to

attract international medical and media attention. We describe the non-lethal medical consequences of inhalant abuse in an individual who engaged in firebreathing pyrotechnics using butane gas. Case Report: A previously healthy 18-year-old male was admitted to a community hospital with complaints of chest pain and difficulty breathing. His illness was described as being abrupt in onset, beginning 2 days prior to his admission. The patient also admitted to engaging in the practice of butane 'firebreathing' and butane 'huffing' 3 days prior to his admission. The initial physical exam was remarkable for rales in both lung fields and a temperature of 39.2°C. A chest X-ray revealed diffuse bilateral pulmonary infiltrates with increased markings in the right basilar region. Small pleural effusions were noted bilaterally. The heart was normal in size. White blood cell count (WBC) = 18,100/mm^3 (PMN 87%, lymphocytes 12%, monocytes 1%). The patient was discharged 3 days after his admission following treatment with supportive measures, IV methylprednisolone, and IV cefazolin. Discharge labs included a WBC = 9,500/mm^3 (PMN 52%, lymphocytes 32%, monocytes 3%, eosinophils 13%). No pathogens were isolated from blood and sputum cultures. His chest X-ray on discharge revealed minimal residual infiltrates. On a follow-up exam five months later, the patient still exhibited a persistent cough with localizing rales in the left lower lobe. His chest X-ray was unremarkable. WBC = 8,500/mm^3 (PMNs 62%). Conclusion: The aspiration of liquid hydrocarbons has been well documented, but there is only limited information reported on the inhalation abuse of gaseous hydrocarbons resulting in pulmonary injury. The rapid onset and long-term sequelae, together with the physical and laboratory findings, are not necessarily consistent with either bacterial or viral pneumonia in this case. It is estimated that 1 in 5 students of high school age have engaged in inhalant abuse at least once in their lifetime. Hydrocarbon inhalation abuse should be considered as a possible etiology in adolescent patients presenting with unexplained pulmonary findings resembling pneumonia when infectious etiologies have been ruled out.

116 POISON CENTRE AND PRODUCT SAFETY SURVEILLANCE: CHLORINE EXPOSURE DUE TO HOUSEHOLD CHLORINE TABLETS

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Objective: Data collected by a poison center allows detection of new types of poisoning. Bleaching agents are widely used in Belgium, usually as hypochlorite solutions. For a few years, the increasing use of chlorine tablets instead of solutions leads to a new pattern of chlorine exposure at home. Methods: We studied retrospectively 59 cases involving chlorine tablets, registered by the Belgian Poison Centre in 1998. Results: Out of the 59 cases, 32 were inhalational exposures. Most of the accidents (75%) were symptomatic. Inhalation accidents mainly occur while opening the container, probably due to the instability of the formulation. Presentation in large containers favored accidents. Strikingly, callers often were unable to identify the commercial/manufacturer name on the package. Chlorine tablets reached the consumer not only through the regular channel but also by door-to-door sale. Conclusions: Inhalation accidents question the stability of chlorine tablets in large containers. Proposals for prevention may include reduction of the number of tablets per container or by making blister packs or even by packing the tablets individually. The unusual difficulty experienced by the callers in identifying the product/manufacturer name on the package suggests non-compliance with current legislation on dangerous product labeling. We recommend a survey of these preparations by the competent federal authorities.

117 VIAGRA®–THE UK EXPERIENCE

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Objective: Sildenafil (Viagra) was introduced in the US and UK in 1998 by Pfizer Ltd as a novel treatment for erectile dysfunction. Until that time the only licensed treatments available for erectile dysfunction were invasive, non-oral medications. State subsidized sildenafil is only available to men with specified clinical conditions. However it can be obtained on a private prescription and via the Internet. Sildenafil works by inhibiting phosphodiesterase type 5 (PDE5), which inhibits cGMP, a vasodilator, in the corpus cavernosum, thus an erection can be sustained. All cases of sildenafil ingestion reported to NPIS(L) since its launch in the UK were followed up by postal questionnaire. In addition data has been requested from all UK and ROI Poisons Centres, the UK National Statistics Office (for mortality data), the manufacturer, and the Department of Health (Hospital Episode Statistics and Medicines Control Agency [MCA] adverse reaction data). The data collected has been reviewed to determine a toxicity profile for sildenafil in overdose, abuse and therapy and was compared with that reported in the US. Case series: NPIS(L) have received 41 case enquiries,

with the UK+ROI total being 49. Of these reports, 45% of those, in the London series, resulted from an intentional non-therapeutic act. Sufficient detail was available to allow 21 cases to be followed up by postal questionnaire, 9 have been returned (43%). Clinical features reported to us include: nausea, vomiting, abdominal pain, headache, palpitations, dizziness, chest pain, tachycardia, flushing, agitation, hematemesis, red vision, hypertension, difficulty in breathing, myocardial infarction and cardiac arrest. The age range of patients from follow-up (n = 23) is 2 to 60 years old (n = 18, mean 29 years), 5 described just as adults. Prior to the introduction of sildenafil to the UK there were 77 deaths associated with it reported to the Federal Drugs Administration (FDA) in the US. 62% of those verified as being associated (n = 39, aged 48–67 [mean 66]), had a cardiac arrest. Reports to the manufacturer are in-line with these findings and include serious cardiovascular events. MCA data shows 46 deaths reportedly associated with sildenafil of which 40 were cardiovascular, 4 were cerebrovascular and 2 were suicides. Conclusion: Review of our cases, MCA and FDA data show that, in general, effects reported are similar. However the severity of NPIS(L) cases appear to be less than those reported to adverse drug monitoring systems. This finding may be due to our small case series and that the mean age, and age range, are markedly lower than in the US.

118 SEVERE NEPHROGENIC DIABETES INSIPIDUS AFTER CUMULATIVE LITHIUM INTOXICATIONS

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Case reports: We observed two cases of severe long lasting diabetes insipidus after an iatrogenic cumulative lithium intoxication. Pat.1: A 56-year-old female developed all signs of a lithium intoxication under lithium treatment for a psychotic disorder. Lithium concentration at admission was 3.56 mmol/L, 1.68 mmol/L after the first and 0.7 mmol/L after the second hemodialysis. Polyuria began on day one after admission with 6180 ml/24 h and reached a maximum of 19,050 mL/L at day 9. Intravenous substitution of fluids was necessary. Thirst tests on day 9 and day 21 led to an increase in serum osmolality with little increase in urine osmolality. 30 days after the onset the 24 h urine volume was still 6L. 60 days after the onset of diabetes insipidus the patient showed near normal 24 h urine output. Pat.2: A 45-year-old female under lithium medication developed an unintentional lithium intoxication. Lithium concentration at admission was 2.5 mmol/L. Without hemodialysis the lithium levels decreased to 1.7 (2.day), 0.8 (3.day) and 0.2 (4.day). Polyuria started on day 3 with 8,400 mL and reached a maximum of 51,000 mL (!!) on day 17. Treatment with a high dose of desmopressin, indomethacin and amiloride improved the polyuria to 14,390 mL on day 29. But this medication did not bring long lasting success. On day 43 the urine output was back to 30,750 mL. Thirst test always led to a severe increase in serum osmolality. After day 53 it was possible to reduce the volume input. The patient left the hospital after 57 days still with polyuria (5–6 L). 71 days after admission she was able to concentrate her urine under water restriction. Conclusion: Cumulative lithium intoxication can lead to nephrogenic diabetes insipidus. Desmopressin can only temporarily improve the urinary output. The disturbance seems irreversible for several months.

119 USE OF KINETIC INVESTIGATIONS FOR THE INDICATION OF HEMODIALYSIS IN ACUTE LITHIUM POISONING

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Objectives: Hemodialysis is the treatment of choice for rapid removal of lithium. It has been proposed that hemodialysis may only be indicated in patients satisfying precise clinical and kinetic criteria[1]. We report a case of acute lithium poisoning in which, according to these criteria, hemodialysis was not performed despite a serum lithium level of 7.14 mmol/L. Methods: The management included the monitoring of clinical symptoms and of kinetic parameters (serum lithium levels and half-life, urinary lithium elimination). hemodialysis was only indicated if the following criteria were present: Severe clinical poisoning (coma, convulsions, respiratory failure), increased lithium serum half-life, impaired lithium renal excretion, amount of lithium expected to be removed by a 6 h hemodialysis markedly higher than the 24 h renal excretion. Case report: A 39-year-old patient with manic-depressive psychosis was admitted 10 hours after the ingestion of 648 mmoL of lithium (sustained-release form) associated with paroxetine and chlorazepate di-K. On admis-

sion, examination was normal except for slight obtundation and agitation. Biological investigations were normal and serum lithium level was 4 mmol/L. Treatment included infusion of saline solutions (NaCl: 27 g/day). Over the first 26 hours, serum lithium increased progressively up to 7.14 mmol/L and the patient developed myoclonus and diarrhea. Hemodialysis was considered but was postponed because lithium analyses showed a high lithium urinary elimination of 69 mmol/L with a normal renal clearance of 10.5 mL/min. Moreover, the calculated amount of lithium which could be removed by a 6 hour hemodialysis was 128.5 mmol, whereas the 24 h urinary lithium elimination was estimated at 101 mmol. From the 30th hour, serum lithium decreased regularly (0.8 at the 88th h) with a serum half-life of 16.54 hours. Over the following 3 days, 219 mmoL of lithium were eliminated in urine with a mean renal clearance of 21 mL/min. The patient's clinical condition improved progressively and he was discharged on the 5th day. Conclusion: This case confirms the usefulness of the monitoring of lithium kinetics in serum and in urine in order to determine necessity of hemodialysis. Hemodialysis was not used because the expected amount removed was not markedly higher than the 24 h urinary elimination and because the patient did not develop severe symptoms. References: [1]Jaeger A, Sauder P, Kopferschmitt J, Tritsch L, Flesch F. When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. *J Toxicol Clin Toxicol* 1993;**31**:429–447.

120 RECTAL HYDROFLUORIC ACID EXPOSURE

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Background: Two published case reports exist describing the same nonfatal case of inadvertent rectal exposure to hydrofluoric acid. We present a case of intentional rectal exposure to hydrofluoric acid with a fatal outcome. Case: A 51-year-old male with a remote history of deep vein thrombosis was referred to our regional trauma unit following a suicide attempt. While inebriated, he became despondent and claimed to have ingested an undetermined amount of Acti-Brite® metal cleaning solution (8% hydrofluoric acid, 6% phosphoric acid–Virginia KMP Corporation, Dallas). He then he stabbed himself in the larynx with a kitchen knife. Upon arrival in the emergency department, an urgent cricothyrotomy was performed and he was transferred to our hospital for definitive care of his neck injury. He was taken to the operating room where a tracheostomy was performed. Fiber-optic laryngoscopy revealed a grossly swollen epiglottis and cords but no obvious burns. Urgent esophago-gastroscopy was likewise normal, suggesting that he had not swallowed any of the metal cleaner. Rigid sigmoidoscopy was then performed and revealed a gray eschar extending from the anus to 25 cm from the anal verge. The patient was transferred to the intensive care unit where he was treated with intravenous calcium gluconate (8 g total) and topical calcium gluconate enemas (24 g total) over the ensuing two days. His serum calcium reached a nadir of 1.55 mmol/L approximately 7 hours after exposure. Neither arrhythmias nor tetany were noted. On the day following exposure, signs of peritonitis developed and the patient was brought to the operating room where a Hartman procedure was performed. The resected segment of bowel was covered almost circumferentially with hemorrhagic, necrotic fibroadipose tissue and fibrinous exudate. Irregular areas of necrosis and ulceration were noted measuring up to 4 cm in diameter. Microscopically, an acute necrotizing hemorrhagic transmural colitis was present. The mucosa was extensively ulcerated and replaced with inflammatory exudate. The patient convalesced well and was discharged to the ward on the fourth postoperative day. On the seventh postoperative day he developed dyspnea followed shortly by a cardiac arrest from which he could not be resuscitated. Postmortem examination revealed a 31 cm long saddle-type pulmonary embolism. There was no evidence of thrombosis of the mesenteric vessels and the surgical stump appeared viable. Conclusions: We report the first case of intentional rectal exposure to hydrofluoric acid. Systemic hypocalcemia developed but responded to treatment. While the postoperative state may have contributed to the development of a fatal pulmonary embolus, the hydrofluoric acid exposure cannot be directly related to the patient's death.

121 EPIDEMIOLOGY OF INTOXICATIONS IN PENITENTIARY INSTITUTIONS

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Objective: Toxicovigilance and prevention are two major goals of a poison center. Since environment greatly contributes to the probability of a toxic exposure, we wanted to study the epidemiological features of poisonings in the penitentiary population. Methods: A descriptive analysis of cases consulted to our Poison Centre from January 1991 to December

1998 was made. Data from the Spanish Observatory for Drugs of Abuse (SODA) such as the mortality rates in prison and circumstances of prisoners related to the consumption of psychoactive agents in the emergency room were also analyzed. Results: Patients reported to the Spanish Poison Centre included 124 male and 14 female; all except one were adults (median range of age: 20–25 years). SODA data included only male, mean age 30. The first cause of intoxications in our Centre was suicide 79.7% followed by other etiologies: accidental (13.7%), occupational (0.7%), homicide (0.7%), chronic abuse (2.4%, with solvents and aerosol propellants) and others (2.8%). The majority of cases were consulted on weekdays (10:1), and the peak of suicides corresponded to November-December. Batteries were involved in more occasions than outside the penitentiary institution (16.4% versus 0.5%) as well as bleaches (16.5 versus 2.4%). Antiviral agents were other important substances ingested in high doses: 5 cases with zidovudine, up to 12 g; 2 with idoxiuridine, 1 with didanosine, 1 with stavudine, 1 with indinavir 36g; and 1 with nelfinavir 1.5g. Isoniazid and rifampicin were implicated on 2 occasions. Psychiatric drugs such as benzodiazepines or antipsychotic agents caused acute self-poisoning with a frequency of 32% versus 46% in the general population. Routes of entry and the estimated prognosis were similar. Due to their severity we would like to highlight two incidents: the intravenous administration of milk and the homicidal use of fluosilicate. According to SODA the first cause of death in the penitentiary institutions was HIV infection followed by drug abuse (50% of prisoners are drug dependent and 45% of them HIV-positive) and the fourth cause was suicide. 11.6% of consultations to the emergency room were due to psychoactive substances, mainly heroin (65.6%) and cocaine (29.1%) and 2.3% deaths of people in prison were for acute reactions after the consumption of these substances or acute intoxication. Conclusion: Due to the important percentage of suicide attempts as a cause of intoxication and the easy availability of drugs for HIV and tuberculosis infection in penitentiary centers, psychiatric evaluation and specific prevention measures are important aspects to be played by health care professionals in these institutions.

122 ACCIDENTAL POISONING OF CHILDREN AND THE EFFECT OF CHILD-RESISTANT PACKAGES

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Objective: Annually in the Netherlands (15.9 million inhabitants), approximately 1850 children, aged zero to five years need to be hospitalized and 1200 children need treatment at a First Aid and Emergency department following an accidental intoxication. Despite the introduction in the Netherlands of guidelines on childproof packaging of household chemicals (1986) and medicines (1990), intoxications still occur with child-resistant products. The aim of this study is to increase insight into the causal factors of accidental intoxications of children aged zero to five years in the Netherlands and to assess the role of child-resistant packages. The results will be used to formulate recommendations, which can help to improve the policy regarding child-resistant packages. Methods: An analysis of the database of the National Poisons Control Centre on poisonings was performed in order to assess the product groups which are most frequently involved in causing exposure in children. After this analysis a telephone inquiry was carried out among parents/guardians of children aged 0-6 years, who had been exposed to these product groups and consulted a general practitioner. Results: Medicines (39%), household products (21%) and cosmetics (7%) are most frequently involved in causing exposure in children. Pesticides are less frequently involved but are potentially very hazardous. In total 600 telephone inquiries with parent/guardians were held in the period May–November 1999. The average age of the children was 25.4 months (1.7 years). Practically always someone was present to watch over the child (94%). However, most accidents occurred when the parent or guardian left the room where the child was (54%). The product was often readily available for the child (77%), mostly due to the fact that the product was in use (37%) or had not been put away (21%). At the time of the accidents, only a quarter of the products were stored properly. At the time of the accidents, 55% of the products were in a closed container only 8% of which had a childproof closure. The majority (60%) of these childproof products could be opened by the children in the correct manner. In addition, another 11% of the child-resistant closures were malfunctioning or broken. Conclusion: The product was often readily available for the child, because most of the time it was being used. In order to reduce the number of intoxications in these children, attention should be focused on general public information regarding the use and easy availability of these consumer products in housekeeping. Furthermore, products that legally require childproof closures should be sold in properly designed packages.

123 PEDIATRIC TRICYCLIC ANTIDEPRESSANT OVERDOSE: IS THERE A RELATIONSHIP BETWEEN ECG CHANGES AND SEIZURE?

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Objectives: To determine if there was a relationship between ECG changes and seizure in children who presented after tricyclic antidepressant (TCA) overdose; and to describe the nature of the corresponding ECG abnormalities. Methods: In this retrospective case-control study, 7 Canadian academic health centers participated in identifying pediatric patients who met inclusion criteria (i.e. evidence of TCA ingestion; inpatient status; 12 lead ECG done within 24 hours of ingestion). Cases were patients with TCA overdose who seized. There were two types of control groups: 'internal' controls were patients with TCA overdose who did not seize; 'normal' controls were healthy children with normal ECGs. All ECGs were sent to a single center for blinded pediatric cardiology review: the cardiologist was asked to identify cases from internal controls as well as from normal controls. Results: Ninety-nine patients who met inclusion criteria were obtained; of these, 17 were patients seized (i.e. 'cases'). Chi-square analysis revealed that the relationship between ECG abnormalities and incidence of seizure could be identified ($p < 0.001$). The presence of prolonged QRS duration ($p < 0.0001$) and QTc ($p = 0.0001$) corresponded best with the likelihood of seizure. The R:S wave ratio and S:QRS duration ratio in V3 were also useful markers to distinguish normal from abnormal ECGs in this population ($p = 0.0002$ and $p < 0.0001$, respectively). Conclusions: Children who seize after TCA overdose have identifiable abnormalities on their first ECG. Children who do not have these abnormalities, do not seize. Clinicians can use the presence of abnormal QRS duration, QTc, and specific V3 changes to guide their management of pediatric TCA overdose patients.

124 ACCIDENTAL INTRATHECAL CYTARABINE OVERDOSE AND THE EFFECT OF DELAYED CEREBROSPINAL FLUID EXCHANGE

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Objective: Cytarabine is indicated in the treatment and prophylaxis of leukemic meningitis and meningeal metastasis. Although serious systemic side effects after intrathecal administration are usually not to be expected, meningismus, paresthesiae and seizures have been described in leukemic children. Systemic cytarabine is intensively metabolized by deamination into uracil arabinoside, which is neurotoxic. Deaminase activity in the cerebrospinal fluid (CSF) is low and CSF clearance of cytarabine has been reported to meet the CSF-turnover rate: 0.3 to 0.4 ml/min. Intrathecal injections do not lead to detectable cytarabine concentrations in plasma. There is only one report of an overdose of cytarabine in a 4-year-old child who underwent CSF exchange 1 hour after intrathecal administration of 200 mg cytarabine: 27% of the total dose was removed in 50 minutes, 17% of the dose was removed by the patient's own clearance. We evaluated the effect of CSF exchange when performed 5 hours after administration of an intrathecal overdose. Case report: A 53-year-old male patient accidentally received 800 mg cytarabine intrathecal, which was 10 times the prescribed dose. There were no marked systemic or neurological side effects immediately after administration besides pain at the injection site after lumbar puncture. Thirty minutes after administration the error was discovered and 5 hours later exchange of CSF was started. During 1 hour a total of 70 mL liquor was extracted and replaced by isotonic saline in three sessions. In this way 50 mg cytarabine was removed. Although this accounts for 21% of the amount of cytarabine present at the time of exchange, the majority of the total dose of cytarabine (80%) had already disappeared due to the patient's own CSF clearance which was 1 mL/min. The exchange recovery calculated on the total dose was low due to late treatment compared to the short half-life of cytarabine (3 hours in the terminal phase). Model independent estimation of the exchange clearance was 0.9 mL/min. Our patient did not experience neurological effects from the overdose but suffered from severe paresthesiae and complained of pain in the legs at the times where saline was administered, making continuation of the treatment impossible. After 3 months of follow up no signs of late toxicity were noticed. Conclusion: High dose intrathecal cytarabine did not lead to serious toxicity. Although it is difficult to estimate the value of CSF exchange in cytarabine overdose, it should be performed in an early stage if one is aiming on removing a substantial part of the overdose.

125 SURVIVAL AFTER PROLONGED CARDIAC ARREST FROM VENLAFAXINE

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Background: Venlafaxine is an inhibitor of the reuptake of serotonin, norepinephrine and dopamine. Overdose of this drug has rarely been associated with cardiac conduction disturbance. We report a case of prolonged cardiac arrest

following venlafaxine overdose. Case Report: A 38-year-old woman with a history of depression phoned the emergency line after taking 7.5 g venlafaxine and an unknown amount of oxazepam at an unknown time in a suicide attempt. In the ambulance she was initially alert and aggressive but suddenly lost consciousness and went into cardiac arrest. She was defibrillated and intubated enroute to the hospital. On arrival she was in ventricular tachycardia (VT) reverting repeatedly to ventricular fibrillation (VF) despite repeated defibrillation. A number of arrhythmias were observed during the prolonged resuscitation which followed including VT, VF and supraventricular tachycardia. She received epinephrine, atropine, lidocaine and adenosine without benefit according to standard ACLS guidelines. Flumazenil and naloxone were given without effect. Shortly after receiving bicarbonate and calcium chloride she converted to a sinus rhythm with a pulse. Total resuscitation time was approximately 1.5 hours under full CPR. The patient was admitted to the intensive care unit (ICU), remained in sinus rhythm, was decontaminated with gastric lavage and activated charcoal and received dopamine and intravenous fluids for hypotension. Blood tests taken on arrival at the hospital were remarkable for a potassium of 2.8 mmol/L, an ABG of pH 7.25, pCO_2 31 mm Hg and pO_2 52 mm Hg on room air, a venlafaxine level of 16.3 μg/mL, a desmethylvenlafaxine level of 2.7 μg/mL and an oxazepam level of 1.8 μg/mL. She regained consciousness six hours after ICU admission, was tapered off pressors on hospital day 2 and was transferred to the psychiatry service on hospital day 6. A head CT scan and 24-hour Holter monitoring were normal. Neurological evaluation revealed no residual abnormalities. Conclusion: A case of prolonged cardiac arrest following venlafaxine overdose is reported whose termination followed shortly after administration of bicarbonate and calcium.

126 SEVERE EEG ABNORMALITIES IN A CASE OF ORAL BACLOFEN OVERDOSE

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Objective: To report clinical and electrophysiological findings in a case of oral baclofen overdose. Case report: A 29-y-old woman was found comatose (Glasgow coma scale 4/15) several hours after a supposed drug overdose. She was intubated by the first medical rescuers and mechanically ventilated. This patient had suffered from limb spasticity for many years and was chronically treated by oral baclofen. The relatives suggested that she could have ingested an unknown amount of baclofen in a suicide attempt. There was no evidence of seizure. On arrival in the Emergency Department, the neurological examination disclosed intermediate unreactive pupils, abolition of deep tendon reflexes and limb flexion in response to painful stimulus. She was correctly ventilated and had a normal arterial blood pressure. A brain CT scan was performed and ruled out a gross anatomical disorder. Routine laboratory data were irrelevant and no other toxic substance could be found at the comprehensive toxicological screen. The first EEG was done 6 h after admission. Background activity was highly abnormal: diffuse and marked slowing (theta activity at 4 to 5 Hz), discontinuity, and lack of reactivity were noted. Numerous transients (sharp waves, triphasic waves and paroxystic slow waves) were recorded either isolated or following a pseudoperiodic pattern; most of them were generalized but some were lateralized to the left hemisphere. The second EEG performed 24 h later showed an alternating pattern with short periods (4–5 seconds) of better defined background activity at 5–6 Hz and large periods of generalized rhythmic delta waves anteriorly predominant. Spontaneous clinical resolution was obtained after 30 h without any antiepileptic drug. The patient could be extubated and was discharged from the ICU without neurological defect. Control EEG performed 5 days later showed a global improvement with a slightly slowed background activity (6–7 Hz), delta and theta activity in excess but no sharp transients were noted at this time. Conclusion: Baclofen is a GABA (gamma aminobutyric acid) analog which is now widely used in the treatment of spasticity. Encephalopathy with confusion, disorientation, slurred speech, agitation, lethargy, euphoria, and hallucinations have been described at therapeutic doses and early in the course of overdose by intrathecal or intravenous administration. It is known that EEG changes associated with baclofen-induced encephalopathy include periodic sharp waves, bursts of triphasic waves, trains of delta activity, intermittent rhythmical delta waves, and diffuse background slowing, but these findings seem uncommon following oral overdose. The recognition of such EEG activity could help to avoid unnecessary prescription of antiepileptic agents.

127 DEXTROPROPOXYPHENE POISONING: PROLONGED CARDIOTOXICITY IN PRESENCE OF RHABDOMYOLYSIS AND ACUTE RENAL FAILURE

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Objective: To report a case of dextropropoxyphene (DP) intoxication with severe and prolonged cardiotoxicity, coma and acute renal failure. Case report: A 54-year-old woman, with a medical history of chronic ethanol and benzodiazepine

abuse, was admitted to the emergency department 24 hours after the presumed time of poisoning. She presented with mild hypothermia (34°C) and deep coma (Glasgow coma scale 3/15) with miotic pupils. She had been intubated and mechanically ventilated before admission. Opiate overdose was suspected on the basis of neurological examination. However, the physical examination had also revealed a low blood pressure (70/44 mm Hg) with a pulse of 77 bpm. The patient was oliguric with evidence of muscle compression. The admission ECG showed sinus rhythm 70/min, PR interval 240 msec, QRS duration 110 msec and prolonged QT interval (QT/QTc: 550/370 msec). Toxicological screening revealed the presence of dextropropoxyphene and prothipendyl in the urine. Other relevant biological data were: serum creatinine 1.7 mg/dL (<1.2), creatine phosphokinase 27530 IU/L Blood arterial lactate concentration was initially normal but rose to 24 mg/dL 12 h later. Initial treatment consisted of mechanical ventilation, fluid resuscitation, dopamine and norepinephrine infusion. A Swan-Ganz catheter was inserted as the patient remained severely hypotensive. The dopamine infusion had been increased up to 1250 μg/min and norepinephrine up to 33 μg/min. Cardiac index was 2450 mL/min/m^2, pulmonary capillary wedge pressure 25 mm Hg, systemic vascular resistances 594 dyn*sec/cm^5 and left ventricular stroke work index 29.4 g*m/m^2. Naloxone IV administration (0.4 mg at 30 min interval, up to a total dose of mg) improved consciousness without any change in hemodynamic data. Her condition improved gradually and extubation was possible on day 3 but, due to altered consciousness, she had to be reintubated on day 8 until day 12. Acute renal failure developed and hemodialysis was started on day 10 (serum creatinine 6.75 mg/dL, clearance 8 mL/min). The weaning of vasoactive drugs was achieved on day 6, but the prolongation of the QT interval persisted until day 38. The patient left the ICU on day 13 and was discharged from the hospital on day 56 with a complete cardiovascular and renal recovery. Conclusion: The possibility of prolonged cardiotoxicity and central nervous system depression in the presence of renal failure has to be outlined following DP overdose. In contrast to some other anecdotal observations, the administration of large doses of IV naloxone was here unable to influence hemodynamics. Reference: Hantson Ph, Evenpoel M, Ziade D, Hassoun A, Mahieu P. Adverse cardiac manifestations following dextropropoxyphene overdose: can naloxone be helpful? *Ann Emerg Med* 1995;**25**:263–266.

128 TRAZODONE POISONING WITH *TORSADES DE POINTE* AND PROLONGED NEED FOR INOTROPIC SUPPORT

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Objective: To report a case of trazodone intoxication resulting in two episodes of *torsades de pointe*, prolonged QT interval and need for inotropic support for several days because of hypotension and bradycardia. Case report: A 37-y-old woman was admitted to the emergency department after drug ingestion. Her medical history consisted of depression and chronic ethanol abuse. She was usually taking fluoxetine 40 mg/d, diazepam 10 mg/d and furosemide. At admission, we noted a severe hypotension (70/40 mm Hg) and a relative bradycardia in an otherwise well-awake and responsive patient. She admitted having ingested about 20 pills of trazodone 10 mg and some ethanol. Laboratory data revealed a marked hypokalemia (2.7 mmol/L) without any other disturbance. The ECG showed normal sinus rhythm (64 bpm) with prolonged QT interval (QT/QTc: 520/370 msec). Initial treatment included fluid resuscitation and potassium supplement. Four hours after admission, she presented an episode of *torsades de pointe* with cardiovascular collapse which was successfully treated by external electric countershock (EEC) at 240 joules. The patient was transferred to the ICU where the treatment remained unchanged unless IV magnesium supplement. At this time, the potassium concentration was 3.25 mmol/L. Four hours later, *torsades de pointe* and cardiovascular collapse developed again but reversed after EEC (200 joules) and IV magnesium. Transthoracic echocardiography was normal. Because of persistent hypotension, continuous dopamine infusion (doses up to 583 μg/min) was administered with a subsequent increase in heart rhythm (up to 96 bpm) and arterial blood pressure (up to 109/52 mm Hg). Epinephrine infusion with doses up to 5 μg/min had been found ineffective. The need for inotropic support lasted for six days, so did the time for the correction of the QT/QTc interval. The patient was discharged from the hospital three days later. Conclusion: Cardiotoxicity of trazodone is rarely reported. It is known to prolong QT interval in healthy volunteers. Trazodone overdose may result in cardiac conduction abnormalities and dysrhythmias including *torsades de pointe* that are related to a prolonged QT interval. In our case, the first episode of *torsades de pointe* was associated with hypokalemia, but not the second. Of more interest is the prolonged need for inotropic support. High doses of dopamine were required to achieve a mild increase in arterial blood pressure. This could be explained by the fact that trazodone should be regarded as an antagonist of the central α-adrenoreceptors. We recommend thus close ECG and hemodynamic monitoring in patients admitted with trazodone intoxication associated with ECG abnormalities and/or hypotension.

129 EYE EXPOSURES REPORTED TO A NATIONAL POISONS INFORMATION SERVICE CENTRE

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Objective: To review enquiries concerning eye exposure with a view to improving the information provided by our on-line service. Method: Five hundred and sixty-three successive cases of eye exposure during the period 1997–1999 (3% of all enquiries) were analyzed for age, sex, type of product and severity of exposure. Results: Sixty-five per cent of enquiries where sex was known concerned males, compared with 51% for all enquiries ($p < 0.001$). Where age was recorded 29% were in the age range 1–4 years and 41% were aged 20–49, compared with 39% and 35% for all enquiries ($p < 0.001$) i.e. children were under-represented and adults over-represented. Fifty-four per cent of the childhood exposures (0–14 years) were to household products, 14% others (including essential plant oils, superglue, lightsticks), 11% to what were coded as industrial chemicals, 10% cosmetics and toiletries and 10% pharmaceuticals. For adults major groups were industrial (42%), others (22%), household (18%), pharmaceuticals (7%) and cosmetics and toiletries (6%). The top products involved in the exposures were Dettox Antibacterial Cleanser—a household product containing 1–2% cationic surfactant (39 enquiries), bleach (12), Olbas Oil—an inhalant for the relief of nasal congestion containing essential plant oils (11), petrol (8), superglue (7), Asda Antibacterial Spray—a household product containing <5% cationic surfactant (7), sodium hydroxide (7). Most medical professionals are aware that alkalis in particular can cause serious eye problems. It is less well known that essential plant oils can cause severe irritation with corneal damage and that superglue may cause corneal abrasions. Four hundred and fifty-five enquiries (80%) showed no or minor symptoms, 40 (8 children) were coded as moderate, none severe, in the rest features were not recorded. Severely injured patients would be expected to go straight to an ophthalmology unit and they seldom consult us. The most common features recorded were redness, irritation and pain. Systemic effects were not generally found but one patient exposed to the plant Angel's Trumpet had dilated pupils. Of the top products there were no moderate or severe cases of Dettox, bleach, petrol, superglue or sodium hydroxide exposure. Four antibacterial sprays and 2 Olbas Oil exposures caused moderate toxicity. Corneal abrasions or corneal damage were reported in 8 cases (1 each) antibacterial detergent, quaternary ammonium detergent, Olbas Oil, professional cleaner and five automobile-related products–battery acid, antifreeze (possibly burns from exploding radiator), traffic film remover and exhaust assembly paste. Conclusions: The agents causing the most serious features did not reflect the frequency of eye exposures and were diverse. Medical professionals should be aware that it is not just alkaline products that can cause eye damage.

130 OVERDOSE OF OVER-THE-COUNTER (OTC) MEDICATIONS IS LESS LIKELY TO CAUSE SEVERE POISONING THAN PRESCRIPTION DRUGS

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Objectives: OTC drugs are generally believed to be less toxic than prescription drugs, but data supporting this assumption are virtually non-existent. Some of the more toxic substances such as acetaminophen (paracetamol) or salicylates are widely used as OTC medications. Therefore the aim of our study was to test the hypothesis that OTC medications in general lead to less severe symptoms in overdose than prescription drugs. Methods: All cases of human toxic exposure with therapeutic drugs registered by the Swiss Toxicological Information Centre (STIC) during 1997 and 1998 were included in the study. Data acquisition was prospective. In multidrug ingestions, the toxicologically most relevant substance determined the classification of the case. For the assessment of severity, cases without written follow-up reports from treating physicians including detailed description of symptoms and findings, and cases with low causal relationship between symptoms and exposure were excluded. In multidrug exposures only cases with exclusively OTC-medications (no combination with prescription drugs) were considered as OTC cases. Severity was classified according to the Poisoning Severity Score (PSS) of the EAPCCT/EC/IPCS. Statistic calculations were made using logistic regression, with $p < 0.05$ considered statistically significant. Drugs were classified according to their ATC codes. Results: In 1997 and 1998 the STIC registered 16179 calls related to therapeutic drugs, 4852 of which related to OTC medications. The majority were drugs for the nervous system (43.3%, prevalent in the prescription group) and the respiratory tract (15.2%, prevalent in the OTC group). Seventy per cent of the patients were children (<16 years old) in the OTC group compared to 35% in the prescription group. Eighty-seven per cent of the calls related to monointoxications in the OTC group (69% in the prescription group). Fifty-five per cent were calls from the public in the OTC group (33% in the prescription group). The ratio between intentional and accidental poisoning was 0.39 in the OTC group and 1.50

in the prescription group. Four thousand, six hundred and fifty-seven cases with follow-up reports were included (OTC 14%). The severity in the OTC/prescription cases was none in 227/711 (34%/18%), mild 340/2260 (51%/57%), moderate 90/677 (13%/17%), severe 13/327 (2%/8%), and fatal 0/12 (0%/0.3%) respectively. There was an independent statistically significant correlation of severity with prescription status ($p = 0.0073$), multidrug poisoning ($p < 0.0001$), age ($p < 0.0001$), intentional poisoning ($p = 0.015$), and sex ($p = 0.017$) (severe or fatal vs. moderate, mild or asymptomatic). Conclusions: OTC medications are less dangerous in overdose than prescription drugs. Other factors contributing to the difference of severity are sex, age, and circumstances of poisoning (deliberate vs. accidental). Reference: Persson HE, Sjöberg GK, Haines JA, de Garbino JP. Poisoning severity score. Grading of acute poisoning. *J Toxicol Clin Toxicol* 1998;**36**:205–213.

131 SCREENING FOR LAXATIVE ABUSE

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Objectives: Screening for laxatives and laxative metabolites in urine samples of patients suspected of laxative abuse during a three year period (1997–1999). Methods: Urine samples were analysed with a validated method described earlier, based on isocratic reversed phase HPLC with diode array detection.[1] This method, developed in our laboratory, has superior sensitivity in comparison with the thin layer chromatographic (TLC) method we formerly used. Stationary phase: Lichrosphere 100 RP-18 end capped 119 x. 4.6 mm (Merck, Darmstadt). Mobile phase: 530 mL water + 146 µL triethylamine + 670 µL phosphoric acid 85% adjusted to pH = 3.3 with KOH 10% and 470 ml acetonitrile. Assay: 0.2 mL acetate buffer (pH = 5) containing 1000 E glucuronidase was added to 1.8 mL urine sample and incubated overnight at 37°C. The deglucuronidised urine was added to a Extrelut 3 column (Merck) and extracted with 3–5 mL chloroform/isopropanol 9 + 1. The extract was washed with 2 mL phosphate buffer pH 7.5 and evaporated to dryness at 37°C. The residue was redissolved in 0.5 mL mobile phase and 20 µL was injected. Positive samples were reanalysed for confirmation with a thin layer chromatographic method.[2] Results: A total of 83 urine samples from 44 patients were screened with the HPLC method. Laxative metabolites were detected in 35 samples of 7 patients. Analytical results of these patients are shown in the table. All samples found positive with HPLC were reanalysed with TLC with identical positive results with exception of patient no. 4. The small amount of sample combined with the low concentration of emodine prohibited confirmation with TLC analysis. Eventually it was discovered that this patient had ingested large amounts of a food supplement, which contained the laxative herbs *Rhamnus cathartica/frangula*, *Rheum palmatum* and *Aloe vera*.

Patient No.	Bisacodyldiphenol (mg/L)	Rheine (mg/L)	Emodine (mg/L)
1	6.96	Negative	negative
2	6.73	1.8/2.8	negative
3	0.73/0.43/0.38	Negative	negative
4	Negative	Negative	0.05
5	29.0	Negative	negative
6	14.1	Negative	negative
7	Negative	Negative	0.55/0.36

Conclusion: Laxative screening with HPLC-diode array detection and subsequent confirmation with TLC is useful tool for diagnosis of unexplained gastrointestinal problems. References: [1]Stolk LML, Hoogtanders K. *Pharm World Sci* 1999;**21**:40–43; [2]de Wolff FA, de Haas EJM, Verwey M. *Clin Chem* 1981;**27**:914–917.

132 THE EFFECT OF LIMITING THE AVAILABILITY OF PARACETAMOL ON OVERDOSE SEVERITY

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Objective: To determine whether changes made with regard to the availability, packaging and labeling of paracetamol had any impact on overdose severity. Methods: Data were collected during two equal six month periods before and after the changes were introduced i.e. 01/01/98–30/06/98 and 01/01/99–30/06/99. All patients who ingested paracetamol-containing products during the study period were included. Chi squared tests were used to detect differences in the number of patients demonstrating toxicity as assessed by administration of an antidote and admission to hospital. The Mann Whitney U-test was applied to analyze differences between the two groups in the estimated quantity of paracetamol ingested, serum paracetamol concentration at 4-6 hours post overdose, AST and ALT levels, and INR at 24–48 hours after the poisoning episode. The results are expressed as the medians and interquartile ranges and the level of significance was chosen at 5%. Results: The 1999 group ($n = 594$) presented with a reduced severity of overdose compared with the 1998 group ($n = 590$) for estimated quantity of paracetamol ingested (median 8[IQR 5–14] vs 10[5–18], $p < 0.005$, number of patients given antidote (149[25.1%] vs 183[31.0%], $p < 0.05$) and serum paracetamol concentration at 4–6 hours post overdose (27[6–64] vs 37[14–80], $p < 0.005$). No statistically significant difference was found between the two groups when the admission rates were compared, and there was no difference in the INR, AST and ALT at 24–48 hours after the poisoning. Conclusion: Limiting the availability of paracetamol to the public has reduced the quantity of tablets ingested, number of patients receiving *N*-acetylcysteine and serum paracetamol concentrations. However, no impact was observed on the admission rate or frequency of life-threatening or fatal overdoses.

133 RESTRICTIONS ON SALE OF PARACETAMOL IN IRELAND HAD NO IMPACT ON THE NUMBER OF TABLETS INGESTED IN ACUTE DELIBERATE OVERDOSE

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Introduction: Paracetamol is a widely used analgesic that can cause severe hepatotoxicity when taken in overdose. The number of paracetamol overdoses reported to the National Poisons Information Centre in Dublin rose by more than 25% between 1994 and 1998. In an attempt to reduce severe overdoses, the Irish Medicines Board made a number of recommendations on the sale of paracetamol in Irish retail outlets. Restrictions on pack size were introduced in October 1997 with a transition period of 3 months during which old supplies could be sold. We looked at the impact of these restrictions on the number of tablets being ingested in overdose. Methods: We examined all cases of acute paracetamol overdose reported to the NPIC in 1997 and 1998. We noted the age and sex of the patient involved and eliminated any case involving children under the age of 10. We counted the number of tablets involved in each case and compared the two years using non-parametric statistical analysis. Results: We found a total of 2020 cases of acute deliberate overdose, 1044 in 1997 and 976 in 1998. More than 50% of the cases involved 24 tablets or less. There was no significant difference between 1997 and 1998 ($\chi^2 = 1.276$, $P > 0.1$). The number of cases involving more than 48 tablets fell slightly but was not statistically significant ($T = 127$; $T_l = 120$, $T_u = 180$). Discussion: Most overdoses reported to the NPIC involved less than 24 tablets but 10% involved more than 48 tablets. Voluntary restrictions on the sale of paracetamol had no impact on the number of tablets being ingested in overdose. Legislation on the sale of paracetamol packages may be useful in reducing severe overdoses.

134 SNOOKER CHALK—AN UNUSUAL CAUSE OF LEAD POISONING IN A CHILD

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Objective: Blood lead concentrations in Europe have fallen considerably over the last ten years. However significant cases of lead poisoning continue to occur. This case report illustrates some of the difficulties that occur in establishing the source of lead poisoning in a child. Case Report: A 3 year 9 month old girl was taken to her general practitioner in March 1996 with a suspected upper respiratory tract infection. She had a history of pica of soil and concrete. Her height and weight were on the 3rd centile, she had conjunctival pallor but neurological examination was normal. Blood results: Hb 6.3 g/dL, MCV 57.2 fl, blood lead 360 μg/L. She was started on iron supplements and an environmental assessment was carried out to identify the source of lead poisoning. The following samples were taken from the home: paint (lead concentration 98 μg/g), plaster (lead concentration 0 μg/g), soil (lead concentration 12 μg/g) and first-run morning drinking water (lead concentration 16 μg/L). Her parents were questioned regarding additional lead sources, in particular the use of traditional medicines or surma cosmetics. Her blood lead concentration fell to 300 μg/L in September 1996 and 240 μg/L in March 1997 but rose again to 460 μg/L in July 1997, at which time her Hb was 10.7 g/dL and her weight on the 3rd centile. As a result of this rise in her blood lead, a course of chelation therapy was

prescribed. Due to her poor compliance with oral medication, she was admitted for a course of intravenous calcium disodium edetate, 40 mg/kg bodyweight twice daily for five days. She tolerated this well and fourteen days after chelation her blood lead was 140 μg/L. It was only during this admission that further very detailed questioning of the parents revealed that she was often seen with snooker chalk in her mouth. Analysis of this chalk showed a lead content of 7200 μg/g. Three months after chelation therapy (November 1997) she was no longer exhibiting pica, her Hb was 12.2 g/dL and her blood lead was 240 μg/L. At follow up in January 1999 her Hb was 12.5 g/dL and her blood lead was 130 μg/L, her height was on the 40th centile and weight on the 25th centile and she was progressing normally in school. Conclusions: Snooker chalk is a possible source of lead poisoning of sufficient severity to require chelation therapy. This is the first such case to be described in Europe.

135 ORAL LEAD POISONING TREATED SUCCESSFULLY WITH DMSA AND SURGERY

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Objective: The role of treatment with DMSA versus surgery in lead poisoned subjects with lead retained in their body is unclear. The aim of this study was to evaluate DMSA treatment and lead kinetics in a patient with an unusual type of oral lead poisoning. Case report: A 52-year-old man was admitted to hospital complaining of nausea and abdominal pain. He also had problems concentrating. Blood lead concentration was measured to 3.4 μmol/L (0.7 mg/L). He claimed the lead poisoning to be a result of an accident with melted lead in which he was severely burned. Abdominal X-ray demonstrated large amounts of radiopaque small pellets in the colon ascendens area. The patient, however, denied oral intake of lead. He was given DMSA treatment (7 days) 3 times, each associated with a decrease in blood lead concentration, and a rebound effect in blood lead concentration after treatment. Urinary lead excretion was significantly increased during DMSA therapy. Colonoscopy revealed lots of lead shots in the ascending colon. Because of the large amount, shots could not be removed by endoscopy. Confronted with these findings, the patient admitted oral intake of lead presumably because he was confused. The blood lead concentration remained high despite DMSA treatment, and the shots did not move on repetitive abdominal X-rays. Laparatomy was therefore performed. A total of 895 lead shots (total weight 120 g) was removed. He was given two additional treatments with DMSA with similar beneficial effects on the lead kinetics. His clinical condition gradually improved as the blood lead concentration fell to reference values. Control X-ray of the abdomen revealed only a couple of shots left in his right flank. Conclusion: Although DMSA treatment is associated with a significant decrease in blood lead concentrations and an increase of lead urinary excretion, invasive procedures should be considered if lead is retained in the body. If endoscopy fails to remove lead shots from the gut, surgery might be indicated as demonstrated in the present case.

136 DMPS IN THE TREATMENT OF CHRONIC LEAD POISONING

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Background: 2,3-Dimercapto-1-propane sulfonic acid (DMPS) is a newer water-soluble metal chelating agent, useful for treatment of chronic lead poisoning, available in intravenous and oral form. In the literature only a few clinical data and experiences exist about lead chelation with DMPS. Case Report: A 59-year-old woman had vague, non-specific gastrointestinal symptoms—loss of appetite, abdominal pain, severe constipation—for three months before admission. Physical status was normal, except evident pallor. The laboratory evaluation revealed normocytic, normochromic anemia (Hb 80), basophilic stippling, reticulocytosis and mild increase of liver transaminases. In further diagnostic processes δ-aminolevulinic acid dehydratase: 242 nmol/L (normal 500–1000 nmol/L), erythrocyte protoporphyrin: 7670 nmol/L (normal $<$ 534 nmol/L), δ-aminolevulinic acid in urine: 69 μmol/L (normal $<$ 53 μmol/L), coproporphyrin in urine: 2150 nmol/L (normal $<$ 336 nmol/L) were found. Whole blood lead concentration was (86.4 μg/dL). The reason for poisoning was the lead containing polish of a small earthen pot, which she had been using. Our patient was treated with DMPS (Dimaval®). On the first day she received 250 mg Dimaval every 4 hours in short infusions, on the second day 250 mg every 6 hours and during the next 10 days 3 capsules per day. She becomes asymptomatic after a few days of treatment. Because of still persistent moderate anemia and blood lead concentration 53.4 μg/dL we continued treatment with Dimaval in doses recommended by the producing company (4 days intravenous and 8 days oral). Three weeks after treatment all laboratory findings were in normal ranges, blood lead concentration was 11.1 μg/dL, except erythrocyte protoporphyrin was 9500 nmol/L. The provocative chelation test with Dimaval was negative. We stopped the treatment. Conclusion: Treatment of this chronic lead poisoning was successful and without complications. The

patient has not developed any side effects. During the treatment the renal function remained normal, concentrations of microelements (Zn, Mg, Cu) and iron were at normal levels. DMPS has proved to be an effective chelating agent in intravenous as well as in oral form. In two successive treatments 19.45 mg lead was excreted in urine. The daily urinary excretion of lead in the first two days was abundant: 10.48 mg in the first treatment and 3.82 mg in the second. In following 10 days mean daily urinary excretion was 0.276 mg. During the treatment daily diuresis was 2000–3000 mL. Unfortunately we do not have any experience of treatment by oral doses of DMPS only.

137 URINARY EXCRETION OF TRACE ELEMENTS IN HUMANS AFTER SODIUM 2,3-DIMERCAPTOPROPANE-1-SULFONATE (DMPS) THERAPY

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Objective: To evaluate the effects of intravenous 2,3-dimercaptopropane-1-sulfonate (DMPS) on urinary excretion of essential trace elements in subjects who received this chelating agent as a mercury 'challenge' test. Subjects: Eleven subjects sought medical attention due to hearsay about the toxicity of mercury released from dental amalgam fillings. Design: The subjects were given intravenous DMPS 3 mg/kg. Spot urine samples were collected 1 hour before and after the DMPS dose and sent to us for laboratory analysis. Besides the mercury analysis we measured the urinary excretion of copper (Cu), zinc (Zn), selenium (Se), magnesium (Mg), manganese (Mn), molybdenum (Mo), chromium (Cr), cobalt (Co), and aluminum (Al). Results: A significant increase in the urinary mercury excretion (2 to 151 fold) was observed after the DMPS dose. The DMPS treatment lead to an increase of 1.2 to 103-fold in the Cu excretion, 1.9 to 43-fold in the Se excretion, 1.5 to 43-fold in the Zn excretion and 1.5 to 38.5-fold in the Mg excretion. Conclusions: In this study an intravenous DMPS 'challenge' test produced a significant increase in urinary Hg excretion and leads to an increased excretion of Cu, Se, Zn and Mg.

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138 A CASE OF SERIOUS BISMUTH POISONING TREATED WITH EARLY DMPS WITHOUT SEQUELA OF RENAL FAILURE

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Background: Tripotassium dicitratobismuthate (TDB; De-Nol) is an effective and safe treatment for peptic ulcer. Acute bismuth poisoning is a rare event which usually results from deliberate overdose with De-Nol or absorption of bismuth from gauze in wounds. In acute overdose it causes gastrointestinal upset, acute renal failure and peripheral neuropathy. Objective: We report a case of acute bismuth overdose resulting from De-Nol which was treated with oral sodium 2,3-dimercapto-1-propane sulfonic acid (DMPS). Case report: A 13-year-old girl was admitted 4 h after a deliberate overdose of 24 De-Nol tablets (2.88 g bismuth subcitrate). On admission she was well and examination was unremarkable. Baseline investigations showed normal full blood count and renal function. Blood was taken for bismuth levels. In view of the high risk of morbidity associated with this overdose a decision was made to start chelation treatment. DMPS (30 mg/kg/day) was given orally for 10 days followed by a further 9 days at 10 mg/kg/day. No adverse effects of chelation treatment were observed. She remained asymptomatic throughout the chelation therapy and 2 weeks later was clinically well with normal renal function. Bismuth levels were measured by atomic absorption spectroscopy. Serum bismuth level was 300 μg/L 4 h post ingestion. Chelation treatment was started approximately 24 h post ingestion. Forty eight hours post-ingestion blood bismuth levels were 14 μg/L and 72 h later were 8μg/L. Ten days post ingestion blood bismuth level was 1.8μg/L. Discussion: We are aware of only 6 cases of bismuth poisoning resulting from ingestion of De-Nol. Five cases are in the published literature and 1 in records of the National Poisons Information Service, London. In these cases the serum bismuth levels ranged between 260 and 1600 μg/L. All patients had significant morbidity resulting from bismuth poisoning including renal failure (6/6), gastrointestinal upset (3/6), confusion (1/6) and proximal myopathy (1/6). Only 1 patient died. Only one previous patient has been treated with DMPS. This patient had established renal failure and also received haemodialysis before and during chelation therapy. Conclusions: We have described a case of bismuth poisoning treated with early chelation therapy. This treatment appears to be safe and

should be considered in all cases of significant bismuth overdose. In this case it is likely that renal failure has been avoided by the early use of chelation therapy.

139 CLINICAL COURSE OF AN INTOXICATION WITH 5.8 G BARIUM NITRATE $BA(NO_3)_2$

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Case report: A 23-year-old male after having dissolved 13 sparklers in water drank this solution of 5.8 g of barium nitrate in a suicide attempt. He experienced nausea, vomiting, generalized muscular weakness. He complained about tingling paresthesiae in his hands and feet. He was unable to stand upright or to sit. In an upright position he could not hold his head nor raise his arms for more than four seconds. Ventilation was not compromised with a peak flow of 400 L/sec. He showed no signs of shock. The ECG showed no abnormality. Under potassium substitution at admission he still exhibited hypokalemia and hypophosphatemia. Abdominal X-ray revealed no opaque deposits. Treatment consisted of symptomatic measures and replacement of potassium 240 mmol/24 h. Symptoms resolved within 28 hours after ingestion. Toxicokinetics of barium: Barium concentrations in serum declined according to a two compartment kinetic. The α-half life was 5 hours, the β-half life 14 hours. In urine not more than 10 mg barium could be found within 36 hours. Barium excreted in the stool amounted to 57 mg in this time. Even if the bioavailability of barium after barium nitrate ingestion is low the barium recovery was tiny in this case. Discussion: Intoxications with soluble barium salts leads to muscular weakness, hypokalemia and hypophosphatemia. Paresthesiae and cardiac dysrhythmias are common. Most of the barium is excreted with the stool, renal clearance is very low. From our case it is likely that most of the barium may be retained in the body. Possibly barium is stored in bones, like strontium which is a ion with similar physicochemical properties.

140 INTRAVENOUS ELEMENTAL MERCURY INTOXICATION IN A DRUG ADDICT

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Objective: Intravenous self-administration of metallic mercury is rare. Roden and Fraser-Moodie (1993)[1] report over 30 cases, among which there have been three deaths. Case reports are usually associated with suicide attempts and psychiatric patients. Mercury may be oxidized to the soluble mercuric ion and may produce chronic poisoning. Case report: A 16-old boy heroin addict injected elemental mercury from one thermometer into his antecubital vein in an attempt at suicide. Mercury level on admission in blood and urine was 21.4 μg/L and 183.3 μg/L, respectively (limits: 15 μg/L and 20 μg/L in blood and urine, respectively). The patient was treated with the chelator (DMPS) in two courses during 17 days altogether. Six weeks after the therapy blood level fell to 8.1 μg/L and increased in urine to 397.6 μg/L. A chest radiograph showed widespread deposits of metallic mercury throughout both lungs. The patient was followed up for 1 year. The last levels of mercury were 4.59 μg/L and 27.1 μg/L in blood and urine, respectively. With the exception of temporary increased enzymuria (NAG, *N*-acetyl beta-glucosaminidase) no other signs and symptoms of mercury poisoning were observed. The deposits on X-ray disappeared almost completely. Conclusion: Prompt chelation therapy probably prevented serious mercurialism in intravenous elemental mercury intoxication in young drug addict. Temporary increased enzymuria was the only sign of subtle renal tubular injury. Reference: [1]Roden R, Fraser-Moodie A. Self-injection with mercury. *Injury Br J Accid Surg* 1993;**3**:191–192.

141 THE CLINICAL MANIFESTATIONS, PATHOPHYSIOLOGY, AND MANAGEMENT OF INTRAVENOUS MERCURY: A CASE REPORT

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Objective: Mercury is a complex toxin; clinical manifestations are determined by the chemical form, route, dose and acuity of exposure. We describe the pathophysiology of intravenous mercury exposure. Case report: A 40-year-old African American male, in previously good health, injected 3 mL of elemental mercury (Hg) intravenously into his left hand as a suicide attempt. He also ingested an additional 3 mL of Hg. Chest (CXR), abdominal and left extremity radiographs revealed metallic foreign bodies overlying both chests, without evidence of infiltrate or atelectasis, within the abdomen, especially the bowel, and the vasculature at the injection site. Immediate symptoms were local tenderness

and erythema at the injection site. Within 24 hours, the patient became increasingly short of breath (respiratory rate 24), tachycardic (heart rate 104 bpm), and febrile (101°F). The patient was placed on 40% O_2 facemask. Initial ABG revealed a pH of 7.49, pCO_2 of 35.5, pO_2 of 60.9 and HCO_3 of 26.5. CXR revealed right basilar atelectasis, scattered pulmonary infiltrates, and embolized mercury bilaterally. The ECG revealed sinus tachycardia with changes consistent with pulmonary embolism. Blood/urine mercury levels were 20.8 μg/dL and 216 μg/L respectively. A V/Q scan demonstrated matched ventilation/perfusion deficits. Diffusion and pulmonary function tests revealed a diffusion deficit and restriction pattern, respectively. Aggressive pulmonary therapy and chelation using DMSA (Chemet) was started. Over the next 36 hours the patient's pulmonary function improved. Three days later supplemental oxygen was discontinued; the patient could perform daily functions without dyspnea or shortness of breath. Follow-up ABG revealed a pH of 7.47 pCO_2 of 33, pO_2 of 72, and HCO_3 of 24. Symptoms at discharge were mild exertional dyspnea. Discussion: Mercury is found in three forms: elemental, organic and inorganic. Elemental mercury inhalation can produce pneumonitis and respiratory distress. In the body elemental mercury is oxidized to inorganic mercury, a potent irritant, and directly toxic to a variety of organ structures, including the kidneys. Chelation therapy is used for a variety of metal poisonings. BAL and DMSA can be used for both elemental and inorganic mercury exposures. BAL is associated with increased brain levels of Hg, is administered parenterally, and can cause a variety of adverse reactions. DMSA can be given orally, and has a good safety profile. Conclusion: Clinical manifestations of intravenous elemental mercury vary from the asymptomatic to the significantly symptomatic. Whether to initiate chelation therapy, the choice of agent, and the duration of treatment for these patients remains controversial. The impact of chelation on long-term outcome remains unclear.

142 URINARY MERCURY EXCRETION DUE TO DENTAL AMALGAM FILLING IN CHILDREN

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Objectives: Dental amalgam (DA) is the major source of inorganic mercury (Hg) exposure in the general population. DA contains around 50% Hg, which is a toxic element. Since children are more at risk, it was aimed to study the relationship between amalgam filling and urinary Hg excretion in 5–7-year-old children prospectively. Methods: Children admitted to the Pedodontic Department with no previous amalgam fillings and in a good state of health, who had one or more carious posterior teeth were selected. Morning urine samples were collected in polyethylene containers before and 9–12 days after amalgam fillings. All fillings were placed in one session for each child using Sina (Iran) amalgam powder and Degussa (Germany) Hg, which were mixed by an automated electric amalgamator (Dentomat3, Germany). A rubber dam was used to prevent amalgam contact with the soft tissues of the oral cavity. The children were asked not to consume chewing gum until the end of the second urine collection. Specific gravity (SG) of the urine samples were measured by a densitometer (ATA60, Japan) and urine Hg concentrations were estimated by an atomic absorption (Perkin Elmer, Model 3030) using the mercuric hydride system. The data were analyzed by the statistical package for social sciences using paired samples t-test and parametric correlation tests. The numeric values are shown as mean ± s.d. Results: Thirty one children (14 M & 17 F) aged 6.13 ± 0.92 years and weighing 19.70 ± 3.28 kg were studied. Urinary Hg concentrations before and after amalgam fillings were 3.11 ± 1.58 and 4.26 ± 1.81 μg/L, respectively ($p < 0.0001$). The mean SG in both groups of urine samples were similar (1021.97 ± 7.21 and 1021.45 ± 6.93, respectively). Therefore, the results after adjustment were identical (3.11 ± 1.58 and 4.26 ± 1.82 μg/L, respectively). There was no statistically significant correlation between the urinary Hg concentrations and any other variables including number and surfaces of filled teeth, weight, age or sex. Conclusion: Although there were highly significant increases in urinary Hg concentration after amalgam filling with no apparent health effect, no significant correlation was found between the urinary Hg concentration and the amount of amalgam in filled teeth. However, more investigation is required to find out the possible health hazard effect of Hg released from amalgam.

143 ACUTE COLLECTIVE THALLOTOXICOSIS: THREE CASES

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Since thallous salts are colourless, tasteless, and odorless, their sale in France is strictly licensed because of their toxicity

and potential for use in murder. Hence thallium poisoning has become exceptional. We report a collective intoxication where the three victims died. Case report: 1. A 23-year-old man was admitted on May 15th, 1999 to a clinic Emergency Room in Madrid, Spain, following digestive signs and a rapidly progressive sensory-motor polyneuropathy evoking a Guillain-Barré syndrome. Four hours later, this resulted in hypoventilation and led to respiratory failure, so the patient was intubated and placed under mechanical ventilation. Two months later, he presented alopecia. Death occurred on day 90 after a refractory cardio-vascular failure. 2. The victim's mother's aunt, a 71-year-old woman, came to visit the patient in July 1999. She presented a rapidly progressive sensory-motor polyneuropathy affecting mainly the lower limbs, myalgia, and digestive signs six days after a meal taken with the third victim. Five days after the first signs she was admitted to the Neurology Department of Orthez Hospital, France. Three days later, palsy of the cranial nerves occurred as well as cardiovascular autonomic neuropathy with variations in blood pressure. Lumbar puncture, biological results and CT scan were not contributive to diagnosis, and botulism was eliminated. The patient died on day 10, after a period of refractory cardiogenic shock. 3. The father of the first patient, a 55-year-old male, was admitted into the same clinic in Madrid, with the same initial neurological and digestive symptomatology. This occurred on the same day as the meal taken with the second victim. Results of EMG, lumbar puncture, CT scan and MRI also showed no abnormality. A respiratory failure led to intubation and he was placed under mechanical ventilation. The victim also died on day 10, after a period of refractory cardiogenic shock. Toxicological analyses were made on autopsy pieces: thallium was found in all the samples of the three victims. The origin of the thallium was not clearly established. Discussion: The main clinical features of thallotoxicosis are gastroenteritis, peripheral neuropathy, and alopecia. The last sign usually occurs at least two to three weeks after the intoxication, and is not evident in the acute forms of thallotoxicosis. The final diagnosis was delayed here because the call to the Poison Center was made very late in the course of the poisoning.

144 DO PESTICIDES DESERVE THE 'BAD RAP' THEY GET IN THE US?

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Objectives: Currently, public opinion pollsters report that Americans fear pesticides far more than tobacco smoke—apparently even more than Europeans fear 'Frankenfoods'. The question is, of course, 'Do data from the last decade support such a phobia?' Methods: Acute morbidity and mortality data from pesticides were gathered from the annual reports of the American Association of Poison Control Centers for the last decade and compared with comparable data for carbon monoxide and ethylene glycol. In addition, data dealing with exposures were culled from the annual reports of the state of Washington's Pesticide Incident Reporting and Tracking Panel since 1989. Finally, national data dealing with chronic conditions in childhood were appraised on the assumption that detrimental effects of chemicals—were they to exist—would be reflected in chronic morbidity and mortality data. Results: Over the past decade, more than 595,000 total pesticide cases were reported to the AAPCC; among these there were 124 deaths, with 67% being classified as suicidal. Moreover, a total of only 14 deaths in children aged less than 10 were attributed to 'pesticide poisoning'. In contrast, carbon monoxide accounted for some 130,000 cases, with 327 deaths, again with many suicidal efforts. Similarly, ethylene glycol's track record continues to burgeon with some 45,000 case reports with 104 deaths—more than 80% of which were related to suicide, but with only 1 death—a homicide—among 7,100 children. Review of chronic morbidity and mortality figures from the United States shows a continuing decline in incidence of both—save for the occurrence of what is classified as 'asthma' and certain unusual forms of acute leukemia—wherein improved diagnostic accuracy serves as an enormous confounder. Conclusion: In the author's opinion, current data simply do not begin to explain in any way, shape, or form the US public's paranoia about pesticides. Conceivably, exaggerations and extrapolations from the 'DDT fiasco' as popularized by Rachel Carson's 'Silent Spring' in 1962 is etiologic. Perhaps our society is simply experiencing hesitancy in accepting 'any and all synthetic chemicals' as it seeks to return to the 'good old days'. Or conceivably our media have been more successful than might be expected in popularizing the heritage of organophosphate pesticides from their forebears of 'nerve gases'—still available to terrorists on a worldwide basis. Personally, I would hypothesize that paranoia about genetically modified foods in the US is unlikely to achieve enough status to replace pesticides as the leading target of ridicule. But, candidly, I'd be optimistic that a media campaign alerting our population to the horrendous dangers of 'aliens from outer space' might just succeed in removing the focus from pesticides.

145 DEATHS FROM PESTICIDES POISONING IN NORTH OF FRANCE: 1988–1998

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Objective: To describe the epidemiology of recent pesticide poisoning deaths in the north of France. Method: Descriptive analysis of pesticide-related deaths in the north of France from 1988 through 1998 based on death reports from both sources: hospitals and forensic institutes. Population studied: All poisoning deaths, 1988 through 1998. Results: We reviewed data from 354 poisoning death reports, of which 30 (8.5%) were considered to be related to pesticides. Of these, 23 were suicides by ingestion and 7 were unintentional. Two unintentional deaths occurred after occupational respiratory exposure. Twenty died during hospitalization after 1 to 30 days (mean time: 3 days). Mean age was 42 years (min: 17; max: 82). No deaths occurred in children under 16 years. Deaths in males were almost two times higher than in females. Poisoning resulted from exposure to one pesticide in 24 deaths, 2 pesticides in 5 cases and 3 pesticides in 1 case. Herbicides caused 16 deaths of which 8 were paraquat or diquat; insecticides caused 11 deaths of which 4 were organophosphates and 3 pyrethroids; rodenticides and fungicides were involved in 3 and 2 deaths respectively. Although pesticides are an uncommon source of suspected poisoning in the region (4–5% of cases reported to Lille Poison Center, LPC), the mortality remains high at least in male adults due to suicidal ingestion. If pyrethroid toxicity seems to be underestimated, paraquat and diquat are well known for their high toxicity and remain the most frequent pesticides responsible for poisoning deaths despite preventive measures concerning formulation and information. Probably because of the general public and workers' awareness of pesticide toxicity, these substances may be an easily available means to commit suicide. No deaths were reported in children under 16 years although 54% of suspected pesticide exposure incidents involve this age group (2839 reported by LPC, 1988–1998). This can be explained by the small amount of accidentally ingested pesticide by children compared to intentional suicidal exposure by adults. Conclusion: Prevention of deaths related to pesticides should give priority to reduction of the concentration of pesticides in products available for consumers to reduce as much as possible the amount of substance possibly ingested during suicidal attempts.

146 SERUM GLUFOSINATE LEVEL PREDICTS SEVERITY OF POISONING CAUSED BY THE INGESTION OF A HERBICIDE CONTAINING GLUFOSINATE

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Objectives: The suicidal ingestion of a herbicide BASTA® containing 20% glufosinate ammonium and 33% anionic surfactant is increasing in Japan. This herbicide is used over 80 countries, including Canada and USA where recombinant plants resistant to glufosinate are cultivated. In 1998, a severe case of BASTA® ingestion was recorded in Canada. BASTA® produces central nervous system (CNS) signs, such as coma, apnea, and generalized convulsions, with a latent period of 8-38 hours.[1] Though, patients look asymptomatic during the latent period, they deteriorate unexpectedly. If we can predict the severity during the latent period, the treatment will be more safe and effective. Because the CNS signs are considered to be due essentially to glufosinate,[2] we studied the relationship between the serum glufosinate level ([GLF]s) and severe CNS signs. Method: We collected cases of acute BASTA® poisoning, referring to MEDLINE and Japana Centra Revuo Medicina, and records of the Japan Poison Information Center. From 1990 to May 1999, we found 74 cases of acute BASTA® poisoning where [GLF]s on admission was measured. The severe cases were defined as those who developed at least one of the following signs: coma, apnea, and generalized convulsions that are common and need life-saving respiratory management. Patients who developed none of these signs were defined as non-severe. Results: We obtained 42 severe cases (male 16, female 26; 22-86 year-old), and 32 non-severe cases (male 21, female 11; 20–86 year-old). When [GLF]s on admission was plotted semi-logarithmically related to the time from ingestion, severe cases were located higher than non-severe cases. Above the A-line, connecting 200 ppm at 2 hours and 15 ppm at 8 hours, all cases were severe. Below the B-line, connecting 70 ppm at 2 hours and 5 ppm at 8 hours, all cases were non-severe. Between A-line and B-line, 50% (6/12) were severe cases. Eighty percent of cases were above the A-line or below the B-line. Conclusion: [GLF]s on admission had a close relation to the development of severe CNS signs in acute BASTA® poisoning. Measurement of [GLF]s on admission by HPLC, which needs only 2–

3 hours[3], may be valuable in the treatment of acute BASTA® poisoning. References: [1]*Oxford Textbook of Critical Care*. Oxford University Press 1999:657–659. [2]Koyami K. Glufosinate and a surfactant: which component produces effects on the central nervous system in acute oral BASTA poisoning? *Vet Hum Toxicol* 1999;**41**:341. [3]*Bunseki Kagaku* 1997; **46**:66–74.

147 SEVERE POISONING WITH THE HERBICIDE GLUFOSINATE (BASTA®)

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Objective: Glufosinate is a derivative of glutamic acid, which inhibits glutamine synthetase selectively in plants. In the literature 80 poisoning cases were reported in Japan. Experience shows that the ingestion of more than 100 ml Basta® (18.3 g glufosinate) may produce coma, severe seizures, and respiratory and cardiovascular depression. We recorded a case of ingestion of a very high dose, that was treated successfully. Case report: A 50-year-old woman ingested 1000 mL Basta® with suicidal intent. She vomited spontaneously some minutes after ingestion. Early gastric lavage, forced diarrhea, administration of activated charcoal and forced diuresis were performed. Despite these measures, critically increasing central, respiratory and cardiovascular depression occurred 14 hours after ingestion. The patient was intubated intratracheally and artificial respiration performed. High doses of catecholamines (norepinephrine, dobutamine) were necessary to stabilize blood pressure and renal function. For the next 7 days the patient was adjusted under controlled sedation with diazepam. On day 9 sufficient spontaneous respiration was restored. Psychomotor function recovered slowly during the next 4 days. The patient presented retrograde amnesia, motor and amnestic aphasia, diminished vigilance and poor cooperation. A motor weakness of the right leg persisted for a longer period. Conclusion: After ingestion of potentially lethal doses of glufosinate a life-threatening situation may develop several hours after ingestion, despite vigorous and early measures to prevent absorption and to enhance elimination. Because the chemical structure of glufosinate is similar to glutamate, a potent excitatory neurotransmitter, sufficient sedation with benzodiazepines may reduce the risk of severe seizures and cerebral damage.

148 CHLORALOSE POISONING. A SERIES OF 49 CASES

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Objectives: Chloralose is still used as a rodenticide. It has a depressant action on the CNS and a stimulant action on spinal activity. Poisonings are often severe, especially because of the occurrence of coma and respiratory failure. We report a series of 49 cases with an analysis of the epidemiological, clinical, biological and therapeutic data. Case series: Over a period of 30 years, 49 cases (37 patients) of acute chloralose poisoning were admitted in the ICU: 27 were males and 10 females with a mean age of 30.9 years. Poisoning was voluntary in 96% of cases and 17 cases were due to multiple poisonings in 5 patients. Other poisons had been ingested in 19 cases: alcohol (13 times) and drugs (6 times). The ingested dose of chloralose could be estimated in 17 cases and ranged from 3 to 30 g. Symptoms included: coma (94%), myoclonus (92%), convulsions (14%), respiratory failure (77%), bronchial hypersecretion (32%), hypothermia (25%), hyperthermia (44%). The EEG showed in 34 cases either an irritative aspect or a more typical aspect of myclonic and/or epileptic status. Biological abnormalities included metabolic acidosis (10/41 cases), hyperleukocytosis (46%) and rhabdomyolysis (10/21 cases). Qualitative analysis of chloralose by a colorimetric method was positive in urine (15/16 times), in gastric lavage fluid (9/10 times) and in plasma (4/4 times). In one case, a quantitative analysis by 'head-space gas chromatography' showed concentrations of 96.9 mg/L in blood and of 41.8 mg/L in urine. In this case 228 mg chloralose (7.6% of the dose ingested) was eliminated in urine during 48 hours. Symptomatic treatment included mechanical ventilation in 37 patients and anticonvulsants, especially diazepam, in 40 patients. High doses of anticonvulsants were often needed in order to control convulsions and myoclonia. Gastric lavage was performed in 40 cases but its efficacy was not evaluated. Seven patients developed complications, especially bronchopulmonary infection. All patients recovered. The mean hospital stay was 3.8 days. Conclusion: Chloralose poisoning is usually severe, often life-threatening and justifies the admission of the patient into an intensive care unit. The exact toxic dose is not known and individual sensitivity seems to play a role. Despite the clinical severity, prognosis is good if adequate symptomatic treatment is applied rapidly.

149 THE SCOTTISH EXPERIENCE OF PESTICIDE POISONING SINCE 1963

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Objective: To evaluate the impact of enquiries concerning pesticides on the work of the Poisons Centre. Method: Enquiries concerning pesticides were reviewed from 1963. Five hundred and eighty-two pesticide enquiries received since 1 Jan 1997 were retrieved from our relational database and analysed in more detail. Results: The Scottish Poisons Information Bureau (NPIS Edinburgh Centre) has been answering telephone enquiries on poisoning since 1963, mainly from Scotland and the North of England, both of which contain large rural areas. In that time we have received 157564 telephone enquiries of which 10632 (7%) concerned pesticides. Pesticide enquiries reached a maximum annual rate of 502 in 1981 and have now fallen to around 200. This contrasts with developing countries where pesticide ingestion is a common method of attempted suicide. Since 1997, 9% of the 582 enquiries were for general information (compared with 4% of all enquiries), 4% concerned animals (<1% of all enquiries) and 7% concerned chronic exposure. The types of pesticides involved were insecticides (42%), herbicides (27%) rodenticides (15%), slug killers (6%), fungicides (3%), wood preservatives (3%), others (4%). A comparison of the groups 0–14 years and 15–84 years showed similar percentages for insecticides, but higher percentages of rodenticides (20% against 9%) and slug killers (12% against 7%) in children and higher percentages of herbicides (33% against 19%) in adults. For calls where age was known there was a lower proportion of enquiries concerning children than in total enquiries (41% against 50%). The male/female split in children was about even but in adults there were more males than females. All exposures in children were accidental and PSS scores showed no symptoms or minor symptoms. In adults 14% were deliberate, with PSS score moderate (28) and severe (5). Only three patients were reported to have died, 2 after ingestion of paraquat and one after metaldehyde liquid. A total of 7 were coded as PSS severe. Of these 5 had features which were considered probably to be unrelated to the pesticide exposure. Overall in 8% of pesticide enquiries features were thought to be unrelated to the pesticide exposure compared with 2% of all enquiries. The most common pesticides involved in enquiries were paraquat (10%), permethrin (7%), glyphosate (6%), metaldehyde (3%) and difenacoum (3%). Twenty-three enquiries referred to sheep dips or pour-on treatments for infestation in sheep. Conclusions: Pesticide enquiries do not form a large part of enquiries to a poisons centre in a developed country but exposure can rarely be fatal. Exposure or potential exposure to pesticides seems to cause undue concern to patients and doctors.

150 EXTRAPYRAMIDAL SIGNS RELATED TO ORGANOPHOSPHATE POISONINGS: 2 CASE REPORTS

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Objective: It has been documented that the poisoning by organophosphate (OP) pesticides manifests three categories of symptoms including acute cholinergic crisis, intermediate syndrome, and delayed polyneuropathy. Theoretically, cholinergic overactivity within the CNS resulting from OP poisoning may disturb the balance of neurotransmitters between dopamine and acetylcholine in basal ganglia and substantia nigra, which should have led to extrapyramidal symptoms. However, extrapyramidal signs, including acute dystonia, coarse tremor, rigidity, choreoathetosis, drooling etc., following OP poisoning have only rarely been reported. We will present two cases with transient extrapyramidal signs following OP poisoning and try to further delineate the clinical picture of OP poisoning. Case report: Two patients were referred from local hospitals to our emergency department within one month because of OP poisoning. The first was a 71-year-old female patient who drank an unknown amount of some OP. PAM and atropine were given soon after admission. Initial RBC and plasma cholinesterase levels were both 2 UKAT/L. She developed respiratory failure several hours after poisoning. Tremor, blepharoclonus, drooling, hyperreflexia, dysarthria, neck stiffness, cog-wheel rigidity, pill-rolling tremor, and shuffling gait had been experienced during hospitalization. Brain CT was done and revealed no intracranial hemorrhage. She was discharged on the 41st day with only mild gait disturbance. The second was a 44-year-old male patient who swallowed 10 ml of monocrotophos. PAM and atropine were also given soon after admission. Initial RBC and plasma cholinesterase levels were 5 and 4 UKAT/L respectively. He developed asymmetrical facial and shoulder muscle spasm, chorea, rigidity, trismus, tremor, blepharospasm and occasional facial grimacing in the subsequent days, and all the signs diminished on the 14th day. Major tranquilizers were not prescribed during hospitalization in either patient. They were discharged with no sequelae. Conclusion: Extrapyramidal signs result from the decreased ratio of dopaminergic to cholinergic activity within basal ganglia and substantia nigra. Although the mechanism of the CNS effect of OP is not well understood, it is very likely that the imbalance of the neurotransmitters

caused by OP plays an important role. We suppose that OP related extrapyramidal signs are probably not uncommon, compared to intermediate syndrome or delayed polyneuropathy, and the antidotes do not seem effective for these symptoms and signs. It should be considered for differential diagnosis when any involuntary movements other than muscle cramp or muscle fasciculation were encountered in OP poisoning patients.

151 RENAL FAILURE AFTER INGESTION OF CORTINARIUS RUBELLUS (SPECIOSISSIMUS) AND CORTINARIUS ORELLANUS

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Objective: Nephrotoxins of *Cortinarius rubellus* (previously named *C. speciosissimus*) and *C. orellanus* can give the orellanus syndrome after a characteristic long latent period (3–17 days). We present two cases of renal failure, one after ingestion of *C. rubellus*, and one after ingestion of *C. orellanus*. The latter case is the first serious poisoning reported in Norway due to *C. orellanus*. Case 1: A 56-year-old previously healthy man was admitted to hospital with renal failure. Ten days before admission he had consumed mushrooms identified as *C. rubellus*. Three days after ingestion he started complaining of diffuse bilateral loin pain, increased crude urine, nausea and malaise. Physical examination showed BP 200/100 mm Hg, pulse 84 bpm, the other findings were normal. Laboratory tests included creatinine 1975 μmol/L, K 6.8 mmol/L, Na 135 mmol/L, BUN 52 mmol/L, Ca 1.73 mmol/L, P 5.6 mmol/L. Hemoglobin, WBC and liver function tests were normal. At admission hemodialysis was started. The patient was transferred to his native country (Germany) for further treatment. Case 2: A 32-year-old previously healthy man was admitted to hospital with nausea, vomiting, vertigo and bilateral loin pain lasting for six days. Ten days before admission he had ingested part of a mushroom identified as *C. orellanus*. Blood pressure, pulse and other physical examination were normal. Urine examination revealed albumin, leucocytes and erythrocytes, but no casts. Laboratory tests included creatinine 1291 umol/L (increased to 2064 the next day), K 6.4 mmol/L, Na 128 mmol/L, Cl 85 mmol/L. Other extensive diagnostic tests for the etiology of the renal failure were negative, including testing for *C. orellanus* toxin (orellanin) in renal biopsy material. Renal biopsy demonstrated normal glomeruli, but tubulointerstitial damage and inflammation. Hemodialysis was started, and his renal failure appears to be permanent (for 5 months so far). The brother of the patient is presently under examination as a possible donor for future kidney transplantation. Conclusion: This is the first report of renal failure after ingestion of *C. orellanus* in Norway. Ingestion of *C. rubellus* and *C. orellanus* both resulted in end-stage renal failure following a latent period of about 10 days. No specific treatment is available. Therapy is aimed at the end-stage renal disease, including dialysis and possible transplantation.

152 HEPATIC INJURY AFTER INGESTION OF *GYROMITRA ESCULENTA IN CHILDREN*

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Objective: A frequent cause for mushroom poisoning is mistaking edible mushrooms for their poisonous doubles. There are also poisoning cases with poisonous mushrooms considered edible after appropriate cooking. The false morel *(Gyromitra esculenta)* belongs to the latter group. We report two severe cases in children. Case 1: An 11-year-old boy complained about abdominal pain 12 hours after ingestion of only short roasted fungi. About 30 hours after ingestion relapsing vomiting began. He was admitted 48 hours after ingestion in a bad state with somnolence, abdominal pain, paleness, and scleral icterus. Laboratory parameters: Quick's time 45%, antithrombin III 77%, total bilirubin 164 μmol/L, indirect bilirubin 164 μmol/L, direct bilirubin <20 μmol/L, transaminases in the normal range. Course: 50 hours after ingestion hemodialysis was performed aimed at a fast decrease of bilirubin and the elimination of possible toxic metabolites of the mushroom poison. The patient was hemodialysed again accompanied by symptomatic measures on both following days. The control of the EEG showed negligible changes of cerebral functions 60 hours after ingestion, and was inconspicuous after 84 hours. Total bilirubin decreased rapidly, transaminases rose 110 to 130 hours after ingestion (aspartate aminotransferase up to 268 U/L, alanine aminotransferase up to 461 U/L), lactate dehydrogenase up to 537 U/L. Seventeen days after ingestion all laboratory parameters had been normalized. Case 2: The patient's sister complained about abdominal pain 24 hours after consumption of the same mushroom meal. She was also admitted 48 hours after ingestion with nausea, abdominal pain, paleness, as well as scleral and skin icterus. Laboratory parameters: Quick's time 50%, antithrombin III 92%, total bilirubin 132 μmol/L, indirect bilirubin 132 μmol/L, direct bilirubin

<20 μmol/L, transaminases in the normal range. Urinalysis: erythrocyturia. The further course was dominated by the abnormal coagulation parameters (minimum 4 days after ingestion) and a rise of the transaminases (maximum 7 days after ingestion). The patient was hemodialysed three times. Under further symptomatic measures the clinical features and laboratory parameters returned to normal. Conclusion: In both cases an acutely toxic quantity of the false morel was ingested, resulting in liver damage within 48 hours. Evidently the toxin was not destroyed by the kind of cooking employed (short roasted mushrooms). Symptomatic measures and hemodialysis were sufficient for complete remission of all symptoms without detectable organ damage until now.

153 THE CLINICAL EXPERIENCE OF TAIWAN COBRA (*NAJA NAJA ATRA)* BITE

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Background: Six epidemiologically important poisonous snakes currently exist in Taiwan. The cobra is classified as a neurotoxic snake. Its venom possesses neurotoxic, cardiotoxic and hemotoxic properties, the clinical features of cobra bite are various, depend on the species and the ratio of the venous component. Methods: All the cases of Taiwan cobra bites recorded by the Poison Control Centre (PCC) during the period 1986–1998 were retrospectively reviewed. Their clinical pictures were abstracted. Results: We studied 36 patients from PCC during 1986–1998. The primary lesion, almost all patients being bitten presented with local swelling (94.4%); 13.9% had limb paresthesia, 8.3% patients had local bruising, 2.8% had hemorrhage or blisters. Among the patients with local swelling, 26.4% had swelling over one joint. Complications included 27.8% with tissue necrosis, and 11.1% had poor wound healing. One patient who had tissue necrosis developed osteomyelitis later. Neurotoxicity was suspected in only one patient, but no definite diagnosis was confirmed. Regarding general symptoms and signs, 22.2% of patients were febrile; 8.3% with a decrease in blood pressure; 11.1% with GI symptoms, 5.6% with headache/dizziness, 5.6% with lethargy, 5.6% with sore throat and 5.6% with chest tightness/difficulty in breathing. Both mortality and typical signs of neurotoxicity were absent. One patient had atypical neurotoxic symptoms. The management modalities included incision 13.9%, neurotoxic antivenin 94.4%, debridement 19.4%, skin graft 13.9%, amputation of finger 2.8%, hyperbaric oxygen therapy 2.8% and herb therapy 16.7%. Conclusion: Bites by the Taiwan cobra produce a distinctive clinical picture characterized by prominent local effects with little neurotoxicity. A high percentage of necrosis and infection was noted even after anti-venom administration. The reasons might include improper dosage, late timing of administration, or lack of antivenin efficacy against tissue necrosis. To minimize the morbidity and mortality of snakebites, a system to assist diagnosis and appropriate treatment needs to be exercised.