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1 INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

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Background: Pharmacokinetics is a term that is used to describe the processes by which drugs and xenobiotics reach their sites of action in man and are subsequently eliminated. The processes involved include absorption, distribution through the blood to other organs, for many compounds subsequent metabolism, and finally processes by which the parent and metabolites are eliminated from the body. The term pharmacodynamics describes the effects of the interaction that occurs between drugs and chemicals at their sites of action. These sites of action may be receptors, enzymes, or in the case of some toxins, molecular mechanisms in cells or membranes. Pharmacokinetics: In clinical toxicology most compounds are ingested via mouth and exert their effects after systemic absorption. Absorption usually occurs in the small bowel, very little occurring from the stomach directly. The principal reason for the small bowel being the site of absorption is its very large surface area and the fact that the stomach has a low pH. The distribution of drugs around the body is governed by factors such as blood flow, which will influence the speed at which drugs accumulate in any organ, and lipid and water solubility, which alters membrane permeability. The principal routes of elimination of drugs are via the kidney (unchanged and metabolites), and liver, where metabolism occurs to more water-soluble compounds, including conjugates. These compounds are again either excreted via the bile or via the kidney. In some instances drugs excreted directly into bile (e.g. digitoxin) and are then reabsorbed as they pass down the gut. This process is known as entero-hepatic recirculation. For most drugs the quantity of enzyme available to metabolize them exceeds the amount of drug present in the body and in these circumstances the drugs undergo what is termed first order kinetics. Under these circumstances the amount of drug metabolized is proportional to dose and it is possible to plot the fall in blood concentration against time. This fall is log-linear and enables the calculation of a half-life. Elimination can also be measured by using clearance, that is the apparent volume of blood from which all of drug would be removed in a fixed time. This term is pharmacokinetically more pure, but used less often in practice than the half-life. For some drugs the processes of elimination can be saturated either at therapeutic dose (e.g. phenytoin, ethanol) or at toxic dose (e.g. aspirin) and under these circumstances it is not possible to plot a simple half-life. This is called zero-order or saturation kinetics. The quantity of a drug or toxin removed can be expressed in terms of mass/unit time (e.g. g/h) but plots of log concentration against time are non linear. The clinical consequences of zero order kinetics are that unexpectedly large increases in blood concentrations occur from relatively smaller increases in dose of the drug. The distribution of drugs through the body can be expressed by a theoretical space, apparent volume of distribution. This relates the plasma concentration of the drug to the total amount in the body in any one time. For very fat-soluble drugs it may be large, several L/kg and for water-soluble drugs will be proportionally smaller, of the order of 0.5–0.6 L/kg body weight. This knowledge may have implications for the appropriateness of treatments such as hemodialysis, which is only likely to be effective for drugs with relatively small volumes of distribution that are water-soluble. Pharmacodynamics: Drugs and receptors usually behave in a fashion that can be understood by using the law of mass action. The higher the concentration present, the greater the effect. A ceiling effect occurs beyond which increases in dose of drug produce no greater effect. Terms used to describe pharmacodynamic actions include the word agonist, a compound that acts on a receptor to produce a response. Antagonists are compounds that interact at a receptor producing no intrinsic effect of their own, but preventing the effect of agonists when present. Partial agonists are drugs that produce a partial effect on the receptor, preventing the effects of full agonists, and failing to achieve the same maximal effect as a full agonist, even in high dose. Examples would be: full agonist–morphine; partial agonist–buprenorphine; antagonist–naloxone. Similar interactions occur when drugs or xenobiotics acts on enzyme sites. Here however the interaction tends to be

between a substrate and an active site, or an enzyme inhibitor and an active site. In toxicology the pharmacodynamic effects being observed, whether they are on receptors or enzymes, may sometimes occur as a result of metabolites of the ingested compound, furthermore, because of organ failure that may occur as a result of ingestion of a toxin, the distribution and elimination of agents during the poisoning may be different from those observed under normal conditions. To illustrate some of the implications of these theories in practice four examples will be used: atenolol, morphine, thioridazine and paracetamol.

2 INFLUENCE OF PHARMACOKINETICS AND TOXICODYNAMICS ON ANTIDOTE USE

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Background: The efficacy of an antidote to reverse the effects of a specific poison depends on several factors which include: (1) the kinetic, dynamic and mechanism of action of the toxic compound, (2) the kinetic, dynamic and mechanism of action of the antidote, (3) the kinetic of the antidote-poison complex if the antidote acts by a chelating mechanism. An ideal antidote should fulfill the following criteria: a kinetic which is not modified by repetitive or continuous administration and/or by organ failures and which is adapted to the kinetics of the poison, a rapid effect and a close kinetic-dynamic relationship with a wide therapeutic index and without adverse side effects. Furthermore, the modalities of administration should be easy and the cost cheap. Discussion: According to their mechanism of action, antidotes can be classified into 3 groups: (1) The antidotes which modify the kinetic of the poison either by a chelating effect (chelating agents of heavy metals, immunotherapy, hydroxocobalamin) or by interfering with the metabolism of the poison (ethanol, 4-methylpyrazole, *N*-acetylcysteine), or by increasing the elimination routes (sodium sulfate); (2) The antidotes which modify the dynamic of the poison by removing the poison from its target organ or receptor (flumazenil, naloxone, oxygen) or by reactivating enzymes (oximes); (3) The antidotes which reverse partially or completely the toxic effects but without direct effect on the kinetic or dynamic of the poison (Na^+–Ca^{++} salts, catecholamines, atropine). The duration of action of the antidote is closely related to its kinetic but the modalities of administration (dosage, repeated doses) have also to take in account the kinetic of the poison. The clinical efficacy of the antidote is dependent on the mechanism of action of the poison. For functional poisons (benzodiazepines, opiates, digoxin, organophosphates) the administration of the antidote usually improves the symptoms (dynamic effect) if adequate doses, depending on the law of mass action, are administered. Antidotes are indicated if clinical or biological abnormalities are present and the dosage and duration of treatment can mostly be easily adapted according to the evolution of the clinical or biological disturbances: coma score and respiratory failure for benzodiazepines and opiates, ECG disturbances and hyperkalemia for digoxin, cholinesterases for organophosphates). For lesional poisons (paracetamol, methanol, ethylene glycol, heavy metals), antidotes should be ideally administered before cellular or organ damages have occurred. Indeed, if cellular damage has occurred, the antidote may have no clinical effect despite a kinetic efficacy: e.g. chelating agents in symptomatic heavy metal poisonings. The administration of the antidote should be based on the dose ingested or, preferably, on the plasma concentration of the poison. The duration of the treatment depends on the kinetic of the poison and should be guided by the monitoring of the plasma concentrations. Conclusion: The understanding of the kinetic-dynamic relationships of antidotes and poisons is essential for an adequate use of the antidotes. In practice, most antidotes can be used without monitoring of the antidote and/or poison plasma concentrations (Table 1). However, the monitoring of the plasma concentration is essential in poisonings where there is a delay in the onset of symptoms or where precise clinical or biological criteria are not available.

Table 1

Dynamic and Kinetic Criteria for the Administration of Antidotes

	Criteria for the Use of the Antidote			
Antidote	Clinical Symptoms	Biomedical Investigations	Plasma Concentrations of Poison	Antidote
Atropine	+++	—	—	—
Calcium gel	+++	—	—	—
Flumazenil	+++		—	—
Naloxone	+++		—	—

Table 1. Continued

Antidote	Criteria for the Use of the Antidote			
	Clinical Symptoms	Biomedical Investigations	Plasma Concentrations of Poison	Antidote
Catecholamines	+++	ECG	—	—
Antivenom	+++	Coagulation	—	—
Hydroxycobalamin	+++	Blood gases, lactates	—	—
Dantrolene	++	CPK	—	—
Methylene blue	++	Methemoglobinemia	—	—
Glucagon	++	ECG	—	—
Calcium IV	++	ECG	—	+Ca
Sodium bicarbonate IV	++	ECG	—	+Na
Oximes	++	Cholinesterases	—	—
Beta blockers	++	ECG	+/−Theophylline	—
Anti-digoxin Fab	++	K, ECG	+Digoxin	—
Deferoxamine	+		+Iron	—
BAL	+		+Metal	—
DMPS	+		+Metal	—
DMSA	+		+Metal	—
Ethanol	+	Blood gases, osmolality	+EG, methanol	+Ethanol
4-methylpyrazole	+	Blood gases, osmolality	+EG, methanol	—
N-acetylcysteine	—		+Paracetamol	—

3 CHALLENGES OF TOXICOKINETIC STUDIES FOR CASES OF HUMAN POISONING

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Introduction: The application and utility of toxicokinetics has achieved general acceptance in animal models of toxicity with toxicokinetic data used in studies for risk assessment, new drug development, and regulatory compliance. The determination of pharmacokinetic variables in humans who have overdosed or have been poisoned is an area with substantial promise and pitfalls. Discussion: In contrast to pharmacokinetic studies in healthy human volunteers, studies in poisoned patients differ in their uncontrolled, ill-defined, dynamic, and extreme circumstances, which can influence the toxin's absorption, distribution, metabolism, and elimination. Examples of these factors include slowed absorption due to formation of poorly soluble concretions in the gastrointestinal tract, slowed gastrointestinal motility, or toxin-induced hypoperfusion; decreased serum protein binding; increased volume of distribution associated with toxin-induced acidemia; slowed elimination due to saturation of biotransformation pathways or toxin-induced hypothermia; and prolonged toxicity due to formation of longer-acting metabolites. Concurrently ingested toxins may further alter the pharmacokinetic or pharmacodynamic characteristics of a toxin. Measurements of serum concentrations are made in a dynamic physiologic environment that is influenced by the treatment, toxin and patient's general state of health. Limitations of toxicokinetic studies in human poisonings are exemplified by the apparent poor correlation of serum concentrations with toxic symptoms in several life-threatening overdoses such as those from iron, calcium channel antagonists, cocaine, and tricylic antidepressants. The promise of toxicokinetics may be better fulfilled with the development of a scientific framework for its application for human poisonings. To facilitate harmonization of toxicokinetic findings, reports should include essential criteria such as a reasonable estimation of time of exposure, only single substance exposures with laboratory confirmation thereof, a sufficient number and timing of samples, reporting of vital signs and level of consciousness concurrent with sample acquisition, history of recent exposure to other drugs, stratification of single overdoses versus chronic or acute on chronic exposures, reporting of the detection limits of analytical techniques, and the relative time of starting gastrointestinal decontamination procedures. Overarching initiatives should include the development of meta-analysis techniques to aggregate clinical reports, validation of limited sampling models to adequately characterize pharmacokinetic variables, and determination of the value of population pharmacokinetic estimation techniques. These approaches require a balance of ethical concerns, financial costs, clinical utility, and scientific benefit to justify toxicokinetic studies in humans who have been poisoned. Conclusion: Systematic analysis of toxicokinetics holds promise

to identify unique patient risk factors, new treatment approaches, and improved understanding of pharmacological activity under extreme conditions. With efforts directed towards some standardization of the application of pharmacokinetics to poisoned patients, a better understanding of the principles, techniques and value of toxicokinetics can be achieved.

4 TOXICOKINETICS AND TOXICODYNAMICS: THE IMPACT OF pH CHANGE

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Introduction: Despite the wide use of alteration of pH in treating some poisoned patients the actual mechanism of its effect is not always clear. The mechanisms that are understood will be reviewed and theoretical possibilities will be discussed. The most easily understood clinical use relates to the manipulation of pH to alter the ratio of ionized and non-ionized drug. The passive diffusion of drugs across the charged phospholipid barriers of cell walls is dependent on lipid solubility, concentration gradient and the ionization status of the drug. Ionized drugs are effectively trapped by their poor lipid solubility. The magnitude of the potential effect on the ratio between ionized and non-ionized drug by altering pH can be predicted using the Henderson-Hasselbalch equation: where a pH change of X produces a 10^X change in the ratio of ionized to non-ionized drug (See table). As most drugs exist as either weak bases or weak acids all drugs are potentially susceptible to pH alteration.

Table of pKa Values

Acidic Drugs: $HA + H_2O \Leftrightarrow H_3O^+ + A^-$		Basic Drugs: $A + H_2O \Leftrightarrow HA^+ + OH^-$	
Drug	pKa	Drug	pKa
Acetylsalicylic acid (Aspirin)	3.5	Carbamazepine	7.0
Phenobarbital	7.4	Verapamil	8.7
		Theophylline	5.2
		Dothiepin	8.5
		Pralidoxime	8.0
		Amphetamine	9.8

For acidic compounds:

pH = pKa + log ([ionized drug]/[non-ionized drug])

For basic compounds:

pH = pKa + log ([non-ionized drug]/[ionized drug])

The clinical utility of pH alteration is dependent on the drug having significant renal excretion, which can be influenced by changes in ionization, and/or altering the distribution of drugs. Drugs that may benefit from altering distribution should have a concentration response curve that is steep enough to anticipate that a physiologically tolerated change in pH will result in a fall in effective drug concentration at the target site. In addition pH may have direct effects on receptor binding sites, alterations to a drug's binding affinity or influence metabolism. Renal excretion: Enhancing renal salicylate excretion by altering urine pH is possibly the best understood intervention. Salicylic acid is filtered by the glomerulus and secreted in the proximal tubule. Non-ionized salicylic acid can diffuse back into renal tubule cells. A shift in urinary pH from 6.0 to 8.0 will increase the ionized:non-ionized ratio by 100 fold (316:1 to 31600:1) The effect of such changes on drug clearance can be easily measured. For drugs where there is a clear concentration response relationship enhancing elimination translates into clinical improvement. Known physiochemical properties of compounds (e.g. pKa) along with knowledge of their renal handling allow us to predict the effect of altering pH. Other clinical uses include the acidification of urine to reduce phenobarbital clearance in the treatment of barbiturate withdrawal. Non-clinical uses include the alkalinization of urine to reduce amphetamine clearance. Systemic drug redistribution: In salicylate toxicity the correction of systemic acidosis increases the ionization fraction and should reduce the movement of salicylate through the cell wall. Tricylic antidepressants provide a dramatic example of the therapeutic benefit of systemic alkalization. The administration of sodium bicarbonate or hyperventilation can produce a rapid improvement

in cardiac conduction. The alteration of pH is likely to achieve this effect through multiple mechanisms. The most commonly cited mechanism is increased protein binding that may lead to a reduction of free TCA. Evidence from other sodium channel blockers suggests that there is significant ionization trapping within the sodium channel and that altering pH increases non-ionized drug fraction and diffusion back into the cell. Finally, altering pH may have a direct effect on the function of voltage-gated channels. Thus for the example of tricyclics it is plausible to entertain at least 3 pH dependent mechanisms that can ameliorate toxicity. If that is the case what are the possibilities for other drugs. Other mechanisms: In organophosphate poisoning it is known that the function of organophosphate hydrolase is pH sensitive. In addition, the binding of pralidoxime is pH sensitive. The function of acetylcholinesterase (AChE), aging of OP-AChE complex and reactivation is also pH sensitive. Conclusion: Altering pH has an established role in clinical toxicology. An appreciation of the potential number of pH sensitive sites of action that may be operative suggests that theoretically alterations of pH may have an adjunctive role in other poisons and merits further examination for those toxins which still present significant clinical problems

5 IMPLICATIONS OF TOXICOKINETICS AND TOXICODYNAMICS FOR ADMISSION AND DISCHARGE OF PATIENTS

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Background: The study of toxicokinetics-toxicodynamics (TK-TD) relationships may be helpful not only for the determination of severity scores or prognostic criteria, but also for the decision about patient disposition. According to the clinical findings and to the results of investigations including toxicological analysis, the emergency physician has to define the following strategy: should the patient be admitted to the hospital? In which environment: general ward, emergency room or intensive care unit (ICU)? For which purpose: monitoring, epuration techniques or specific antidotal therapy? Which criteria should be applied for patient discharge? These questions can partly be answered by the knowledge of the mechanisms of toxicity. Schematically, the toxic substances may be classified into functional toxins, lesional toxins or substances with combined toxicity. It is usually admitted that with functional toxins, there exists a good relationship between plasma concentrations and toxicity, when toxicity is caused by the main substance and not by the metabolites. The severity of the symptoms is then related to the present concentration of the toxin at the target organ. With central nervous system (CNS) depressing drugs, this simplistic relationship is observed after barbiturates or meprobamate overdoses in patients who are not chronically treated by these substances. The determination of blood concentration on admission may predict the depth of coma or the risk for cardiovascular collapse and the patient should be referred to the appropriate medical facility. Additionally, the duration of the life-threatening manifestations is influenced by toxicokinetics, and, with some experience, it is not so difficult to estimate when the patient could be weaned from the ventilator or discharged from the ICU in the absence of unexpected complications. But, in clinical practice, such clear-cut TK-TD relationships are often missing. This can be explained by several factors affecting either toxicokinetics or toxicodynamics. For example, with benzodiazepines, there is a weak relationship between blood concentrations and clinical symptoms. This is mainly due to the presence of active metabolites that are not routinely detected. Another usual explanation is the development of tolerance in patients chronically treated by benzodiazepines. But the most common reason is probably multiple drug ingestion. Synergetic effects are then observed on the CNS and benzodiazepine blood levels do not predict toxicity. Admission or discharge of the patient should be based on the importance of neurological or respiratory disturbances. Exceptionally, the combination of two substances may exert protective effects: the co-ingestion of benzodiazepines in tricyclic antidepressant overdose can prevent seizures. The significance of TK-TD relationships for patient disposition is also illustrative in theophylline and lithium poisoning. Toxicity in both cases is amplified by the chronic use of the substance. Young patients with acute ingestion of immediate release preparations of theophylline have usually mild clinical effects. They should be admitted to the ICU when the serum level exceeds 80 to 100 μg/mL or when they develop more serious clinical symptoms. In contrast, patients who have ingested sustained release products should be admitted to a monitored setting. This is also the case for elderly patients with chronic overdose and with serum levels greater than 40 to 60 μg/mL. The same reasoning applies for lithium toxicity. Patients with acute overdose may tolerate higher lithium levels without developing neurological effects and patients with chronic toxicity may develop significant neurological effects at levels that are only mildly elevated or even within the normal range. These should be referred to the ICU until clinical symptoms resolve. To conclude with CNS acting drugs,

serotonin syndrome is now frequently observed since the introduction of selective serotonin reuptake inhibitors (SSRI). The toxic manifestations are not dose-related but idiosyncratic. Life-threatening manifestations may progress rapidly. The admission of the patient to a specialized area should be guided only by the prompt recognition of severity signs (hyperthermia, hypertonia and autonomic disturbances). This latter situation illustrates the limits of TK-TD relationships with some functional toxins. For cardiovascular agents, the toxicity is often related to the total amount of drug ingested and to the pharmacological properties of the substance (e.g., chloroquine). For most of the substances (calcium channel blockers, beta blockers), toxicokinetic studies are not routinely performed or are not directly helpful for the management of the patient (kalemia is more relevant than digoxin determination in digitalis poisoning). In this setting, factors influencing toxicodynamics are particularly important for patient disposition, as we know that cardiotoxicity will usually be enhanced in patients with underlying cardiovascular disease. All symptomatic patients should be admitted to a monitored setting for at least 24 hours. But in view of the toxic potential of some substances (chloroquine, calcium channel blockers), even asymptomatic patients should be monitored (or treated in case of severe chloroquine poisoning) for at least 6–8 hours until evidence of favorable outcome. This delay should be prolonged in case of ingestion of sustained release products. In the second category, lesional toxins, there is no direct relationship between blood concentrations and symptoms. However, the analysis of toxicokinetic data is important to establish prognostic criteria. The main problem is to obtain the precise timing of poisoning. This is illustrated by paracetamol poisoning. Following a single acute ingestion, plasma paracetamol concentration obtained 4 hours post-ingestion identifies the patients who are at risk of delayed hepatotoxicity and who need hospital admission. A second sampling is helpful in confusing conditions. Even at this early phase, toxicodynamics are also of importance as patients with pre-existing liver disease could develop hepatotoxicity with lower blood concentrations. When the patient is admitted with delay, toxicodynamics refer to the monitoring of liver function tests before transferring the patient to a specialized liver transplantation unit. Finally, some substances behave as functional and lesional toxins according to the timing of exposure or therapy. For example, in ethylene glycol or methanol poisoning, the decision to admit the patient to the ICU could be influenced either by toxicokinetic or toxicodynamic factors. In an asymptomatic patient, a high ethylene glycol or methanol blood concentration may justify transfer of the patient to a medical unit equipped with hemodialysis (modification of toxicokinetics), or the physician could prefer to treat the patient with recent antidotes (4-methylpyrazole) that have become available in most centers. When acidosis is present, admission to an ICU is required to correct the metabolic consequences (toxicodynamics) of poisoning. Conclusion: The understanding of the factors influencing TK-TD relationships is important before establishing admission or discharge criteria for poisoned patients. Poisoning is a dynamic process and the severity of the symptoms may be immediate or delayed according to our knowledge of the influence of TK or TD in specific poisonings. This can explain why, with some poisons, asymptomatic patients may sometimes require closer monitoring than symptomatic patients poisoned by less toxic compounds.

6 INTERACTION OF OPIATES WITH BENZODIAZEPINES IN OVERDOSES

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Objectives: Opiates and benzodiazepines are commonly used conjointly, both licitly (in the clinic and operating room) and illicitly (by drug abusers). It is well known that these two drug classes may interact to provoke untoward reactions such as respiratory depression, particularly in the setting of overdose. However, the mechanisms and quantitative relationships of these interactions remain poorly understood. Given the frequency of combined use of these drugs, particularly in the setting of drug abuse, a better understanding of the interactions between benzodiazepines and opiates appears essential. We thus undertook a randomized study of the interactions of the commonly abused benzodiazepines, flunitrazepam, with three opiates, morphine, buprenorphine, and methadone, in a median lethal dose animal model. Methods: We performed randomized, operator-blinded intravenous median lethal dose (MLD) studies in rats of morphine, buprenorphine, and methadone both alone, and proceeded by a single intraperitoneal dose of flunitrazepam. We employed the up-and-down method of Dixon and Bruce, performed in quadruplicate, also comparing time to death following opiate injection. Results are expressed as median (IQR). Results: The MLDs of morphine, buprenorphine, and methadone alone were 64.0 (34.3), 234.6 (74.1) and 22.5 (7.5) mg/kg, respectively, given alone. Their MLDs were 60.6 (30.2), 38.4 (17.7) and 13.0 (2.2) mg/kg, respectively, after pretreatment with flunitrazepam 40 mg/kg ip. Time to death for morphine, buprenorphine, and methadone alone were 2.5 (3.0), 0.02 (0.15), and 2.0 (3.5) h, respectively, and 13.5 (24.0), 24.0 (65.9), and 0.0 (0.4) h, respectively, after pretreatment with flunitrazepam 40 mg/kg ip. Flunitrazepam

significantly altered methadone ($p = 0.02$) and buprenorphine lethality, ($p = 0.02$). Morphine lethality was not significantly altered ($p = 0.77$). Time to death was only altered for buprenorphine ($p < 0.01$). Discussion: Flunitrazepam-opiate drug-drug interactions appear complex. Flunitrazepam augmented lethality two-fold in methadone-treated rats and six-fold in buprenorphine-treated rats, without significant effect on morphine lethality. Time to death was altered in the buprenorphine plus flunitrazepam group, suggesting an alteration in the mechanism of death. A review of the pharmacology of these drugs provides possible explanations for the discrepancies observed in these interactions. Particular attention is warranted with respect to differential drug-drug interactions in terms of absorption, distribution and tissue uptake, metabolism and excretion, as well as toxicodynamic interactions at opiate and benzodiazepine receptor sites. Alteration of the metabolism of one drug group by the other appears inadequate to explain the variable observations in our study. Action at various opiate receptor sites (μ, κ, δ) by the same drug may have conflicting effects, the predominant effect depending perhaps not only on the inherent propensity of the specific opiate for binding to that receptor type, but also to the dose administered. Additionally, there is a growing body of knowledge which suggests that benzodiazepines and opiates, while each having their own specific receptor sites, may modify the effects of the other drug group's specific binding sites. These interactions and their possible role in overdose deaths will be discussed.

7 NECROKINETICS: THE PRACTICAL ASPECTS OF INTERPRETING POSTMORTEM DRUG CONCENTRATIONS

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Background: Necrokinetics describes the changes in drug concentrations that occur between the time of death and the collection of the biological sample at autopsy. Drug concentrations often increase after death resulting in autopsy sample concentrations that are higher than the concentrations at the time of death. Interpretation of these analytical results requires input from both clinical and analytical toxicologists as well as medical examiners. The accurate interpretation of postmortem analytical results involves several factors: sample collection, necrokinetic changes, and the traditional concentration-toxicity relationship of the drug involved. These issues must be incorporated into the design of protocols studying the impact of death on venous blood drug concentrations. The ideal circumstance: There would be no need to interpret drug concentrations measured in autopsy samples if a blood sample was collected immediately before life ended, however, this is an uncommon situation even in the hospitalized patient. In order to understand the variables involved with postmortem sample interpretation, a description of the components of an ideal circumstance is helpful. In the ideal circumstance, the interpretation of a postmortem blood drug concentration will have a detailed description of factors associated with traditional pharmacokinetics/pharmacodynamics including 1) a description of antemortem drug dosing and time of exposure, 2) the pharmacological effects measured in the patient, and 3) the potential for tolerance to drug effects. With this information, knowledge of the blood drug concentration-effect relationship in living humans can be applied to postmortem concentrations to determine the likely contribution of the drug to the fatal event. In order to properly interpret the drug concentration measured in a post-mortem sample however, additional information is required to determine the impact of death on the concentration measured. The process of postmortem change in drug concentrations: The mechanisms of change in drug concentrations after death can be considered comparable to the physiologic mechanisms that drive pharmacokinetics. Changes appear to occur secondary to passive diffusion within the body as cell function ceases, and cellular integrity is lost. Decreases in fluid pH and shifts in water content among organs occur and can impact drug concentrations. Finally, postmortem blood flow secondary to manipulation and movement of the body as well as the development of rigor may result in changes in postmortem drug concentrations. The postmortem absorption of ethanol from the gastrointestinal tract is an example of some of these processes. Increased ethanol concentrations are observed when samples are collected from sites close to the gastrointestinal tract compared to peripheral sites.[1] There is currently no good measure of how much these factors predictably impact a blood drug concentration. In pharmacokinetics, the variable time is utilized to predict changes. After death some measure of the loss of physiologic function and decomposition is more likely to be a useful predictor of drug concentration changes than time. In order to study these factors, a concentration immediately prior to, or at the time of death must be used as the starting point. Practical issues–sample collection: One of the most clearly identified practical issues is the method and site of sample collection. Peripheral venous sites are generally used in clinical settings and provide the best data regarding blood concentration–effect relationships. Postmortem samples from peripheral venous sites would be expected to best correlate with antemortem concentrations. In addition, peripheral venous sites appear to be less susceptible to

postmortem change than central samples like heart blood. Drug concentrations can vary widely when samples are obtained from different postmortem sites.[2] Documentation of sample collection site and sample handling should always be part of drug concentration interpretation. Practical issues–drug characteristics: Ideally, different drug characteristics could be used to predict whether or not significant postmortem changes in drug concentrations will occur. There are some data suggesting that a drug's antemortem volume of distribution and the drug concentration at the time of death may be useful in predicting whether postmortem change occurs. A large volume of distribution suggests a relatively large concentration gradient between extravascular and intravascular drug concentrations. A volume of distribution greater than 2 to 3 liters per kilogram of body weight suggests that there will be significant postmortem increase.[3] It has been demonstrated that cardiac blood digoxin concentrations will increase when antemortem concentrations are therapeutic, but not when antemortem concentrations are high.[4] Ratios of parent drug to metabolite have been recommended to determine whether the ingestion of a drug was acute or chronic, however, dosing chronicity has not been evaluated as a characteristic impacting necrokinetics. Conclusion: Necrokinetic processes can result in significant changes (usually increases) in blood drug concentrations between the time of death and collection of a sample at autopsy. This change in blood drug concentration can have a profound impact on the determination of the drug's potential contribution to the cause of death. The sampling site and the drug's volume of distribution are currently the best-defined parameters that determine whether the postmortem blood drug concentration likely reflects the time of death concentration. Additional data are necessary before the prediction of perimortem drug concentrations based on autopsy samples (necrokinetics) will be routinely feasible. References: [1]Pounder DJ, Smith DRW. Postmortem diffusion of alcohol from the stomach. *Am J Forensic Med Pathol* 1995;**16**:89–96. [2]Jones GR, Pounder DJ. Site dependence of drug concentrations in postmortem blood-a case study. *J Analytical Toxicol* 1987;186–190. [3]Hilberg T, Bugge A, Beylich K, et al. The extent of postmortem drug redistribution in a rat model. *J Forensic Sci* 1999;**44**:956–62. [4]Koren G, MacLeod S. Postmortem redistribution of digoxin in rats. *J Forensic Sci* 1985;**30**:92–96.

8 HEALING METALS: THE USE OF HEAVY METALS IN THERAPEUTICS

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Through the ages heavy metals have played a central role as therapeutic agents. While the inherent toxicity of metals and the discovery of less toxic and more efficacious alternatives limit their current therapeutic use, their pharmacological utility continues to be revisited as demonstrated by the recent use of arsenic trioxide in the treatment of acute promyelocytic leukemia, and ongoing debates about mercury containing thimerosal preservatives in vaccines. Arsenic, mercury, thallium and antimony have all been used as medicines during one time or another. Arsenic: Arsenicals have been administered as nonspecific tonics and in the treatment of anemia, psoriasis and syphilis. In 1786, Thomas Fowler first reported the use of a flavored potassium arsenite solution containing 1 gram arsenic trioxide in 100 mL potassium bicarbonate for the treatment of chills, fevers, and headaches. Fowler's solution would become the first chemotherapeutic agent used for leukemia in 1865 and its use as a first line chemotherapeutic agent would continue until the 1950s. Organic arsenicals have also enjoyed wide use in therapeutics. A pivotal breakthrough in the early history of antimicrobial therapy occurred in 1907 when Paul Ehrlich discovered that arsphenamine (Salvarsan) proved to be an effective spirocheticidal agent. Ehrlich hoped that this long sort after "magic bullet" would prove the salvation of mankind. Other organic arsenicals that were used for syphilis included neoarsphenamine (31% arsenic by weight) and arsenoxide (Mapharsen) (10% arsenic by weight). Arsenicals (and mercurials) would remain the mainstay of syphilis therapy until penicillin was introduced in the 1940s. Mercury: Used as medicinal agents since antiquity, mercurial agents also enjoyed widespread use in medicine until the mid 1900s. Paracelsus was an early advocate of the use of mercury to treat syphilis and as a diuretic. Mercury would remain at the forefront of antisyphilitic therapy until the introduction of the arsenicals. Beginning in the 17th century calomel, mercurous chloride, would assume a major role in therapeutics (along with blood letting) producing powerful stimulant and purgative effects. An 1863 medical journal described the role of calomel as "the central sun around which the whole world of medicine revolves." Its use was targeted at eliminating the highly undesirable gastrointestinal contents thought to prevent a proper healthful state and it was prescribed for fevers and all types of infectious diseases. To achieve the desired therapeutic effect, it was not uncommon to increase the dose of calomel until signs of acute mercury poisoning such as salivation and gingivostomatitis were noted. At times as much as 13 grams (200 grains) were given as a single dose. Popular 18th and 19th century mercury formulations included the "Guy's Hospital pill" containing calomel, squills and digitalis, and Townsend's Mixture consisting of red mercuric oxide, potassium iodide, syrup of orange, tincture of cardamon and water. Thomas Dover, the originator of Dover's powder (containing opium and ipecac), was also known as the Quick Silver Doctor for his enthusiastic advocacy of

mercury for the treatment of most everything from apoplexy to worms. Labeled as poison and dispensed as 125 mg or 500 mg tablets, mercuric bichloride (corrosive sublimate) was used as a disinfectant to sterilize clothes (eg. diapers) and was also used for the treatment of scabies and lice. Although calomel therapy would eventually become obsolete, less toxic organic mercurials such as mercurochrome, merthiolate, and thimerosal would continue to be used as antiseptics. Other organomercurials (eg. Novasurol) were used as potent diuretics from 1920s to the 1960s. Thallium: Thallium was used as depilatory in treatment of scalp ringworm in children in 1930s until its toxicity mandated its removal from the market. Antimony: Another metal known to the ancients, was commonly used as a medicinal agent from the 16th to 18th centuries. Despite awareness of its toxicity, trivalent antimonial compounds such as antimony potassium tartrate (tartar emetic) was frequently prescribed for melancholy, wound healing and leprosy, and used as an emetic and purgative. According to the 1941 Martindale's Extra Pharmacopoeia, 60 to 120 mg of antimony oxidium was recommended as a diaphoretic, expectorant and emetic. Less toxic pentavalent antimonials compounds (eg. sodium stibogluconate) continue to be used to treat a variety of protozoal infections such as leishmaniasis.

9 UNUSUAL WAYS TO BE POISONED BY METALS

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Objective: Metals are ubiquitous substances that affect nearly every aspect of daily life and are essential to modern civilization. However, metals may also be a scourge of society. Heavy metal poisoning is a significant environmental issue, especially in developing nations, but it does not discriminate between the social or economic stature of its victims—nearly everyone is at risk of being poisoned inadvertently by heavy metals. The symptoms of heavy metal poisoning may be subtle and not associated with a well-identified toxidrome; therefore, it is incumbent upon the clinician to consider heavy metal poisoning in the differential diagnosis of poorly defined maladies, especially when they occur in special populations. An extensive medical history that explores the use of all recognized and home remedies, as well as an occupational history may reveal exposure to heavy metals. There are a multitude of unusual ways to be poisoned by heavy metals. Discussion: The resurgence of alternative medicine and reliance on folk remedies has resulted in numerous reports of heavy metal poisoning; this is especially true within ethnic communities. Empacho (a stomach ailment) is treated commonly with a variety of lead salts (azarcon-lead tetroxide; greta-lead oxide; albayalde-lead carbonate) and even mercury salts by Mexican-Americans. As the "remedy" is administered, the gastrointestinal symptoms may worsen, prompting the administration of even more of the toxic metal and ultimately a cycle of chronic poisoning. Southeast Asians have been known to utilize a mixture of lead and arsenic (pay-loo-ah) for the treatment of fever and rash. An Indian remedy for the management of back pain (maha yogran guggulu) contains lead and may result in lead poisoning. In addition to the use of metal salts as traditional remedies, there is growing concern over the contamination of herbal products with metals. Significant concentrations of arsenic have been identified in homeopathic medications. Heavy metal poisoning has occurred as a consequence of using metals to treat various forms of cancer. Cottage industries have evolved throughout the world. As such, they may operate informally and illegally and avoid being monitored by federal agencies that are charged with insuring occupational and environmental safety. Heavy metal poisoning has been reported in artisans working with pottery, dyes, stained glass and jewelry. The use of mercury to extract gold from ore while working over a kitchen stove produced mercury poisoning in an infant. Home smelting of old automobile batteries for lead and smelting to recover copper and other metals from discarded electrical wiring continue to be an often unrecognized problem. Lead from ammunition is a source of classical plumbism. Retained lead bullets or lead shot may result in poisoning. Often overlooked is lead poisoning from the inhalation of lead that circulates in the air of improperly vented indoor shooting ranges. Conclusions: The diagnosis of heavy metal poisoning is often a diagnosis of exclusion. It is critical that clinicians be familiar with the common and uncommon sources of heavy metal poisoning so that heavy metal poisoning can be recognized expeditiously.

10 THE BIOLOGY OF ERYTHROCYTE PROTOPORPHYRIN AND ITS ROLE IN THE DIAGNOSIS AND MANAGEMENT OF METALS INTOXICATION

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Heme is an essential molecule found in red blood cells and cytochrome P-450 enzymes. Heme synthesis occurs via a complex pathway that begins with linkage of glycine and succinyl Co-A then ends with the incorporation of an iron atom into erythrocyte protoporphyrin (EP). The liver and bone marrow produce most EP. Porphyrins have a red fluores-

cence when exposed to ultraviolet light, making their measurement rapid and cost-effective. Normal values for EP are <35 μg/dL whole blood (<0.622 μmol/L) or <3 μg per gm hemoglobin (<70 μg per mole of heme). Iron deficiency is the most common cause of an elevated EP. Several inborn errors of EP production exist including acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT) and erythrocytic protoporphyria (EPP). In each of these, a disorder of enzyme function leads to abnormal production of porphyrins with resulting skin and/or neurological toxicity. Secondary disturbances in EP production result from exposure to environmental toxins. For example, halogenated hydrocarbons can produce either AIP or PCT; an outbreak of PCT with >3000 victims occurred after exposure to hexachlorobenzene in Turkey in 1955. Certain metals can also disturb EP synthesis; these include mercury, arsenic, aluminum, cobalt and gallium arsenide. Studies among dentists have found a correlation between mercury exposure and urinary coproporphyrin excretion; the same effect has been observed among arsenic-exposed smelter workers. However, EP is most abnormal after exposure to lead. The hallmark of lead poisoning is an elevated EP; the degree of elevation is a direct measure of physiologic toxicity (EP as a "metabolic sentinel"). EP can also be used to monitor the effects of chelation therapy. Methods: We measured [EP] serially in 56 children undergoing chelation therapy with d-penicillamine for blood lead levels (BLL) 15–40 μg/dL. Results: Mean age was 33 ± 17 months. Mean initial BLL was 24 ± 5 μg/dL. EP was significantly higher in anemic children (58 vs. 33 μg/dL) despite comparable BLL. The correlation between BLL and EP was r = .84, p = .001 for children without iron deficiency. After d-PCN chelation, BLL fell to 15 ± 6 μg/dL (mean fall 37%) while EP fell to 32 μg/dL (mean fall 20%). Conclusions: (1) EP correlates closely with BLL in non-anemic children, and (2) EP falls in parallel with BLL during d-PCN chelation. The same effect occurs after EDTA and DMSA chelation. There is a role for EP in the assessment of individuals with significant metals poisoning. The ease of EP measurement makes it particularly useful for conducting large, population-based studies of environmental exposure to toxic metals.

11 TOXICOKINETICS OF LEAD AND MERCURY IN MAN AND ANIMALS WITH SPECIAL RESPECT TO RENAL CLEARANCE AND ITS IMPACT TO CHELATION TREATMENT

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Objectives: Toxicokinetics of heavy metals are characterised by two main limiting factors, distribution in certain body compartments and redistribution as well as renal excretion via glomerular filtration. It is believed that enhancement of renal excretion may improve the clinical course of intoxications. The treatment of heavy metal intoxications is therefore based primarily on the administration of chelators that increase renal excretion. A number of studies exist that show an increase of urinary concentrations of heavy metals by administration of such compounds (EDTA, BAL, DMPS, DMSA). However, there are only few studies balancing input and output. Heavy metals, in particular, lead distribute into deep compartments that may also contribute significantly to the overall clearance. For instance, experiments with rabbits have shown that renal clearance of lead does only amount to 1/100–1/500 of total clearance showing that distribution limits the clearance and not renal excretion. This contribution will give an overview on the toxicokinetics of lead and mercury, with special respect on studies that characterise and balance the renal clearance. Animal and human studies will be considered. Methods: Taking the term "lead" a literature evaluation in 25 literature databases revealed 54.052 hits, with 18.414 hits linked to "human" and 827 to "kinetics". Out of these 827 citations, in 37 "clearance" data are published. Only in 8 publications, however, data to calculate the renal clearance of lead were found. The same evaluation for "mercury" revealed 88.225, 22.486, 236, and 12 hits. Renal clearance was calculated by the formula $Cl_{ren} = U * V/P$. (U: Urine-concentration, V: Urine-volume, P: Plasma/Blood-concentration). In some papers, only the urine concentration was given. In that case a daily volume of 2 liters of urine was assumed. Results: Lead: The kinetics of lead is characterised by distribution into deep compartments (bone, brain).[1] In blood, 95% of lead is found in erythrocytes. Most of the publications deal with chronic intoxications; with blood levels from 48 to 116 μg/dL.[2,3,4,5,6,7,8,9] Renal clearance of lead was estimated from these publications in a range between 0.7 to 9 mL/min. This is equivalent to ~1–5% of inulin-clearance resp. creatinine-clearance. Animal experiments show similar results. In our own study[10] with rabbits the renal clearance was calculated to 0.01–0.35 mL/min, which is less than 1% of the inulin clearance (~30 mL/min). Only very few data exist evaluating effects of chelators on the renal clearance of lead. Markowitz[4] showed that administration of $CaNa_2EDTA$ led to renal clearance 0.8 to 1.3 mL/min. A study performed by Graziano et al.[7] In a cohort of workers chronically exposed to lead revealed a renal clearance of ~0.2 mL/min without treatment, which was than stimulated during the following days to ~2–9 mL/min, after doses of 10,

20 and 30 mg DMSA/kg/day. To our knowledge, there is no publication studying the renal clearance under administration of DMPS in humans. Our own study in rabbits did not show any enhancement of excretion nor changes in lead blood levels. Mercury: As shown in a study by Sällsten et al.[11] the kinetics of mercury can be characterised by a two compartment model with a mean half life of 3.8 (range 3.1–5.1) and 45 (range 28–121) days for the respective fast and slow phase of the plasma concentration decay. Plasma and whole blood concentrations did not differ. This shows that in contrast to lead mercury does not distribute to erythrocytes. Renal clearance of mercury in persons with acute or chronic exposure revealed 1 to 8.4 mL/min. A study by Cicini et al.[12] showed that renal excretion of mercury can be enhanced 10fold by DMPS. The renal clearance rose from 3.9 mL/min to 33 mL/min. In a case study, however, Pfab et al.[13] stated that chelation treatment did not enhance urinary excretion of mercury after ingestion of thiomersal. Conclusions: The results of the evaluation suggest that the effects of chelators on renal clearance may be very controversial. DMSA seems to be the most effective one, a compound showing the highest binding capacity, although there are reports on clinical improvement on lead intoxications with other chelators than DMSA. Comparing lead and mercury, the clearance of lead seems to be limited more extensively than that of mercury due to its distribution and re-distribution to compartments such as bones and brain, but also to erythrocytes. References: [1]Rabinowitz MB, Wetherwill GW, Kopple JD. Kinetic analysis of lead metabolism in healthy humans. *J Clin Invest* 1976;**58**:260–270. [2]Autenrieth T, Schmidt T, Habscheid W. Bleivergiftung durch griechische Keramiktasse. *Dtsch Med Wschr* 1998;**123**:353–358. [3]Wahid A, Koul PA, Shah SU, Khan AR, Bhat MS, Malik MA. Lead exposure in papier maché workers. *Hum Experi Toxicol 1997*;**16**:281–283. [4]Markowitz ME, Rosen JF. Assessment of lead stores in children: Validation of an 8-hour Ca-Na_2EDTA provocative test. *J Pediatr* 1984;**104**:337–341. [5]Chisolm JJ. Safety and Efficacy of Meso-2,3-dimercaptosuccinic Acid (DMSA) in Children with Elevated Blood Lead Concentrations. *J Toxicol Clin Toxicol* 2000;**38**:365–375. [6]Aono H, Araki S. The effects of CaEDTA injection on lead, zinc, copper and ALAD in erythrocyte, plasma and urine in lead-exposed workers: a 24-h observation. *Int Arch Occup Environ Health* 1984;**55**:13–18. [7]Graziano JH, Siris ES, Lolacono N, Silverberg Sj, Turgeon L. 2,3-Dimercaptosuccinic acid as an antidote for lead intoxication. *Clin Pharmacol Ther* 1985;**37**:431–438. [8]Kákosy T, Hudák A, Náray M. Lead Intoxication Epidemic Caused by Ingestion of Contaminated Ground Paprika. *J Toxicol Clin Toxicol* 1996;**34**:507–511. [9]Araki S, Murata K, Aono H. A comparison of the diminution rates of lead in blood and lead mobilized by CaEDTA after termination of occupational exposure: a long-term observation in two lead workers. *J Toxicol Clin Toxicol* 1983;**20**:475–486. [10]Heinemeyer G, Begemann K, Scharmann W, Wolff D, Palavinskas R, Gundert-Remy U. Effects of DMPS on kinetics of lead in rabbits. *J Toxicol Clin Toxicol* 2000;**38**:222. [11]Sällsten G, Barregard L, Schütz A. Decrease in mercury concentration in blood after long term exposure: a kinetic study of chloralkali workers. *Brit J Industr Med* 1993;**50**:814–821. [12]Cichini GM, Petzl DH, Zeitlhofer J, Wolf Ch, Meisinger V, Strasser K, Schuster E, Jahn O. Effekt von DMPS und D-Penicillamin bei inhalativer Intoxikation mit metallischem Quecksilber. *Intensivmed* 1989;**26**:303–306. [13]Pfab R, Mückter H, Roider G, Zilker T. Clinical course of severe poisoning with Thiomersal. *J Toxicol Clin Toxicol* 1996;**34**:453–460.

12 LEAD TOXICOKINETICS: A BIOKINETIC MODEL

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Objective: Exposure to lead is ubiquitous. From ancient times on this naturally occurring metal has been used abundantly, resulting in environmental exposures of the entire population. This exposure can be increased by additional exposure to occupational, recreational, and hobby lead sources, or the use of lead-contaminated products such as herbal medications and folk remedies. Blood lead levels can be measured quite simple. Interpretation of these blood lead levels can be quite another thing and in order to do this correctly, good knowledge of the circumstances of exposure and the biokinetics of lead in the human body is required. To help understand the behavior of lead a biokinetic model for lead metabolism was developed. Given a certain exposure, this model can be used to calculate total lead body burden and help predict the benefit of chelation therapy. Methods: Based on the concept of Kneip[1] a four-compartment model with first-order kinetics was used. First the kinetic model was fitted and distribution and elimination coefficients were established by using references from the literature. Second, the model was tested and refined by simulating a variety of exposure modalities and therapy situations. Simulation of chelation therapy is possible by adding an extra elimination constant to the model, linked to the blood compartment. In order to develop this biokinetic model two computer programs were used: Ph edsim, copyright MediWare B.V. 1993 and MW-Pharm pharmacokinetic analysis in clinical pharmacy

version 3.0, copyright MediWare 1991. Results: The blood compartment is the central compartment from which lead is distributed after uptake in the body. The blood contains about 4% of the total body burden of lead, and the half-life of lead in blood is about 30 days. From this compartment lead is distributed relatively fast to the soft tissues (represented by the kidney and liver compartments) and the bone. The distribution constant from blood to bone is much higher than the one from bone to blood, which results in an accumulation of lead in bone. Cumulation in soft tissues is much less because the distribution constants from the soft tissues to the blood are much higher than the distribution constant from bone to blood. This means that lead is released from the soft tissues via the blood to the bone and only a very small portion (2%) of the total amount of lead in the body can be found in these soft tissues. The half-life in the soft tissues is about 30–40 days. As lead accumulates in bone, most of the body burden can be found in this compartment: 94%. It is very important to realize that this is a dynamic situation and therefore the amount of lead in the various compartments depends on changes in other compartments. Especially with regard to chelation therapy for elevated blood lead levels due to chronic exposure, the model is very helpful in visualizing the toxicokinetics of lead in the human body. Because of a slow release of lead from the bone compartment blood lead concentrations will return to almost the starting level after cessation of chelation therapy. Simulations carried out over a longer time period very elegantly illustrate the kinetics of lead. Conclusions: Biokinetic models in general are very helpful as a tool to provide insight in the behavior of specific substances or elements in the human body. This specific model on lead biokinetics can be of value in establishing well-considered guidelines for treatment of lead intoxications. References: [1]Kneip TJ, Mallon RP, Harley NH. Biokinetic modelling for mammalian lead metabolism. *Neurotoxicology* 1983;**4**:189–192. [2]Vries I de, Spaans E, Dijk A van, Meulenbelt J. Lead toxicokinetics. Development of a biokinetic model to understand and predict the outcome of treatment. *Przeglad Lekarski* 1998;**55**:500–504.

13 LEAD INTOXICATION: ORAL DMSA–VS–INTRAVENOUS SODIUM CALCIUM EDETATE

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DMSA: DMSA (2,3-dimercaptosuccinic acid, succimer) is a water-soluble analogue of dimercaprol that may be administered orally (usual route) or intravenously. It is absorbed rapidly but incompletely after oral administration. Peak plasma concentrations occur 2–3 hours after oral administration. DMSA is metabolized extensively to mixed disulfides of L-cysteine and one or more metabolites of DMSA undergo enterohepatic circulation.[1] Some 10–25% of an administered dose is excreted in the urine (the majority within 24 hours), predominantly (>90%) as DMSA-cysteine disulfide conjugates. The 1 : 2 DMSA: cysteine metabolite is an active chelator of lead and it appears to play a major role in ameliorating lead toxicity.[2] Renal clearance of total DMSA was greater in healthy adults (77 ± 13.2 mL/min/m^2) than in adults (24.7 ± 3.3 mL/min/m^2) or children (16.6 mL/min/m^2) with lead poisoning. Renal clearance of DMSA metabolites was also much greater in healthy adults (64.6 ± 10.1 mL/min/m^2) than in adults (35.4 ± 8.4 mL/min/m^2) or children (19.5 mL/min/m^2) with lead poisoning.[3] These data suggest that renal elimination of DMSA and/or its metabolites may be impaired in adult patients poisoned with lead (lead may interfere with renal tubular secretion of DMSA) and that the distribution of DMSA in children may be different than in adults. The elimination half-life of DMSA (parent drug plus oxidized metabolites) has been calculated to be 2–3 hours depending in part on the age of the patient. Animal data suggest that DMSA reduces rather than enhances the gastrointestinal absorption of lead[4] and does not result in redistribution of lead to the brain from soft tissues.[5] DMSA 30 mg/kg/day is more effective in reducing the body burden of lead than DMSA 10 or 20 mg/kg/day.[6] The optimal duration of DMSA therapy is not agreed internationally. In the US, at least in children, a five-day course of high dose DMSA therapy (1050 mg/m^2/day) is often followed by low-dose therapy (700 mg/m^2/day) for 14 days, whereas in Europe five day courses of DMSA 30 mg/kg/day are usually administered intermittently, as required clinically. It has been shown recently in a pediatric population that a similar impact on blood lead concentrations is achieved by both the 19 day regimen and two five day high dose courses separated by one week.[7] Adverse reactions reported during oral DMSA therapy include transient elevation of hepatic enzyme activities, skin rashes, pruritis, reversible neutropenia and gastrointestinal disturbances. Sodium calcium edetate: Sodium calcium edetate[8] is an ionic, water-soluble compound. It has a small volume of distribution because of its polar nature. Oral administration is inappropriate due to an oral bioavailability of <5%. Sodium calcium edetate distributes primarily to the extracellular fluid and does not penetrate cells. Renal elimination of sodium calcium edetate approximates to the glomerular filtration rate and results in 50% of an administered dose being excreted in the urine in 1 hour and >95%

in 24 hours. Dosage adjustment may therefore be necessary if sodium calcium edetate is used in patients with renal impairment.[9] The half-life of sodium calcium edetate is some 20–60 minutes. Sodium calcium edetate forms chelates with divalent and trivalent metals in the body. Hence, exogenous and endogenous metal ions with a higher affinity for sodium calcium edetate than calcium will be chelated, mobilized and usually excreted. Experimental studies have shown that the administration of sodium calcium edetate mobilizes several endogenous metallic cations including zinc, manganese and iron. The recommended dose of sodium calcium edetate is 75 mg/kg/day. This should be given in a diluted solution over at least one hour to avoid thrombophlebitis. Moreover, rapid intravenous administration of sodium calcium edetate can cause hypocalcemic tetany, though a slower infusion does not do so because of the ready availability of extracirculatory stores of calcium. To minimize nephrotoxicity, an adequate urine flow should be established prior to and during treatment with sodium calcium edetate. Repeated large doses of sodium calcium edetate can cause degeneration of proximal renal tubular cells; changes have also been observed in the distal tubules and glomeruli. These renal effects are usually reversible upon cessation of treatment and may be due to the interaction between sodium calcium edetate and endogenous metals in the proximal renal tubular cells. Less serious adverse effects include malaise, excessive thirst, fever, myalgia, headache, anorexia, nausea and vomiting. Oral DMSA vs intravenous sodium calcium edetate: The use of oral DMSA in lead poisoning appears to offer several advantages over intravenous sodium calcium edetate. Firstly, since DMSA may be administered orally, in-patient treatment may not be necessary and, potentially therefore, substantial financial savings may be made. Secondly, the urine excretion of key essential trace metals, such as zinc, is much less after chelation with DMSA than with sodium calcium edetate; DMSA has little effect on the urinary excretion of calcium, copper, iron and magnesium. Thirdly, in experimental studies the administration of DMSA did not result in redistribution of lead to the brain,[5] unlike sodium calcium edetate.[10] On the other hand intravenous sodium calcium edetate is more effective than DMSA in promoting lead excretion. The efficacy of chelation therapy in lead poisoning cannot be judged by estimating blood lead concentrations alone; determination of lead excretion is mandatory. Lead excretion was significantly greater in intoxicated smelter workers after a five day course of sodium calcium edetate 12–16 mg/kg/day than following DMSA (mean 18–42 mg/kg/day over five days).[11] In a pediatric study,[12] sodium calcium edetate 29 mg/kg/day also produced greater urinary lead excretion than DMSA 30 mg/kg/day. Urinary lead excretion in an adult was more than five times greater after sodium calcium edetate (approximately 80 mg/kg/day) than after DMSA 30 mg/kg/day.[13] Our own studies confirm that oral DMSA 30 mg/kg/day is some three to four times less effective in increasing lead excretion than intravenous sodium calcium edetate 75 mg/kg/day. Taking into consideration not only the 'therapeutic' dose but also molar equivalence, oral DMSA (MW 182) is substantially less effective than sodium calcium edetate (MW 374) in reducing the body burden of lead. Nonetheless, oral DMSA is an effective lead chelator with few clinically significant adverse effects. This may explain the present clinical preference for DMSA where both chelators are available. References: [1]Asiedu P, Moulton T, Blum CB, Roldan E, Lolacono NJ, Graziano JH. Metabolism of meso-2,3-dimercaptosuccinic acid in lead-poisoned children and normal adults. *Environ Health Perspect* 1995;**103**:734–39. 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14 MANAGEMENT OF LEAD POISONING OF ADULT PATIENTS: EXPERIENCE OF THE POISON CENTRE OF MARSEILLES BETWEEN 1993 AND 2000

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Objective: Lead poisoning can occur in adults from occupational or environmental sources. In order to evaluate the chelation therapy provided in the poison Centre of Marseilles (PCM), the authors studied the cases of adult patients who consulted the PCM between 1993 and 2000 with a history of lead exposure. Method: In order to establish the diagnosis of chronic lead poisoning, EDTA provocation test was used: A lead blood level was done followed by an infusion of EDTA. A 24 hours urine collection was done to evaluate lead elimination. If the test was positive chelation therapy was given. Case Series: 45 cases were studied (9 women, 36 men, average age 44 y). The lead sources had occupational origins for 76% of the cases (welding, heavy metal industries, etc.), and environmental origins for 24% (shooting as a hobby, hunting, etc.). 91% of the patients presented with a clinical feature of possible lead intoxication (asthenia, abdominal pain, anaemia, seizures, etc). For 22 patients, EDTA provocation test was negative (average LBL 156 µg/L - *mini 50 µg/L, maxi 555 µg/L*–and average LUE 277 µg/24H post infusion–*mini 20 µg/24H, maxi 844 µg/24H*). 6 patients with a positive test refused to be treated (average LBL 365 µg/L –*mini 50 µg/L, maxi 760 µg/L*–and average LUE 3137 µg/24H–*mini 1279 µg/24H, maxi 6236 µg/24H*). 16 patients with a positive test were treated with chelation therapy (average LBL 566 µg/L–*mini 320 µg/L, maxi 943 µg/L*–and average LUE 3011 µg/24H–*mini 789 µg/24H, maxi 7229 µg/24H*). 58 treatments were given (1 to 12 courses for each patient). The average quantities of lead eliminated in the urine during the chelation therapy was 30912 µg ± 29059 µg by case. In 12 patients who stopped the lead exposure after the diagnosis of lead poisoning, the chelation therapy decreased the LBL of 69%. In 4 patients still exposed during the treatment, the LBL decreased 7% only. In the 16 treated patients, a clinical improvement was noted, and no adverse effect of EDTA chelation therapy was observed during the 58 treatments. Conclusion: EDTA chelation therapy is a well tolerated treatment which has a good effect on lead poisoning symptoms.

15 NEUROTOXICITY ASSESSMENT IN ACUTE LEAD POISONING

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Objective: We present 3 cases of acute, occupational poisonings in workers exposed to lead during cutting and smelting discarded automobile storage batteries in a "backyard" plant. Neuropsychological, neurological, examinations as well as EEG, CT scan and MRI were performed to assess the CNS lead neurotoxicity. Case Series: In the last days of October 2000, 3 patients were admitted to the Department of Clinical Toxicology with signs and symptoms of acute lead poisoning. Case 1: In a 36-year-old man, exposed to lead for 5 months, clinical examination revealed a severe encephalopathy (coma, brain edema, seizures), moderate anemia and slight liver dysfunction. Lead concentration in blood was 3100 µg/L, excretion with urine 17.6 mg/24h, delta aminolevulinic acid (ALA) in urine–21.0 mg/L. CT scan performed in the first day confirmed diffuse cerebral edema. Chelating therapy with BAL and $CaNa_2EDTA$ was started immediately together with symptomatic and supportive treatment. MRI performed two weeks later revealed cortical and subcortical atrophy of the brain. In neuropsychological examination massive disorders of memory, thought processes, attention and learning ability were stated. In EEG epileptiform waves were observed. The last neurological examination showed proximal paresis in the upper extremities. Case 2: A 34-year-old man was exposed to lead for 5 weeks. At admission generalized weakness, dizziness, headache, abdominal pain and vomiting were observed. Laboratory findings revealed anemia and increased activity of the liver enzymes. Lead blood concentration was 1200 µg/L, lead urinary excretion–16.8 mg/24h, ALA in urine–52 mg/L. Neuropsychological examination showed disorders in non-verbal functions. The CT scan and MRI of the brain showed slight cortical and subcortical atrophy. EEG was normal. Neurological examination revealed tremor of upper extremities and nystagmus. Chelating therapy with BAL and $CaNa_2EDTA$ was started. Case 3: A 21-year-old man was exposed to lead for 1 week. He presented only abdominal pain and weakness. Blood lead concentration was 1200 µg/L, lead urinary excretion–3.8 mg/24h, ALA in urine–55.1 mg/L. Laboratory results: insignificant anemia and increased activity of the liver enzymes were observed. Moderate

impairment of memory was stated in neuropsychological tests. CT scan, MRI and EEG did not reveal significant changes. Neurological examination: nystagmus and dysesthesia were observed. The treatment was started with DMPS and then continuing with $CaNa_2EDTA$. Peripheral nervous system evaluation will be performed and further dynamic investigations are planed. Conclusion: In all patients exposed to lead by inhalation at the workplace, the blood lead concentration was in the range that causes severe neurotoxicity. The severity of the CNS manifestations was related to the blood lead concentration and the time of exposure.

16 TREATMENT OF ABNORMAL LEAD BODY BURDEN (LBB) DUE TO OCCUPATIONAL EXPOSURE USING *CORIANDUM SATIVUM* (CILANTRO OR CHINESE PARSLEY) DRIED LEAVES PREPARATION ORALLY

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Objectives: The search for a cheap, easily administered, efficacious, and safe chelating agent for lead intoxication has led lately to approving of DMSA orally as a good pharmacological agent for use even in intoxicated children. However, in many underdeveloped countries, the use of DMSA is still far from established due to high costs of that molecule. In 1995, Omura et al. and Omura and Beckman, published two reports of the use of infusion extracts and dried leaf preparations of *C. sativum*, popularly known as cilantro or Chinese parsley, in patients with high mercury blood and urine levels. Aiming to verify the possible efficacy in patients with high lead blood levels, we performed a pilot clinical trial, comparing the use of that plant against traditional treatment with $CaNa_2EDTA$. Objective: To compare lead chelating action of *C. sativum* dried leaves preparation orally in a patient with high lead body burden (LBB), due to occupational exposure, to traditional chelating treatment using $CaNa_2EDTA$. Methods: After approval of the pilot study protocol by the committee of ethics of our institution, we selected a patient with previous $CaNa_2EDTA$ treatments for high lead body burden, who continued to present high blood lead levels (>65 μg/dL) and high urine ALA levels (>25 mg/L). This patient presented mild to moderate symptomatology after 3 previous IV $CaNa_2EDTA$ treatments with malaise, muscle pain, episodic cramps, decreasing sexual libido and episodic abdominal pain. Just before the trial he had PbB = 68.7 μg/dL; ZPP = 357.9 μg/dL; U-ALA = 57.3 mg/L; hemoglobin = 11.7 mg/dL. Treatment was done with 100 mg (two 50mg pills) of *C. sativum* each 4 hours (600 mg/day) orally during 6 days. The whole 24 hour urine was collected each day for Pb assessment performed by Flame AAS. The same patient acted as control as immediately after cilantro treatment we started with $CaNa_2EDTA$, 1g per day intravenously for 4 days. The same procedure of collecting urine for Pb assessment was then performed. Results: Means of Pb excretion during *C. sativum* treatment was 199.3 μg/day (total six day excretion of 1,196 μg), and during $CaNa_2EDTA$ treatment mean Pb was 2,770.25 μg/day (total four day excretion of 11,081 μg). No symptomatic relief was noticed during *C. sativum* administration, it being registered, however, after the second day of $CaNa_2EDTA$ administration. Conclusions: The 13.9 fold difference in lead excretion between traditional $CaNa_2EDTA$ and *C. sativum* treatments seen in this patient indicates a probably low efficacy of that plant for high LBB.

17 MERCURY VAPOUR INTOXICATION: FEATURES AND MANAGEMENT

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Introduction: The toxicity of mercury vapor has been recognized for 2000 years; the Romans 'employed' criminals and slaves to mine mercury ore since the life expectancy in this work was short. Occupational exposure remains the principal source of intoxication, notably in mercury mining and refining, in chloralkali plants (producing chlorine gas via the electrolysis of saline), during the maintenance and manufacture of instruments such as thermometers, barometers and sphygmomanometers, in dental practice and in the extraction and purification of gold. Elemental mercury is a volatile liquid and toxic vapor concentrations can be reached readily at ambient temperatures particularly in an enclosed space. Following inhalation, lipid soluble mercury vapor is absorbed completely through alveolar membranes and distributed rapidly via the pulmonary and systemic circulation before oxidation to Hg^{2+} in red blood cells and other tissues. The diffusion of mercury across the blood brain barrier, prior to oxidation serves to 'trap' mercury within the central nervous system and explains the prominence of neurological features following exposure. Mercury accumulates also in the kidneys prior to renal elimination. Features: The features observed following mercury vapor inhalation depend on the dose and duration of exposure. Local irritant and respiratory (or less commonly cardiorespiratory) features are more

common following acute exposures, while general debility, gastrointestinal, renal and neurological features may occur in both acute and subacute/chronic exposures. Local irritant and respiratory/cardiorespiratory features include conjunctivitis, cough, dyspnea, chest pain and palpitation. Following acute massive exposure, an erosive pneumonitis develops which may be complicated by multiple pneumothoraces and/or the Adult Respiratory Distress Syndrome (ARDS). In less severe cases, neuropsychological/neuropsychiatric features predominate and include headache, dizziness, tremor, irritability, anxiety, insomnia, diplopia, incoordination, memory loss, depression, timidity, hallucinations, muscle fasciculations and myoclonus. Renal glomerular and/or tubular toxicity and liver damage have been reported. Common nonspecific features include fatigue, weakness, fever and weight loss. There may be a maculopapular rash. Gastrointestinal toxicity manifests typically with nausea, diarrhea, colicky abdominal pain, anorexia, a metallic taste, hypersalivation, stomatitis/gingivitis and blue/black discoloration of the gums. Subtle effects have been described following chronic exposure to relatively low mercury vapor concentrations, including abnormal EMG or EEG studies, subclinical color vision loss and tremor, disturbances of concentration, memory and psychomotor performance. Chronic ocular exposure may lead to granular opacification of the lens (mercurialentis). An association between chronic occupational mercury vapor exposure and lung cancer has not been substantiated. Management: Adequate occupational hygiene, environmental monitoring and health surveillance are prerequisites to limiting occupational mercury vapor exposure; the 8-hour TWA exposure limit in the UK is 25 $\mu g/m^3$ and the US minimal risk level is 0.2 $\mu g/m^3$. Even prompt removal from exposure to high concentrations of mercury vapor may not prevent the development of serious sequelae. Conventional supportive measures are the mainstay of management of mercury vapor-induced pneumonitis, ARDS and renal failure. The thiol chelating agents DMSA and DMPS have been shown to enhance mercury elimination significantly, protect against renal damage and increase survival in inorganic mercury-poisoned rodents.[1] However, few studies have dealt specifically with mercury vapor. A single administration of oral DMPS or oral DMSA 1 mmol/kg (220 mg/kg DMPS; 180 mg/kg DMSA) significantly reduced the brain mercury concentration of rats exposed to mercury vapor 1294 $\mu g/m^3$ for five days, but the same effect was not seen when the mercury vapor concentration was reduced to 425 $\mu g/m^3$.[2] A modest, though not significant reduction in the brain mercury concentration was found when DMPS 220 mg/kg was administered parenterally for two weeks, five weeks after exposure to mercury vapor 2190 $\mu g/m^3$ for seven days.[2] In this study DMPS was more effective than DMSA in reducing the kidney mercury concentration, though the reduction in brain and liver mercury concentrations were not significantly different for the two chelating agents. In clinical studies, DMPS, DMSA and *N*-acetyl-D,L-penicillamine (NAP) have been shown to enhance urine mercury excretion.[3-8] Subjective and objective improvement occurred in several workers acutely exposed to mercury vapor when they were treated with oral DMSA 90 mg/kg/day for 4 days some 80 days post exposure.[7] In this study DMSA more effectively enhanced urine mercury elimination than did oral NAP 1 g daily.[7] Among 84 men diagnosed with mild chronic mercury vapor poisoning, parenteral DMPS 125 mg daily on four days each week and removal from exposure, led to subjective improvement in gum bleeding, toothache, anorexia, fatigue, insomnia, dizziness, myalgia and headache in at least half the individuals who originally reported these symptoms.[9] Campbell et al.[3] described a 23-year-old man occupationally exposed to mercury vapor in whom paresthesiae, muscle cramps, hypersalivation and an abnormal electromyogram resolved following eight weeks oral DMPS 300–400 mg daily. We have treated a patient with severe mercury vapor-induced neurological damage who improved subjectively and objectively following three five-day courses of oral DMPS 30 mg/kg/day.[10] Conclusion: Mercury vapor exposure may result in severe irreversible toxicity, predominantly affecting the central nervous system. Experimental data suggest that DMPS chelation therapy is the antidote of choice and there is some clinical evidence that it may reverse mercury-induced neurological damage. Further studies are required to clarify the optimum dose and duration of treatment. References: [1]Aaseth J. Recent advance in the therapy of metal poisonings with chelating agents. *Hum Toxicol* 1983;**2**:257–272. [2]Buchet JP, Lauwerys RR. Influence of 2,3-dimercaptopropane-1-sulfonate and dimercaptosuccinic acid on the mobilization of mercury from tissues of rats pretreated with mercuric chloride, phenylmercury acetate or mercury vapors. *Toxicology* 1989;**54**:323–333. [3]Campbell JR, Clarkson TW. 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18 MERCURY SPILL IN A SCHOOL: THE ROLE OF THE POISON CENTER

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Objective: To describe the actions taken by a regional poison center (PCC) in response to the accidental elemental mercury contamination of a school. Case Report: The PCC was contacted shortly after a spill of elemental mercury in a science classroom. Mercury beads were noted throughout the school. Many children played with the mercury (several ounces) and had already returned home. Early PCC actions to mobilize appropriate authorities (EPA, Health Department) and recommendations to retrieve students' personal items, many later found to be highly contaminated, potentially limited the extent of exposure. The PCC then responded to the school's desire to offer medical screening to potentially impacted children by 1) developing medical screening forms 2) developing a strategic plan for medical staffing/equipment acquisition 3) creating a tracking system and 4) providing risk communication to the public through media releases, fact sheets, and parent meetings. The PCC further coordinated laboratory result interpretation and medical follow-up. 256 patients had blood mercury levels performed over the 3 day period (results: range 0–17 mcg/L, mean 0.52); 115 had 24° urine collections (results: range 0–14 mcg/L, mean 0.68); 123 patients' bagged clothing was tested (range 0–706 mg/m^3); and follow-up air sampling of 8 homes was negative. One asymptomatic child received a course of chelation therapy with DMSA and remains symptom-free. Air sampling in the affected classroom detected mercury levels of 16–28 mcg/m^3, all other areas were at safe (<2 mcg/m^3) levels. Testing of personal items was not predictive of home contamination and did not correlate with blood or urine mercury results. Finally, the PCC spearheaded the formation of a Mercury Reduction in Schools Taskforce, which has coordinated the following agencies: local public schools; county school systems; state science teacher's associations; USEPA; local, county and state health departments; department of environmental quality; hospitals; ATSDR; media relations; and other interested agencies. Teacher workshops highlighting chemical safety in schools and mercury risk to the community and environment have been sponsored by this taskforce and have reached over 150 schools to date. Conclusions: The PCC can potentially play a key role in mitigating the effect of hazardous materials incidents through early mobilization of appropriate agencies, coordination of medical response, and sponsorship of activities designed to prevent future occurrences. This incident also served to provide useful information regarding blood and 24-hour urine mercury screening results in a large number of urban children.

19 CADMIUM INTOXICATION: FEATURES AND MANAGEMENT

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Introduction: Cadmium belongs to the heavy metals. Cadmium can be found in rocks, soil, water and coal, as well as in zinc, lead and copper ore. Cadmium is intensively used in industry. Exposure to relatively higher cadmium concentrations or doses predominantly takes place at the working place. Cadmium oxide is the compound most frequently inhaled. Depending on the kind of cadmium compound and particle size up to 50% of the inhaled cadmium can be absorbed. The major route of cadmium exposure for non-occupational settings and non-smoking persons is via food (leafy vegetables or potatoes). Normal daily exposure is around 30 μg/day and about 1–3 μg/day is absorbed. In smokers this can be 2–6 μg/day. The smoke of one cigarette contains 1–2 μg cadmium. Iron deficiency increases cadmium absorption[1] while oral zinc supplemention decreases cadmium absorption. About 25% of cadmium administered with food is retained after 3–5 days. Retention decreased to about 6% after about 20 days.[2] Whole body retention ranged from 1.2 to 7.6% with a mean of 2.7%.[3] Most cadmium inhaled or ingested is excreted in the faeces. Cadmium (+2) ion binds to anionic groups (especially sulfhydryl groups) in proteins (albumine and metallothionein). Cadmium is absorbed by the intestinal mucosa and bound to metallothionein. Cadmium-metallothionein complex is transported to the target organs. The cadmium concentrations in most tissues accumulate with age, especially, in the kidneys and liver. Spleen, pancreas and testis also have relatively high concentrations. Half-times for cadmium in the kidney is circa 12 years, and in the liver circa 7.5 years.[4] Features: Acute inhalation of high cadmium levels may cause lung damage. During exposure the

symptoms are generally mild (symptoms comparable to those seen in metal fume fever), but within a few days severe lung oedema and pneumonitis can develop, leading to respiratory failure, which may be lethal.[5] If the patient recovers from acute inhalatory cadmium poisoning, recovery appears to be rapid and complete, but limited information is available concerning follow-up after acute exposure. Lung cancer risk may also be increased after long cadmium exposure through inhalation. Eating or inhalation of lower levels of cadmium for a long period may cause a high cadmium body burden, which may cause kidney damage and fragile bones. The kidney is the main target organ of cadmium toxicity, especially, the proximal tubules. Cadmium not bound to metallothioneins presumably is responsible for the cadmium related tissue injury. The mechanism of kidney damage is not fully understood. There is no convincing evidence that cadmium causes hypertension. Increased cadmium body burden may also alter central nervous system function as was found by means of neuropsychological functioning tests.[6] Cadmium has been shown to alter zinc, iron, and copper metabolism[7] as well as selenium.[8] Cadmium interacts with calcium metabolism of men. Painful bone disorders, including osteomalacia, osteoporosis, and spontaneous bone fractures, have been reported in persons chronically exposed to cadmium in food (e.g. Atai Atai disease). Dietary deficiences of calcium, protein, and vitamin D are likely to account for increased susceptibility to bone effects following cadmium exposure. Cadmium exposed persons exhibit a progressive disturbance in renal metabolism of vitamin D to its biologically active form.[9] Cadmium exposure is associated with a higher incidence of renal stone formation. Renal reabsorption of calcium among cadmium alloy workers was decreased.[10] Diagnosis: Cadmium can be measured in blood, urine, hair, or nails. Blood concentration of cadmium is the best indicator for recent exposure. Urinary excretion of cadmium is related to body burden, recent exposure, and renal damage. Cadmium exposed persons with proteinuria generally have increased cadmium excretion. The urine cadmium excretion may decrease if renal damage is severe. Hair or nails are less reliable, because they can easily be contaminated. Cadmium in blood is mainly in the red blood cells, and plasma concentration is very low. Blood cadmium levels range from 0.4 to 1.0 μg/L for nonsmokers and 1.4 to 4 μg/L for smokers. Blood levels up to 10 μg/L are considered acceptable in occupational exposures. Urine concentration is normally below 1 μg/g creatinine. The average urine cadmium concentration is 0.35 μg/g creatinine in nonsmokers and levels above 2 μg/g creatinine are rare. Proximal tubular damage can be diagnosed by increased levels of low molecular weight proteins in the urine. These proteins such as β_2-microglobulin, lysosomal enzyme *N*-acetyl-β-D-glucosaminidase (NAG), ribonuclease, light chain immunoglobulins, and retinol-binding protein are filtered by the glomerulus and reabsorbed in the proximal tubules of the kidney. NAG may be more sensitive than β_2-microglobulin at low cadmium exposure levels (urine cadmium $<$ 102 μg/g creatinine). Decreased reabsorption of amino acids, glucose or some enzymes may be more sensitive for tubular dysfunction than low molecular proteins. In severe kidney damage high-molecular weight proteins like albumin can also be detected in urine. Management: Adequate occupational hygiene, environmental monitoring, and health service are important to limit occupational cadmium exposure. Chelating agents such as ethylenediaminetetraacetic acid (EDTA), penicillamine, British anti-Lewisite (BAL) have been used in acute cadmium poisoning, but these chelating agents were of limited value and/or may increase kidney burden and damage.[11] 2,3-Demercaptosuccinic acid (DMSA) and 2,3-demercapto-1-propane sulfonate (DMPS) were effective in reducing mortality as well as reducing cadmium burden in liver and kidneys in cadmium intoxicated mice.[12,13] DMSA was effective in acute cadmium poisoning in mice.[14] Thus chelating therapy in acute exposure may be useful, but needs to be confirmed in daily practice. Advice on the treatment of chronic cadmium poisonings is troublesome because it is difficult to evaluate the body burden and to recommend a chelating agent for the treatment.[15] At present, chelation is not advised for chronic cadmium exposure. Removal from exposure is advocated. The newer chelators like DMPS and DMPA may provide promise for a safe method to decrease the cadmium body burden. It is unsure whether or not this therapy will decrease chronic cadmium toxicity. Conclusion: Acute massive inhalatory exposure induces pulmonary effects. Chronic cadmium exposure may result in irreversible toxicity predominantly affecting the kidney and skeleton. Further studies are needed to establish if the body burden after chronic exposure with chelators can be reduced in order to diminish the kidney and skeleton toxicity. If so, the optimum dose and duration of the chelating treatment need to be established. References: [1]Flanagan PR, et al. Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* 1978;**74**:841–846.[2] Rahola T, et al. Retention and elimination of 115mCd in man. In: *Health Physics Problems of Internal Contamination*. Budapest: Akademia 1973:213–218. 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20 FEATURES AND MANAGEMENT OF NICKEL INTOXICATIONS

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Introduction: Nickel, a siderophilic metal forming the first transition series group VIIIb of the periodic table together with cobalt and iron, is an ubiquitous element, which is essential, at least in several animal species. There are water soluble (chloride, nitrate, sulfate), moderately soluble (carbonates, hydroxides) and water insoluble (metallic, sulfides, oxides) nickel species. Toxicity decreases from nickel carbonyl = $Ni(CO)_4$ to soluble to insoluble compounds. Acute nickel toxicity can almost entirely be reduced to nickel carbonyl. Features: Symptoms of *acute* nickel poisoning: In case reports 325 mg *nickel sulfate* (73 mg elemental nickel) led to nausea, giddiness, decreased pulse. 0.5–2.5 g nickel (as *sulfate* and *chloride* in drinking water) produced nausea, vomiting, abdominal discomfort, diarrhea, lassitude, headache, cough, dyspnea for 1–2 days without sequelae. A 2.5 yr girl died of cardiac arrest after ingestion of 10–15 g *nickel sulfate* (2.2–3.3 g elemental nickel) with erythema, mydriasis, stupor, nuchal rigidity, tachycardia, and pulmonal congestion. Postmortem changes included acute hemorrhagic gastritis. *Nickel carbonyl* is fatal after inhalation of 30 ppm for 30 minutes. A 47 yr male died of respiratory failure four days after massive *nickel carbonyl* exposure. His urine contained 535 µg Ni/L, and postmortem investigation revealed pulmonary and cerebral edema. The intoxication typically appears in two stages: The first immediate stage involves respiratory irritation and unspecific symptoms such as dizziness, frontal headache, weakness, nausea, and vomiting, followed by tightness of the chest, dyspnea and nonproductive cough. While in minor exposures these symptoms are moderate and resolve within 1 day, in more severe poisoning more pronounced pulmonary (pulmonary edema, pneumonitis) and gastrointestinal symptoms develop within 12–120 hours along with myalgias, fatigue, profound weakness, delirium, and convulsions. Additional complications include hepatorenal dysfunction, adrenal insufficiency, and hyperglycemia. Primary causes of death include diffuse interstitional pneumonitis, and cerebral edema and hemorrhage. A minority of the survivors of severe *nickel carbonyl* poisoning may develop pulmonary fibrosis, although most do not show respiratory impairment. Effects of *chronic* exposure to nickel containing dusts include the development of allergic diseases of the respiratory tract, while skin sensitization occurs frequently after prolonged contact with metallic nickel. Nickel is a common sensitizing agent, and nickel and nickel compounds are recognized carcinogens (IARC 1990). The intestinal absorption of *soluble nickel compounds* is rapid (1–2 h) with a bioavailability of 1–5%, while the absorption of *metallic nickel* and *less soluble compounds* is poor. Dermal absorption of *nickel carbonyl* after cutaneous exposure can be significant. In blood nickel is bound to albumin and nickeloplasmin. Animal studies indicate that highest concentrations of nickel after parenteral administration of soluble nickel salts occur in the kidney, and also in the lungs, liver, endocrine glands, cartilage, and connective tissue. After *nickel carbonyl* exposure highest concentrations are found in lung, brain, kidney, liver, and adrenals. Nickel is rapidly eliminated, mainly via urinary excretion and does not accumulate. Acute nickel toxicity is believed to be associated with its ability to bind to enzymes including hepatic microsomal enzymes, enzymes involved in carbohydrate metabolism and proteins transporting ions across cell membranes. Nickel competes with calcium intracellularly and may cause membrane disruption via lipid peroxidation, ultimately leading to cell death. In unexposed individuals mean nickel concentrations in whole blood are 0.28 µg Ni/L (range <0.05–1.08), in serum 0.34 µg Ni/L (range <0.05–1.05), in plasma generally <2 µg Ni/L, and in 24-hour urine <2 µg/g creatinine. Serum concentration of >8–10 µg Ni/L indicate an excessive exposure to nickel. After exposure to *sparingly soluble nickel compounds*

serum nickel concentrations reflect mainly the lung burden of nickel, while blood and 24-hour urine samples are good measures of exposure to *soluble nickel compounds* over the preceding 1–2 days. After *nickel carbonyl* exposure the concentration of nickel in the urine correlates well with the severity of poisoning during the first three days postexposure. Levels peak at 24–48 hours postexposure and return to baseline within 1–2 weeks. According to Sunderman, levels of 60–100 μg Ni/L are associated with mild, 100–500 μg Ni/L with moderate, and >500 μg Ni/L with severe poisoning (samples collected within 18 hours postexposure). *Treatment:* Nickel carbonyl is the only nickel compound causing acute poisoning after inhalative exposure, while soluble divalent nickel salts may eventually lead to acute poisoning after ingestion. Patients with significant exposure to *nickel carbonyl* should be removed immediately from the source of exposure. Contaminated clothes must be removed to prevent dermal absorption. Attention should be given to maintaining sufficient oxygenation. Symptomatic patients and individuals with heavy exposure should be brought to a health care facility for evaluation. On persons having ingested toxic amounts of *soluble nickel compounds* gastroenteral decontamination should be performed within 1–2 hours post ingestion. Supportive care is the mainstay of treatment. *Antidotes* with potential efficacy in nickel poisoning include sodium dietyldithiocarbamate (DDC), disulfiram, D-penicillamine, *N*-benzyl-*D*-glucaminedithio-carbamate, meso-2,3-dimercaptosuccinic acid (DMSA), and dimercaptopropanesulfonic acid (DMPS). DDC is a investigational antidote forming lipophilic chelates with divalent nickel. In mice it reduces the accumulation of nickel in the lungs by redistribution to fatty tissue including the brain. It is more effective when administered parenterally and early. The protocol proposed by Sunderman for adult human poisoning with *nickel carbonyl* consists of the oral administration of 35–45 mg/kg DDC in divided doses during the first 24 hours followed by 400 mg every 8 hours until symptoms resolve and urine nickel concentrations are back to normal. In critically ill patients DDC may be given parenterally at a dose of 12.5 mg/kg. However, controlled data in human poisoning are lacking, and published case series are controversial. Disulfiram which is metabolized in the body to two molecules of DDC is used as a chelating antidote in nickel carbonyl poisoning. Because human data are almost absent for disulfiram, D-penicillamine, DMSA, and DMPS, these compounds cannot generally be recommended as treatment for nickel (carbonyl) poisoning. References: [1]Barceloux DG. *J Toxicol Clin Toxicol* 1999;**37**:239–258. [2]Bradberry SM, Vale JA. *J Toxicol Clin Toxicol* 1999;**37**:259–264. [3]Sunderman FW. *Ann Clin Lab Sci* 1989;**19**:1–16. [4]Sunderman FW Jr, et al. *Toxicol Ind Health* 1986;**2**:17–78. [5]Da Costa JM. *Med News* 1883;**43**:337–338. [6]Sunderman FW Jr, et al. *Am J Ind Med* 1988;**14**:257–266. [7]Szathmary SC, Daldrup T. Fresenius Z *Anal Chem* 1982;**313**:48. [8]Webster JD, et al. *Ann Intern Med* 1980;**92**:631–633. [9]Jones CC. *Arch Environm Health* 1973;**25**:245–248. [10]Sunderman FW, Kincaid JF. *JAMA* 1954;**155**:889–894. [11]Vuopala U, et al. *Ann Clin Res* 1970;**2**:214–222. [12]Sunderman FW, Sunderman FW Jr. *Am J Med Sci* 1958;**236**:26–31.

21 QUALITY AND ACCREDITATION OF POISONS CENTRES. REPORT OF AN EAPCCT WORKING GROUP

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Objective: To define quality standards for poisons centres and consider accreditation of European poisons centres by the EAPCCT. Methods: In 1998 an EAPCCT working group was established. A number of quality issues relevant to various activities in a poisons information centre were identified. By means of a questionnaire and e-mail discussion the participants of the working group drafted a set of minimum and optimum standards for poisons information centre operations. European poisons centres were then surveyed in order to 'test' these standards against reality. In the light of the information provided by the survey the group considered the role that EAPCCT could play in the quality assurance of poisons centres. The results of this work were presented at the EAPCCT Congress in Amsterdam. The working group was enlarged to 18 members in order to further this work and to finalise the minimum and optimum standards. Results: 71 European poisons centres were identified for the survey and 60 (84.5%) returned the questionnaires. The survey revealed a wide variation between poisons centres in Europe in terms of resources, information systems and responsibilities. Most centres met the minimum standards, however. The working group completed the EAPCCT checklist of minimum and optimum standards, to be used as a self-assessment tool. In addition the group drafted guidelines for carrying out a number of essential poisons centre activities, such as routines for updating information sources, for documenting enquiries and for training new staff. Conclusion: In view of the great diversity of European poisons centres the working group does not at present time recommend an accreditation scheme for poisons centres to be established by the EAPCCT. Instead the association should raise awareness of quality issues and encourage centres to perform

internal audits of their routines and activities. For this purpose the EAPCCT self-assessment checklists for minimum and optimum standards could be used, as well as the special guidelines.

22 EFFECTIVENESS OF PROTOCOLS AND CLINICAL GUIDELINES IN POISON CENTER OPERATIONS

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Objective and background: To describe the development and analyze the effectiveness of protocols and clinical guidelines used in the telephone management of poisonings in a poison center. Since 1997, the California Poison Control System (CPCS) has developed and utilized over 800 protocols and clinical guidelines that range from the identification of non-toxic products to clinical guidelines for the management of hospitalized symptomatic patients. The protocols and guidelines were developed through a process of reviewing and codifying standard practices, literature searches, pilot testing, and approval through a consensus of opinion. Methods: A cross-sectional analysis was performed on a 5-day sample of computerized case charts recorded by 1 poison center within the CPCS. Each case was evaluated to determine whether it was covered by a protocol or clinical guideline, whether the recommendations in the protocol or guideline were appropriate for the specific case, and compliance with the protocol or guideline by poison center staff. The cases were stratified by patient flow (managed on site, referred to a health care facility, en-route to or at a health care facility). Cases and circumstances that were not covered by protocols and clinical guidelines were categorized. The case data element that linked the case to the protocol or guideline was determined. Results: We analyzed 757 poison center charts, which included 137 (18%) information calls and 620 (82%) exposure calls. A CPCS protocol or clinical guideline covered the topic for the call on 525 (69.4%) of the cases. However, 81 of the 525 cases involved a circumstance not included in the protocol, leaving 444 (58.8%) cases that could be managed utilizing the protocols or guidelines. The substance categories covered were evenly divided between those with low toxic potential Vs a potentially toxic substance requiring a dose assessment. The substance categories not covered were evenly divided by pharmaceuticals and non-pharmaceuticals (many were newly marketed products). Patients referred to or in a health care facility were less likely to be covered than patients managed on-site (40.4% vs 74.5%). The staff was non-compliant with the protocols or guidelines in 6 cases. There were only 2 cases in which ipecac was recommended in accordance with the protocols and guidelines. Poison center staff referred 52 cases (8.7% of human exposures) to a hospital. Of these, 42 cases (80%) were covered by a protocol or guideline. The case data elements that linked the protocol or guideline were generic substance or ingredient (72%), trade-name specific product (6.2%), route of exposure (16%) and drug ID request (5.7%). Conclusion: The majority of topics in the case set analyzed were covered by CPCS protocols and guidelines. Protocols and guidelines were most frequently deficient for patients referred to or at a hospital and for more recently marketed products or drugs. Poison center protocols and guidelines need to evolve with new products in the marketplace. Compliance with protocols and guidelines by poison center staff may enhance consistency in care and impact referral patterns and treatment recommendations. The variety of data element links to protocols and guidelines complicates strategies for the development of electronic case management tools to guide poison center staff while managing a case. Future analysis needs to be directed at other indices of effectiveness, to include caller and patient compliance and satisfaction, and validation of protocols and guidelines with prospective studies on patient outcomes.

23 POISON CONTROL CENTERS AT THE CROSSROADS: MOVING FORWARD IN A BRAVE NEW WORLD

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Objectives: Mega-trends in medicine, technology, economics, and socio-cultural movements challenge our ingenuity as professionals in poison control. They may pose external constraints as well as opportunities for change in the operations of our poison control centers. Examples of how poison control centers might respond to improve their organization and the delivery of their services will be offered and recommendations made. Methods: An analysis of how poison control centers can align their mission, vision, and values will frame the discussion. Poison control centers must redefine what they are, what goals and objectives they want to accomplish, what their vision is for the future, and what core values they hold about themselves. The impact of continuous quality improvement (CQI) on the efficiency and overall performance of poison control center operations will then be explored. In CQI effecting positive change in operations

is based on improving error-prone systems, not blaming individuals. Critical performance data are tracked, areas of need defined, rapid cycle change experiments are planned and carried out, and any gains are held by the use of control values, which lead to benchmarks reflecting operational efficiencies. The American Association of Poison Control Centers (AAPCC) is currently reviewing its process for certifying the performance of poison control centers. A national ad hoc committee has been charged with developing outcome measures to evaluate poison center performance. The AAPCC is also exploring the development of more uniform and consistent pre-hospital clinical practice guidelines (CPGs) and best practices for the management of human poisoning, another example of CQI. Results: Real-time telecommunications tracking reports will be shown. Such tracking reports provide the impetus for CQI and can serve as one 'barometer' of the health of the poison control center's operations. The 'quality factor' of completeness in the documentation of a poisoning event is another such barometer. Examples of CPGs and new outcome measures will be shown. These are not yet implemented in the United States, but will be carefully considered and selectively phased in so as to permit a wide range of options to insure poison control center compliance. Conclusion: The poison control center of the future will need to recreate itself in order to function appropriately in a demanding new world. The mission, vision and values of a poison control center may all need to be reconsidered in order to meet the challenges of a new environment. Attention to CQI, implementation of evidence-based CPGs, and the use of outcome benchmarks will be key aspects of evolving clinical operations.

24 THE IMPACT OF A NATIONAL INTERNET POISONS INFORMATION SERVICE. 1. CALLER PROFILE

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Objective: To examine the usage of a national internet poisons database. Background: The UK National Poisons Information Service (NPIS) is funded by the National Health Service and provides a telephone service on poisoning for medical professionals. Following national review each of the 6 NPIS Centres covers a specific geographical area. A single telephone number for the UK directs calls to the appropriate Centre. In 1999 the UK NPIS adopted the Internet version of TOXBASE® as its first line information source, in an attempt to free telephone services for the more serious and complicated enquiries. TOXBASE® provides free on-line information on poisoning to registered medical professionals. Direct public access to health information has been introduced in England and Wales with telephone helplines staffed by specially trained nurses using expert computer systems to triage the calls (NHS Direct). Some of these calls concern poisoning and this has resulted in an increase in enquiries to the NPIS from NHS Direct Centres. Methods: The user database was analyzed for user type. All hits on TOXBASE® were analyzed on an Access database. Results: TOXBASE® went on-line in 1983 but since transferring to the Internet in August 1999 has seen a large increase in its user base. Registered users rose from 694 at 31 October 1999 to 1910 at the end of October 2000. The user base (at 31 Oct 2000) consisted of 1068 hospital departments (including 288 A&E/minor injuries units, 199 drug information/pharmacy, 82 pediatric units), 650 GP surgeries, 20 NHS Direct Centres and 172 others. During October 1999 there were 4661 user sessions on TOXBASE® and 6848 product hits. The figures for October 2000 were 11,566 user sessions and 18,354 product hits. However, only 526 (28%) registered users accessed TOXBASE® during October 2000 (436 hospitals, 56 GPs, 8 NHS Direct Centres and 26 others). Top users of the Internet database (by number of sessions) in October 2000 were 2 NPIS Centres, 3 NHS Direct Centres and 5 A&E departments. These major users of TOXBASE may have more than 250 user sessions in one month. General practitioners and hospital departments, other than A&E use TOXBASE only occasionally. Conclusions: Transfer to the Internet has approximately tripled the user base and usage of TOXBASE in one year. Hospital A&E departments and NPIS Centres remain major users. The introduction of NHS Direct has led to these centres becoming significant users of TOXBASE. The Internet offers the possibility of facilitating the provision of poisons information and enhancing the role of poisons information services.

25 POISON CENTER INTERVENTION DETERMINES NEED FOR AMBULANCE TRANSPORT OF THE POISON EXPOSED PATIENT AND DELIVERS COST SAVINGS

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Objective: One of the current missions of poison centers is to save unnecessary health care visits when poisoning exposures are considered of no or minimal toxicity. Collaboration with a 911 system or ambulance dispatch service may be another way for poison centers to save healthcare costs by avoiding unnecessary use of ambulance transport

services. Methods: In July 1998 the Central Pennsylvania Poison Center began to assist the Dauphin County 911 ambulance dispatch system to determine the need and mechanism for transport of a potentially poisoned patient. By protocol, when 911 is called an ambulance is automatically dispatched. In the case of a poisoning call, the dispatcher may then simultaneously contact the poison center. The poison center specialist is directly linked with the 911 caller. The specialist evaluates the toxicity risks, ultimately determining what interventions the patient needs. The ambulance dispatch can be aborted, if the risks are low such that the patient can be observed at home or be transported by private vehicle. Our poison center computerized database was searched to determine the utilization of this service and whether the recommendation was followed from July 1, 1998 through November 13, 2000. Results: The number of aborted ambulance runs was 14, 74, and 121 for 1998, 1999, and 2000 respectively. In addition, 1, 11, and 7 in each of those years had transport changed to a private vehicle. Although this program was meant to be on a trial basis in the poison center's home county, many other county dispatch units began to utilize the service during these first few years. Nineteen of 34 counties have terminated transports after poison center contact. Some EMS units called the poison center for advice, while en route. From these calls, the poison center identified 33 cases in these years where ambulance transport, although occurring, was unnecessary. Based upon an average cost of $500 per ambulance run, the projected cost savings to date approximate to $114,000. Conclusions: The utilization of poison center expert advice by ambulance dispatch services to terminate ambulance runs appears to have gained acceptance throughout our region. Significant healthcare resources appear to have been saved.

26 MISUSE AND ABUSE OF LABORATORY DATA

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Background: Toxicological analyses are an essential component in evaluating toxic hazards in humans. However, there is potential for misuse and, in some cases, abuse of these investigations. Overuse of analytical toxicology services occurs when physicians request analyses even though the clinical signs are unequivocal and the results will have no relevance to patient management. There has been an abysmal failure of UK laboratories to reach agreement on standard systems of units for reporting quantitative toxicological data. Most striking is the split between those laboratories who advocate SI molar units for toxicological analyses and those who are not convinced that there are any grounds for abandoning mass units. Laboratory reports that are devoid of any comments or guidance on normal and toxic ranges are of little use unless a readily accessible consultant service for interpretation is available. This is a major cause of confusion and misinterpretation that can have disastrous clinical implications. While these deficiencies are regrettable, they fall into the category of misuse rather than abuse. The latter term should apply in circumstances where the analytical tests themselves have no valid scientific merit, either because no evidence for their relevance in diagnosing toxic exposure exists or they are completely inappropriate to a particular patient. Even when the tests may have some perceived value, some laboratory practitioners are unable (or unwilling) to support the accuracy of their results by quality control data. *Bone fide* external quality assessment schemes are not available for many of these tests so that another measure of performance quality is missing. Where schemes do exist, the laboratories are under no mandatory obligation to take part. Reports are frequently accessible to the patient and those sections dealing with interpretation can be presented in ways that cause alarm and distress. Moreover, this practice can lead to incorrect diagnoses, use of treatments of dubious benefit and delays in establishing the true medical condition such that long term and potentially serious health effects develop. There is a pressing need to introduce some measure of control in this area. Conclusion: Laboratories should be prevented from offering tests that are not recognized as valid by a group of recognized authorities. Where the tests may be classified as useful, the laboratories should be required to satisfy the performance criteria laid down by one or more accreditation schemes. Finally, clinicians who use these should ensure that there is genuine scientific evidence for their relevance to the investigation of a particular patient, that the data is sound in terms of analytical accuracy and that they understand fully the ground on which an interpretation is made.

27 ETHANOL AND OTHER VOLATILE COMPOUNDS. KINETICS IN ALCOHOL DEPENDENT PATIENTS POISONED WITH ETHANOL

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Objective: The aim of the study was to evaluate the metabolic disturbances in ethanol dependent patients acutely poisoned with ethanol. This paper presents time profiles of ethanol, methanol, acetaldehyde, acetone, isopropanol and n-

propanol and quantitative relationship between their concentrations and elimination rates. Methods: 171 patients acutely poisoned with ethanol (22 women, 149 men), aged 16–75 years (mean 41 ± 11.6), with a history of alcohol use ranging from one year to more then ten years, participated in the study. The clinical diagnosis was done based on a patient interview, and physical, psychological and psychiatric examination. The liver state was examined based on biochemical tests. Blood samples for toxicological study were taken just after admission to the Department of Clinical Toxicology and after 6, 18 and 24 hours. Concentration of ethanol and other compounds in a series samples were measured using headspace gas chromatography. Chromatograms were recorded and calculations were done using the Turbochrom computer programme. Results: In all patients the addiction was confirmed. The biochemical markers of liver impairment were changed–ALT activity was raised in 62.1% of patients, ALT in 53.1%, in 40.3% of patients bilirubin concentration was elevated, GGT activity was normal only in 36.8% of the studied group, albumin concentration was decreased in 32.1% of patients. At the time of admission average ethanol concentration in blood was 3.06 ± 1.15 g/L and ranged from 0.76 to 6.6 g/L. Except for a few cases other volatile compounds were found in the blood of these patients. The elimination rate constant (zero order) of ethanol ranged from 0.09 to 0.54 g/h/kg (mean 0.262 ± 0.077, n = 122). For patients with a higher ethanol concentration at the beginning, faster ethanol elimination was observed. Average methanol concentration at admission was 28.6 ± 38.7 mg/L, ranged from 0.4 to 324.4 mg/L. The concentration of methanol decreased very slowly when ethanol concentration was high. After 6 hours, while the mean ethanol concentration was around 1.5 g/L, the rate of methanol elimination increased. The calculated elimination rate between 6 and 18 hour was around 0.2 h^{-1}. The $T_{1/2}$ of methanol was 3.36 ± 1.94 h (n = 79) and was independent of ethanol concentration at 6 hour. The mean concentration for other studied compounds was: acetaldehyde 5.56 ± 3.68 mg/L, acetone 10.74 ± 25.5 mg/L, isopropanol 4.56 ± 8.9 mg/L and n-propanol 1.09 ± 1.3 mg/L. The elimination rate constants for these compounds ranged from 0.137 h^{-1} for n-propanol (n = 70), 0.144 h^{-1} for isopropanol (n = 57) to 0.246 h^{-1} for acetaldehyde (n = 73). During the whole study period (24 hours), the acetone concentration was elevated and stayed at the same level–around 10 mg/L. Conclusion: The presence of other alcohols and volatile compounds in the blood of ethanol addicted patients is common. There is not significant correlation between the ethanol concentration and other determined compounds. The elimination of methanol in addicted patients can start when the concentration of ethanol is still high.

28 A COMMUNITY EXPOSED TO STYRENE DURING RELINING OF A SEWER IN TOWN IN SOUTH WALES, UK

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Objectives: To report the effect on a community exposed to styrene during relining of a sewer in a commercial street in Barry, South Wales, UK. The lining was a resin system containing maleic and phthalic anhydride in styrene. The local emergency services closed the area and evacuated buildings. Styrene levels at 17:00 hours on the day of the release were 2–4 ppm in a basement of a commercial premise and 15–20 ppm in the sewer area. Methods: Hospital records of patients who presented for treatment due to styrene vapor-exposure and the records of the NPIS (Cardiff Centre) were examined. Case Series: In total seven patients sought medical attention from local hospitals. Also, the NPIS (Cardiff Centre) received 2 enquiries from members of the public and 2 from GPs. Four patients were admitted to hospital. On the morning of the release a 34-year-old female, who had entered the basement of commercial premises in the affected street, developed a severe cough, dyspnea, headache, and nausea and described smelling a ''glue-like'' odor. Two hours after exposure her oxygen saturation was 99%. Four hours after exposure her respiratory rate was 18 breaths/minute, peak flow was 410 L/minute and oxygen saturation was 98%. She was given oxygen because of coughing. She was monitored for 24 hours before medical discharge. She had a history of asthma. A 25-year-old male bus driver, who had been in the area of the sewer, was admitted complaining of ''jelly legs'', shaking, stinging eyes, chest tightness, headache, flushing, abdominal discomfort and a ''funny taste'' in his mouth. His respiratory rate was 23 breaths/minute and oxygen saturation was 96–97%. He had no evidence of bronchospasm and his peak flow was 525 L/minute. A 47-year-old female living in a neighboring street complained of headache, stinging eyes and was dyspneic was given 35% oxygen. Her breathing improved and her oxygen saturation was 97–98%. She left hospital after 2 hours. A 37-year-old woman living in a neighboring street presented with headache, dizziness, nausea and lethargy. However, her respiratory rate was 16 breaths/minute, oxygen saturation was 97% and peak flow was 400 L/minute. She went home after a short period of observation. Conclusion: Only a small number of styrene levels were

taken after patients reported symptoms. Therefore, the levels reported may not reflect the true exposure of these patients. The symptoms reported indicate exposure to levels greater than occupational limits (50–100 ppm). Exposure to styrene caused irritation to respiratory tract and eyes and CNS toxicity.

29 POISONING WITH PETROLEUM PRODUCTS; 100 CASES TREATED IN FINNISH HOSPITALS

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Objective: Petroleum product ingestion is a not infrequent problem in calls to the Poison Information Centre. During the last years they have accounted for approximately 3% (933 calls in 1999) of the calls and in about 50% the patient has had symptoms. We reviewed the case reports our Centre has received from hospitals in Finland during 1972–1998 to get a better picture of the course and outcome of the petroleum product ingestion in Finland. Case Series: Altogether 100 case reports were included in the study. 70 patients were less than 2 years old, 11 were 3–16 years and 19 adults. The petroleum products most frequently involved were mineral spirits (42), kerosene (33) and gasoline (14). The exposure was mostly oral (88). Other routes were inhalation (5), i.m. (2, one with pressure), subcutaneous (1), skin (1) and eyes (3). After oral exposure, kerosene most often caused immediate symptoms (respiratory, neurological and gastrointestinal), gasoline least often. Delayed symptoms observed were x-ray changes in 45%, leukocytosis and fever in 21%, neurological symptoms 16%, abnormal breathing 16%, cough 15%, vomiting 11%, gastrointestinal pain 7%, diarrhea 4%, and chest pain 2%. Also delayed effects were most often seen in kerosene exposure. Exposures were usually accidental and the amount ingested approximately a mouthful. In 8 cases the exposure was intentional and the amounts ingested varied from 100–1000 mL. In the only case with a fatal outcome reported, the patient ingested 100–150 mL intentionally, aspirated and died after 8 days. The average time of hospitalization was 2.9 days, one day or less in 43%, 2–4 days in 34%, 5–19 days in 16%, and data was not available in 7%. Eye exposure caused only mild irritation; prolonged skin exposure produced severe symptoms. I.M. exposure caused local irritation, high-pressure i.m. exposure led to amputation. IV exposure caused leukocytosis and respiratory symptoms. In the beginning of this time period gastric decontamination was still performed. Then paraffin oil and later cream and ice cream were used with the intention to bind the hydrocarbon and reduce risk of aspiration. Conclusion: Ingestion of even large amounts of the domestic petroleum products, kerosene (charcoal lighter fluid, lamp oil), mineral spirits and gasoline usually cause only mild symptoms, unless aspiration happens. Highpressure i.m. injections may cause severe symptoms. Decontamination treatment has changed from aggressive to conservative. Treatment is symptomatic.

30 LATE ANTIDOTE ADMINISTRATION IN 40 PARACETAMOL (ACETAMINOPHEN) POISONING CASES

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Objective: Paracetamol poisoning is common in Greece and covers 9% of all drug-poisoning cases. *N*-acetylcysteine is an effective specific antidote when administered in time, this being within 15 hours from paracetamol intake. There are some cases that present later than within this time limit. The aim was to study the effectiveness of late (beyond 20 hours) antidote administration in paracetamol poisoning. Methods: We studied 40 cases of paracetamol poisoning where medical attention was sought at least 20 hours post-intake. Sex, age, symptoms, laboratory findings, treatment and outcome were recorded. Results: 24 out of 40 (60%) were female and 16 male (40%). Mean age was 25.6 years (range 14–45). 10 cases (25%) were from Attica (wider Athens area) and 30 (75%) from the rest of the country. 18.2 grams (range 8–35) was the mean quantity of ingested paracetamol, while 6 reported concomitant intake of other drugs or substances. Mean time until arrival to the hospital was 28 hours (range 20–48). The reason for this was mainly the fact that in 38 cases the intake was a suicide attempt, which was revealed only after symptoms occurred. Main symptoms were epigastric pain, nausea, vomiting, dizziness, and drowsiness. Blood tests showed hepatic damage. In 26 cases (65%) transaminase (AST, ALT) values were above 1000 U/L (range 1150–14000) whereas in 14 (35%) were below 1000 U/L. No signs of hepatic encephalopathy were reported, while in one case acute tubular necrosis developed. In all patients, treatment included general supportive measures and administration of *N*-acetylcysteine 300 mg/Kg within 20 hours IV. Mean time of hospital stay was 7 days (range 3–24) and the outcome was favorable in all cases. Conclusion: 1. Paracetamol poisoning is the most frequent cause of drug poisoning and treatment consists of early administration

of the antidote *N*-acetylcysteine. 2. Late administration of the antidote, even 20 hours after intake, is considered mandatory, because it seems to be effective.

31 LOXOSCELISM; ENVENOMATIONS BY THE BROWN RECLUSE SPIDER

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Objective: Loxoscelism, envenomation by spiders of the Loxoscelidae family, is known to occur in South, Central, and North America as well as the Mediterranean area and Europe. The most venomous and prevalent of these spiders in the USA belongs to the genus-species Loxosceles reclusa, commonly known as the ''fiddle-back'' or ''violin'' spider because of the distinctive marking on the back of its cephalothorax. Case Series: The presenter will show a series of slide photographs demonstrating the various manifestations seen in human cases. These findings include a variety of progressive cutaneous lesions, mostly demonstrated among a series of 20 pediatric patients who also had the systemic finding of hemolysis. Shown will be photos of lesions with the characteristic blister formation, effects of hyaluronidase (''spreading'' factor), ecchymosis, inflammation, ischemia, necrosis, eschar formation, and healing. Also included will be pictures revealing extensive soft tissue swelling, the toxic erythroderma rash, the ''halo'' lesion, hemoglobinuria, biopsy of dermonecrosis, autopsy microscopic slides, and pictures of the spider. Conclusion: Most of these cases are ''presumptive'' since rarely does the victim capture the biting culprit. However, the author knows of no other creature in the South Central USA causing the characteristic combination of cutaneous and systemic manifestations. Management of arachnidism is symptomatic and supportive. The fate of the skin lesion is determined within minutes following the bite. Most bite victims suffer only minor consequences. The ''benign neglect'' approach is successful in the vast majority of bites. Presently there is no specific therapy proven to prevent necrosis.

32 DOES CLINICAL TOXICOLOGY HAVE A FUTURE—LOUIS ROCHE LECTURE

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Introduction: ''Clinical toxicology is a dynamic field of medicine; new treatment methods are developed regularly, and the effectiveness of old as well as new modalities is the subject of constant critical review.''[1] Is clinical toxicology still a specialty that creates scientific excitement? Does it remain an area of medical, social and economic relevance? Do other scientists and non-clinical toxicologists endorse such a view? Do clinical toxicologists still have an important role in ''advancing knowledge and understanding of the diagnosis and treatment of all forms of poisoning'', by fostering ''a better understanding of the principles and practice of clinical toxicology in order to prevent poisoning . . .'', and by encouraging ''research in all aspects of poisoning''?[2] Does clinical toxicology have a future? *Clinical toxicology over the past 50 years*: It has been said that if the future is to be predicted accurately and the opportunities presented grasped, the past must be studied and understood. In 1944, Winston Churchill stated, ''The longer you can look back, the further you can look forward.'' Present day clinical toxicology had its roots in an epidemic of cases of acute poisoning in the late 1940s that led to the establishment in 1949 of a treatment center in Copenhagen specifically for the management of cases of acute poisoning.[3] The first poisons information service in Europe was founded in 1960 in the Netherlands.[4] In the United States, the first poisons center was opened in Chicago in 1953[5] and other centers followed; by the mid-1960s there were over 500 centers in the US. In 1964 the European Association of Poison Centres and Clinical Toxicologists was founded. The American Association of Poison Control Centers and the American Academy of Clinical Toxicology were established respectively in 1958 and in 1968. *Lessons to be learned*: What observations can be made and what lessons can be learned from the past 50 years to inform our toxicological future? (i) Most countries now have at least one poisons information center which provides advice to medical practitioners, pharmacists, paramedical staff and, in most countries, the public on the ingredients and general toxicity of the many drugs, chemicals, household products, plants and animals present in today's world. Yet not all centers are able to offer this service on a 24-hour, seven-days-a-week, basis and much of the advice given in many centers is based on that provided by commercially available information systems; few centers have the staff and facilities to develop comprehensive in-house toxicological databases. (ii) As a result of limited resources, and to increase effectiveness, there has been a trend over the past two decades towards larger regional and national poisons information centers, particularly in the developed world. In the US, for example, the number of poisons information centers fell from a peak of 661 in 1978 to 73 in 1998, of which 71 per cent were regionally certified. The decrease in the number of poisons information centers in the developed world, a trend which is likely to continue, has been offset somewhat by the establishment of poisons information centers

in most countries in the developing world. It is inevitable that over the next few years further poisons centers, particularly those providing only a limited service, will close leaving only nationally-designated and some regionally-designated (and funded) centers. (iii) The development of poisons treatment centers encompassing both in- and out-patient facilities has been a most important initiative. An in-patient service, of necessity, must be available at all times and be staffed by physicians with extensive training in clinical toxicology who are respected for their professional competence and authority and who are capable of furnishing reliable opinions as well as being adept at differential diagnosis, so that specific advice on the management of cases of poisoning can be given. If possible, these physicians should be responsible clinically not only for the management of patients suffering from the effects of acute or chronic poisoning but also for the detoxification of substance abusers. If logistically possible, it is a major advantage that the in-patient beds should be in a dedicated area to act as a focus for the provision of expert medical, psychiatric and social care. (iv) The development of centers offering both clinical and poisons information services, and the establishment of treatment centers independent of poisons information services, has accelerated further in some countries the closure of centers providing only advice, especially if treatment centers also offer an advisory service. This is a further reason why all poisons centers should provide a comprehensive service. (v) Some poisons centers do not have a clinical toxicologist on their contracted staff, or if they do the commitment is minimal, thereby limiting the ability of the center to provide a comprehensive clinical toxicology service. (vi) Not all centers are able to advise expertly on occupational and environmental toxicological problems, even though these are growth areas in both clinical and advisory terms. (vii) In the last two decades there have been major advances in treatment in part because of a better understanding of the mechanisms of toxicity and relevant kinetic principles, and partly because of a willingness to abandon treatments that are not evidence based. (viii)The two major international clinical toxicological societies, the EAPCCT and the AACT, have played an important role, particularly in the last two decades, in raising the scientific credibility of the specialty by organizing Congresses and CPD sessions, by jointly publishing Position Statements on key issues in toxicology, by co-sponsoring the journal, *Clinical Toxicology*, and by enabling their members to keep up-to-date by providing them with *Current Awareness in Clinical Toxicology*, a monthly listing of relevant toxicological literature. Conclusions: Clinical toxicology has been placed on the political agenda, both nationally and internationally. In the main, clinical toxicologists have risen to the academic and fiscal challenges presented to them over the last 50 years, though they now have new opportunities to address, particularly within the wider fields of public, environmental and occupational health. If these challenges are to be dealt with successfully, however, and the opportunities presented exploited, not only will substantial changes in the organization of many centers be necessary and considerable additional funding be sought, but also the training of clinical toxicologists will need, of necessity, to reflect these new opportunities and responsibilities. Although the concept of a poisons center offering a comprehensive clinical toxicology service may not be well developed in many countries, the combination of intensive treatment facilities for poisoned patients and substance abusers, a 24-hour, seven-days-a-week, poisons information service and supporting laboratory probably represents the best model for the future. A comprehensive clinical toxicology service will also be able to devote resources to research and training and there will be due emphasis on the occupational and environmental aspects of toxicology. As a result, clinical toxicologists will be able to address adequately both present and anticipated toxicological challenges and opportunities. The future of clinical toxicology will be assured! References: [1]Reigert JR, Roberts JR. *Recognition and management of pesticide poisonings*. Washington, DC: US Environmental Protection Agency. Fifth edition, 1999. p 2. [2]European Association of Poisons Centres and Clinical Toxicologists. Constitution: Aims and Objectives.2000. [3]Myschetsky A. History of barbiturate poisoning. In: *Acute Barbiturate Poisoning*. Matthew H, ed, Amsterdam: Excerpta Medica, 1971. [4]Pikaar SA, van Heijst ANP. The national poisons information center. *Vet Hum Toxicol* 1979;**21**(Suppl):76–80.[5] Scherz RG, Robertson WO. The history of poison control centers in the United States. *Clin Toxicol* 1978;**12**:291–6.

33 CHROMIUM INTOXICATION: FEATURES AND MANAGEMENT

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Introduction: Chromium is found in various oxidation states, principally as elemental chromium Cr (0), trivalent chromium (Cr (III)) or hexavalent chromium (Cr (VI)). Chromium (III) is an essential dietary trace element that serves to potentiate the effects of insulin. Virtually all natural chromium compounds are in the trivalent (III) form, predominantly as chromite. Chromite ore is the only source of chromium used commercially. Some 80% of commercially used chromite is consumed by the metallurgical industry. For example, the iron-chromium alloy ferrochromium, produced by the

electrothermal reduction of chromite, is used in the production of stainless steel, the electrolytic production of chromium metal and in the production of cast iron. Each of these processes involves potential exposure to hexavalent chromium. Chromium chemicals are manufactured predominantly as hexavalent chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) salts. These are used widely in dye and pigment production, in wood preservation, inks, leather tanning, catalyst manufacture and photographic chemicals. Other important occupational sources of hexavalent chromium exposure include chrome plating, and stainless steel welding. Mechanisms of toxicity: Chromium (III) compounds have produced skin sensitization. Chromium (VI) compounds are the most important in human toxicology, but the mechanisms by which they initiate toxicity have not been elucidated fully. Experimental studies have shown that hexavalent chromium produces selective proximal renal tubular damage mediated by reactive intermediates formed during the intracellular reduction of chromium (VI) to chromium (III). Chromium (III) may be the allergen in chromium (VI) sensitivity, via *in vivo* reduction of hexavalent to trivalent chromium. The reduction of chromium (VI) to chromium (III) is a prerequisite to chromium binding to cell nuclei and DNA *in vitro,* and thus trivalent chromium is the final perpetrator also of hexavalent chromium genotoxicity. Hexavalent chromium is a powerful oxidizing agent. Soluble chromium (VI) compounds (e.g. chromic acid and potassium or ammonium dichromate) are corrosive. In addition, hexavalent chromium is a pulmonary carcinogen. Toxicokinetics: Chromium can be absorbed via the lungs, skin and the gastrointestinal tract. Hexavalent compounds are better absorbed than trivalent compounds and soluble compounds are absorbed more readily than insoluble compounds. Inhaled insoluble chromium salts undergo significant ciliary clearance with a large proportion appearing in feces. Some ingested chromium (VI) is reduced in the stomach to chromium (III) before it reaches the small intestine. Once absorbed, chromium (III) cannot readily traverse cell membranes but circulates bound mainly to transferrin and predominantly is renally eliminated, though small amounts appear in bile. Some absorbed hexavalent chromium is reduced in the bloodstream to trivalent chromium but this system is saturable and the remaining hexavalent chromium readily crosses cell membranes so that systemic toxicity may result before renal and biliary excretion occurs. Clinical features: acute exposure: Direct skin contact with hexavalent chromium solutions causes burns with the potential for increased Cr (VI) absorption and systemic toxicity, notably renal and hepatic failure. Inhalation of mists or vapors of Cr (VI) compounds causes respiratory tract irritation with cough, wheeze and chest pain. In severe cases a chemical pneumonitis develops which may be complicated by the onset of the Adult Respiratory Distress Syndrome (ARDS). Ingestion of hexavalent chromium salts causes corrosive damage to the gastrointestinal tract with burning in the mouth, vomiting, abdominal pain, diarrhea and gastrointestinal hemorrhage; cardiovascular collapse may then ensue. Those surviving this phase may go on to develop renal and hepatic failure, which generally has a poor prognosis. Seizures, hypertonia, sluggish reflexes, irritability, coma, thrombocytopenia, and disseminated intravascular coagulation are also recognized sequelae. Clinical features: chronic exposure: Chromium (VI) compounds are skin sensitizers and an important cause of occupational contact dermatitis. Non-occupational chromium dermatitis may follow exposure to chromates in leather, matches, glue, paint and detergents. Chrome ulcers may develop at a site of previous, often trivial, skin damage after repeated topical exposure to soluble chromium (VI) compounds. This effect is independent of chromium sensitization and depends on the frequency and duration of skin contamination. Chronic inhalation of hexavalent chromium compounds, particularly chromic acid mist, may result in ulceration and perforation of the nasal septum. Pharyngeal and laryngeal ulcers may also occur. Occupational asthma has been reported in workers exposed to chromium powder or fumes from chromium containing solutions. Lung fibrosis, bronchitis and emphysema also may result. Proximal renal tubular damage, with microproteinuria has also been reported among workers occupationally exposed to Cr(VI). General management: Decontamination with water is the priority following acute skin or eye contact. Chromium contact dermatitis is managed most effectively by allergen avoidance. Chromium induced-asthma should be treated conventionally and intravenous steroids are indicated for laryngeal edema. Emesis or gastric lavage are contraindicated following chromium (VI) ingestion due to the corrosive nature of many chromium salts. Vigorous resuscitation is required for gastrointestinal hemorrhage complicated by hypovolemic shock; upper gastrointestinal endoscopy should be performed urgently. Hemodialysis/hemofiltration should be employed if acute renal failure supervenes but are otherwise not an effective means of enhancing chromium elimination. Specific management: It has been recommended that ascorbic acid should be administered to patients with chromium poisoning to reduce systemic toxicity and that ascorbic acid should be applied locally as a barrier cream to prevent chromium dermatitis. *In vitro* experiments confirm that the addition of ascorbic acid to plasma containing chromium (VI) leads to a dose-dependent reduction of chromium (VI) to chromium (III). Oral ascorbic acid 4–5.3 g/kg reduced mortality in rats from 100% to 14% when given 2 hours after oral potassium chromate. Parenteral ascorbic acid 0.5–5 g/kg reduced significantly experimental chromium-induced

nephrotoxicity when administered 30 minutes before parenteral sodium dichromate and up to one hour after parenteral sodium chromate dosing. However, the administration of parenteral ascorbic acid more than two hours after parenteral chromate did not protect against renal damage and parenteral ascorbic acid given three hours after chromate increased toxicity. A possible reason for the lack of benefit of ascorbic acid when administration is delayed, is that chromium (VI) cellular uptake has occurred prior to ascorbic acid administration. Based on these experimental studies, substantial amounts of ascorbic acid would need to be administered, preferably parenterally, soon after exposure to prevent systemic toxicity from chromium (VI) in humans. However, as ascorbic acid is a metabolic precursor of oxalate, the administration of ascorbic acid in high dose could lead to acute oxalate nephropathy, particularly in the presence of renal failure. While smaller doses of ascorbic acid (e.g. 10 g intravenously) are not toxic, such doses may not reduce the mortality from systemic chromium poisoning, even if administered soon after exposure. In summary, there is currently insufficient evidence to advocate the use of ascorbic acid in the management of systemic chromium toxicity.[1] Topical 10% ascorbic acid has been claimed to reduce significantly the healing time of experimentally induced chrome ulcers in guinea pigs. The proposed mechanism is reduction on the skin surface of chromium (VI) to chromium (III). Although several case reports suggest that topical ascorbic acid is effective in the management of chromium dermatitis, this has not been confirmed in controlled clinical trials. Reference: [1]Bradberry SM, Vale JA. Therapeutic Review: Is ascorbic acid of value in chromium poisoning and chromium dermatitis? *J Toxicol Clin Toxicol* 1999;**37:**195–200.

34 FEATURES AND MANAGEMENT OF ARSENIC INTOXICATIONS

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Background: Known since antiquity, and memorialized in countless cases of infamous homicidal poisonings, arsenic continues to tantalize us as an unusually problematic poison in cases of acute and chronic exposures. The recent attention to arsenic as an omnipresent water toxicant in Bangladesh and West Bengal emphasizes the continued great peril of arsenic as an environmental poison. There are multiple forms of arsenic including elemental, gaseous (arsine), organic, and the inorganic salts trivalent arsenite (arsenic trioxide) and pentavalent arsenate. Extremely toxic at low doses the minimum lethal oral dose in humans range from 1 to 3 mg As/kg/day and a 20 mg dose in young children may be life threatening. Tasteless and odorless, arsenic is used in a number of occupations including semiconductor industry, glass making and smelting. Although its use as a pesticide has diminished its presence as a preservative, especially in ''pressure treated'' wood as chromated copper arsenate, has continued to generate potential health concerns. Other possible sources of arsenic exposure include homeopathic remedies and contaminated herbal medications. The presence of naturally occurring arsenic in the water worldwide has become a public health problem affecting millions of people. Arsenic is well absorbed enterally and by inhalation. It exhibits a triphasic distribution where 90% is cleared from blood within 2–3 hours with subsequent redistribution to the liver, kidney, GI tract, and lungs by 24 hours and incorporation into hair, nails within 2–4 weeks. Arsenic exhibits biphasic urinary elimination appearing in the urine as early as 2 hours after ingestion. The mechanism of toxicity involves reversible binding to sulfhydryl groups resulting in critical metabolic enzyme inhibition. Oxidative phosphorylation disruption and vascular capillary damage also occur. *Arsenic poisoning* should be suspected in cases of multisystem illness of unclear etiology especially in the presence of neuropathy, hematological disturbances, skin rash or nail changes, and gastrointestinal complaints. The chronicity of the poisoning determines in part the particular system involvement. Acute single dose poisoning is characterized by prominent GI, cardiac, hematological (anemia, pancytopenia), and neurological symptomatology. Gastrointestinal symptoms may occur within minutes to hours after exposure and include nausea, vomiting, abdominal pain and profuse diarrhea. Life threatening cardiovascular decompensation due to capillary leak, vasodilatation, intravascular volume depletion, myocardial dysfunction and the possibility of ventricular dysrhythmias from arsenic induced long QTc syndrome may also occur. Neurological dysfunction after acute exposure may affect both the central and peripheral nervous systems. Early on acutely exposed patients are at risk for encephalopathy and seizures. For those who survive, a peripheral motor-sensory neuropathy resembling Guillain-Barré syndrome may develop within 1 to 3 weeks of ingestion resulting in profound quadriparesis in some cases. Hepatic and renal dysfunction may also occur. Low dose chronic arsenic exposure is more likely to result in the insidious development of a variety of dermatological lesions including diffuses or spotted melanosis, palmoplantar hyperkeratosis, and skin cancer in advanced cases. Whitish horizontal bands on the nail plate (Aldrich-Mee's lines) are a distinguishing hallmark of arsenic poisoning. Neuropathy may also be a prominent feature of chronic arsenicosis. Cancer of lung, uterus, GU tract, and hepatic angiosarcoma has also been associated with chronic arsenic exposure. Arsenic exposure may be confirmed by blood, urine, hair or nail arsenic determinations depending

on the timing of the exposure. Blood arsenic may return to normal within a few days of acute exposure and not demonstrate significant elevation in chronic exposure. Low-level urinary excretion may continue for months after exposure. Speciated urinary arsenic determinations, if available, are preferred since nontoxic organic "fish" arsenic may represent a significant amount of total arsenic measurements. Segmental hair determination is useful in determining the timing of exposure(s). *Treatment priorities* include GI decontamination in cases of recent acute exposure, fluid resuscitation, and antidysrhythmics and anticonvulsants as needed. A variety of chelators have been used to decrease arsenic body burden including BAL, DMSA, and DMPS. Clinical trials to assess efficacy are lacking. Anecdotal case reports and case series data suggests that BAL may be beneficial in acute poisonings prior to the onset of neuropathy. Concerns about BAL increasing CNS arsenic redistribution and difficulties with BAL administration and toxicity have been raised. DMSA and DMPS may be reasonable alternatives. DMSA is not available in the US as an intravenous preparation and lacks significant intracellular penetration while DMPS is not approved in the US and allergic complications including Stevens Johnson syndrome have been reported with its use.

35 MUSEUM ARTIFACTS AS A SOURCE OF ARSENIC AND MERCURY EXPOSURE

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Background: Museums have routinely used a variety of pesticides on perishable artifacts, including arsenic compounds, carbon disulfide, chlordane, chloropicrin, cyanide, dichlorvos (DDVP), DDT, dieldrin, ethylene oxide, lindane, mercury compounds, methyl bromide, naphthalene, paradichlorobenzene, strychnine, and sulfuryl fluoride. Contaminated artifacts pose health hazards to museum workers that have been well recognized since the 1970s. Museums occasionally sell or otherwise dispose of objects in their collections and, in the United States, federally-supported museums have been repatriating sacred cultural objects to Native American tribes because of the Native American Graves Protection and Repatriation Act (NAGPRA) of 1990. Arsenic and mercury are of particular concern because of their high toxicity, high object residue, environmental permanence, subtle and delayed manifestations of toxicity, and difficult decontamination and disposal issues. Discussion: A number of studies of museum storage cases, objects in museum collections and objects already repatriated to tribes have been performed. Makos and Dietrich found arsenic (up to 23,457.6 mcg/ft^2) and mercury (up to 100 mcg/ft^2) contamination of museum storage cases. Muir et al. found arsenic (up to 11,300 ppm) and mercury (up to 200 ppm) on a variety of museum specimens. A 1994 wipe sampling study of three museum objects subject to NAGPRA repatriation found contamination with arsenic (up to 13.8 mcg/wipe) and mercury (up to 6.7 mcg/wipe) in all three specimens. A 1998 wipe sampling study of 19 repatriated artifacts found three contaminated with arsenic (up to 0.5 mg/L). A 1999 study of three repatriated objects found arsenic contamination of two specimens (estimated total object arsenic 60 mg and 1.3 grams, respectively) and trace residue of naphthalene on the third (Seifert et al.). The incidence of other pesticide residues on such objects is unknown, as most investigators have not tested for these. A majority of objects found to be contaminated had no documentation of pesticide treatment. Object residues of arsenic and mercury may be above United States Environmental Protection Agency toxic waste designation levels, requiring special handling in disposal. The application and enforceability of federal regulations on tribal lands, however, is unclear. Repatriated objects may have been stored, used and disposed of in culturally determined ways, resulting in individual and environmental exposures to pesticide residues. Conclusions: Some museum objects being transferred to non-museum settings are contaminated with pesticide residues—particularly arsenic and mercury—and pose particular health risks because of 1) a lack of awareness of their contamination; 2) an inability to rely on museum records of pesticide treatment; 3) toxicological and physiochemical properties of arsenic and mercury; 4) inexperience in or conflicting values regarding display, storage, handling, or other uses of contaminated objects; 5) potential disposal of contaminated objects in non-environmentally appropriate ways; and 6) conflicting laws governing disposal jurisdiction. These objects should be tested, the health risks determined, and regulations enacted to ensure that individual and environmental exposures do not occur. References: Goldberg L. A history of pest control measure in the anthropology collections, National Museum of Natural History, Smithsonian Institution. *JAIC* 1996:23–43. Makos KA, Dietrich EC. Health and environmental safety. In *Storage of Natural History Collections: A Preventive Conservation Approach*, Vol. 1. Rose CL, Hawks CA, Genoways HH, eds, 1995:233–252. Soc Preserv Nat Hist Coll. Muir D, Peace CP. Health hazards in natural history museum work. *Museums J* 1981;**80**(4):205–206. Seifert SA, Boyer LV, Odegaard N, Smith DR, Dongoske KE. Arsenic contamination of museum artifacts repatriated to a Native American tribe. *JAMA* 2000;**283**(20):2658–2659.

36 THALLIUM POISONING: PAST, PRESENT AND FUTURE

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Background: Thallium salts were once commonly used to treat venereal diseases, tuberculosis and ringworm. This practice was curtailed because significant morbidity and mortality resulted from a narrow therapeutic index. Similarly, whereas thallium salts were highly successful rodenticides, their use in the United States was abandoned because substantial human and animal toxicity frequently followed unintentional exposures. Although still used worldwide in industry, and as a rodenticide in some countries, most reported thallium poisonings result from its use as a homicidal agent. Thallium salts can be absorbed through intact skin, alveolar membranes and the gastrointestinal tract, with the latter route being the most consequential. Distribution is rapid into the central compartment, but may take days to complete into the central nervous system. An ionic radius that is similar to potassium allows rapid uptake into cells via potassium channels and Na-K-ATPase. Once inside cells, thallium replaces potassium and disrupts many critical enzyme systems such as succinic dehydrogenase, pyruvate kinase and Na-K-ATPase. Additional toxicity results from binding to riboflavin and various sulfhydryl-containing enzyme systems. Elimination occurs through feces and urine, with a relatively short half-life of about 2 days when renal function is preserved. Clinical effects: Clinically, toxicity from thallium salts bears some resemblance to toxicity from other metal salts. Initially, gastrointestinal symptoms predominate, with nausea and vomiting most commonly reported. Rarely, constipation also occurs and highlights the comparatively benign course of thallium's gastrointestinal toxicity. These symptoms are followed over subsequent hours to days by a characteristically painful ascending peripheral neuropathy. Additional findings include pleuritic chest pain, renal insufficiency, and an autonomic neuropathy, which presents as tachycardia and hypertension. Severe cases develop cranial nerve abnormalities as well as changes in consciousness and respiratory insufficiency. The second characteristic finding, alopecia, occurs about one week following exposure and can progress to complete hair loss. Later, Mee's lines may develop. Diagnosis: The diagnosis of thallium poisoning is usually established based on history and physical examination revealing the characteristic neuropathy and alopecia. Additionally, like most metals, thallium salts are radiopaque. X-rays of patients and contaminated food products may be revealing. Analysis of hair roots by simple light microscopy may demonstrate characteristic pigment changes at the root. The diagnosis can be confirmed by atomic absorption spectroscopy of either the blood or urine. Management: Treatment begins with gastrointestinal decontamination. Unlike most metals, activated charcoal has a high affinity for thallium salts, and multiple dose activated charcoal was beneficial in an animal model. When thallium is demonstrable on an abdominal radiograph, whole bowel irrigation has been suggested, based on theoretical grounds. Although forced potassium diuresis enhances renal elimination, it exacerbates both neurological toxicity in humans and lethality in animals. Furthermore, traditional metal chelators all exacerbate toxicity in animal models and are therefore not used in humans. Prussian blue (at a dose of 250 mg/kg/day) has proven benefit in animals and humans. In severe cases combined hemodialysis and hemoperfusion may provide additional benefit, although this is unclear. Many patients with thallium poisoning will significantly recover with aggressive therapy, the extent of which seems best defined by their clinical condition at the time of diagnosis.

37 CEREBRAL SPINAL FLUID (CSF) ANALYSIS IN FATAL THALLIUM POISONING

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Objective: Although most existing data suggest that thallium distributes into the central nervous system (CNS) within 24 hours, CNS toxicity usually progresses over days. To date, no previous reports document human CSF thallium concentrations. We report a patient with thallium poisoning whose CSF thallium concentrations rose despite a falling serum concentration. This observation may offer insight into the progression of thallium-induced CNS toxicity. Case Report: A 48-year-old male presented to the hospital complaining of painful tingling of his arms, legs, tongue and lips, and stated that it felt as if he were suffering from frostbite. He refused to walk because of severe burning in his feet. The patient denied headache, fever, gastrointestinal symptoms or weakness, but recalled partially eating an unpalatable sandwich the previous night. Physical examination was significant only for the absence of ankle jerk reflexes and vibratory sensation in both legs. All standard laboratory tests were within normal limits, except for slight proteinuria. Viral encephalitis was considered, and a lumbar puncture (LP) was only significant for a protein of 62 g/L. A head CT scan was also normal. Over the subsequent 48 hours his symptoms progressed to include altered mental status, ptosis, slurred speech, weakness (4/5 in UE and 3/5 in LE) and loss of positional sense. Deep tendon reflexes were 2+ in the UE and absent in the LE. A second LP was performed. Because of a suspicion of malicious poisoning, a toxicology consult was obtained, and a diagnosis of thallium poisoning was considered. A urine assay revealed a thallium

concentration of 50,000 mcg/L (normal < 5 mcg/L). Unfortunately, as the assay was being performed the patient suffered a cardiac arrest and could not be resuscitated. Stored specimens of serum and CSF were analyzed for thallium by atomic absorption spectroscopy, as shown below.

Hospital Day	Serum Thallium Concentration mcg/L (Normal < 2)	CSF Thallium Concentration mcg/L
Day 1	8700	1200
Day 3	7200	2100

Conclusion: Thallium toxicity often presents with a mild gastrointestinal syndrome followed by a classically painful ascending neuropathy and alopecia. In severe cases CNS toxicity progresses to include cranial neuropathies and altered consciousness. Although animal models suggest that thallium penetrates rapidly and completely into the CNS, the correlation between this patient's rising CSF concentrations and worsening CNS symptoms might suggest a slower rate of distribution in humans. This further suggests that the progressive deterioration that occurs in thallium-poisoned patients may be related to ongoing CSF distribution rather than progression of an initial insult. This finding also argues for aggressive early therapy to help lower serum thallium concentrations.

38 THE CLINICAL TOXICOLOGY OF GOLD: HOW MUCH OF IT WE SEE, HOW LITTLE WE KNOW

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Introduction: The medicinal use of gold has been reported in China as early as 2500 BC. Since then it has been used in various pharmaceutical contexts up to the present day. The modern era of chrysotherapy (the medical use of organic gold compounds) began in the early part of the 20th Century when it was thought to be a treatment for tuberculosis. Since the 1920s however, gold compounds have found considerable utility as a second line treatment of autoimmune disease. Originally thought to be efficacious for both systemic lupus erythematosus and rheumatoid arthritis, gold salts have emerged primarily for the treatment of the latter. Human contact with gold, however, extends beyond simply its medicinal administration in chrysotherapy. Physical contact with gold from jewelry, dental alloys and even eyelid implants is widespread. Gold is used as a component of some traditional medications, for example, Ayurvedic, Uunani-Tibb, and Gold Kushta.[1,2] Gold is a component of some forms of Schnapps, and reactions to it have been reported in sensitized individuals. More recently, ultra pure metallic gold micro particles have been used as delivery vehicles for the administration of native DNA in gene therapy.[3] Metallic gold is used for this purpose because of its presumed low reactivity toward DNA. Features: Acute non-immunologic gold toxicity has not been described. The most common form of adverse reaction to gold is dermatitis, which may either be non-allergic or a hypersensitivity reaction. With the introduction of gold into common patch testing panels, the frequency of positive skin tests has been shown to be up to 9% of the tested populations.[4] Gold-induced hypersensitivity dermatitis may be associated with eosinophilia and lymphadenopathy. Rashes, with diverse manifestations, are the most common complication of therapy with gold compounds, occurring in up to 30% of treated patients.[5] Patients undergoing chrysotherapy may develop a non-symptomatic gray-blue discoloration of sun-exposed areas of the skin, known as chrysiasis, particularly if they have received large doses. There are several rare but potentially life-threatening, manifestations of gold toxicity. These are immunological in nature. Patients receiving chrysotherapy are at risk for blood dyscrasias, including leukopenia, aplastic anemia, and immune thrombocytopenia. The latter is the most common of these hematological effects, occurring in up to 3% of gold treated patients.[6] Gold-induced thrombocytopenia has been reported to occur with cumulative doses of elemental gold ranging from 50–4,6000 mg, most often during the loading phase of gold therapy, encompassing doses of <1 gram. The mean cumulative dose in patients with gold-induced thrombocytopenia is 840 mg. Gold-induced thrombocytopenia does not appear to be dose-related.[7] The largest series of gold-induced thrombocytopenia reported 23 cases and demonstrated that patients who were HLA-DR3 positive had an 8.9 times increased risk of thrombocytopenia.[8] Gold-induced autoimmune glomerulonephritis is another potential complication of gold therapy.[9] Proteinuria occurs in 6–17% of treated patients; nephrotic syndrome occurs in 2.6–5.3%.[10] If biopsied, these patients are generally found to

have a membranous glomerulonephritis. Leukocyte marker studies have shown that patients that are HLA-DR3 positive have a 32 fold increased rate of proteinuria.[9] Gold has also been associated with drug-induced systemic lupus erythematosus. Collectively, the human studies have shown that only a small percentage of patients receiving gold therapy develop these adverse manifestations, which are non-dose related. These manifestations appear to be immunological in nature and occur predominantly in patients who are HLA-DR3 positive, a leukocyte antigen phenotype that is not associated with rheumatoid arthritis. Animal studies bear out the apparent non-dose related and genetically determined nature of these effects. There have been no controlled trials on the treatment of gold-induced immunotoxicity. The large body of anecdotal clinical experience suggests that most of the manifestations of gold-related immunotoxicity resolve with cessation of exposure, or, in some cases, simple dose reduction. Large doses of gold salts given to animals can be lethal, an effect that is prevented by the simultaneous administration of BAL.[11,12] However, this model has little apparent pathophysiologic similarity to the immunotoxic manifestations of gold exposure in humans. The cumulative, but uncontrolled, human experience suggests that patients whose toxic manifestations do not resolve with cessation of exposure will generally respond to corticosteroid treatment.[7–9] Multiple isolated case reports have described the use of BAL or other chelators. None have provided any convincing evidence of a clinical response to these agents and few have presented any data at all regarding possible enhancement of gold excretion in chelated patients. References: [1]Bajaj S, Vohora SB. Analgesic activity of gold preparations used in Ayurveda & Unani-Tibb. *Indian J Med Res* 1998;**108**:104–111. [2]Nagi AH, Khan AH. Gold neuropathy in rabbits using an indigenous preparation. A morphological study. *Intern Urol Nephrol* 1984;**16**:49–59. [3]Merchant B. Gold, the noble metal and the paradoxes of its toxicology. *Biologicals* 1986;**26**:49–59. [4]Bjorkner B, Bruze M, Moller H. High frequency of contact allergy to gold sodium thiosulfate: an indication of gold allergy? *Contact Derm* 1994;**30**:144–151. [5]Anon. Gold for rheumatoid arthritis. [Editorial] *Brit Med J* 1971;**1**:471. [6]Freyberg RH. Present status of gold therapy for rheumatoid arthritis. *JAMA* 1950;**143**:418–421. [7]Harth M, Hickey JP, Coulter WK, Thompson JM, Disney TF. Gold-induced thrombocytopenia. *J Rheumatol* 1978;**5**:165–172. [8]Coblyn JS, Weinblatt M, Holdsworth D, Glass D. Gold-induced thrombocytopenia–A clinical and immunogenetic study of twenty-three patients. *Ann Int Med* 1981;**95**:178–181. [9]Bigazzi PE. Metals and kidney autoimmunity. *Env Health Persp* 1999;**107**:753–765. [10]Fillastre JP, Godin M. Drug-induced nephropathies. In: *Oxford Textbook of Clinical Nephrology*, Davison AM, Cameron S, Grunfeld JP, Kerr D, Ritz E, Wonearls CG, eds. Oxford, UK: Oxford University Press 1998:2645–2657. [11]Gillmo CS, Freyberg RH. The effects of 2,3-dithiopropanol (BAL) on gold toxicity in rats. *J Lab Clin Med* 1948;**33**:1024–1028. [12]Kuzell WC, Pisslbury PL, Gellert SA. The effects of 2,3-dithiopropanol (BAL) on toxicity and excretion of gold. *Stanford Med Bull* 1947;**5**:197–202.

39 ZINC TOXICITY

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Zinc may be toxic either by inhalation or by ingestion.[1] In the occupational setting, the *inhalation* of fumes from zinc oxide is one of the factors responsible for the "*metal fume fever*" syndrome. This syndrome is usually a self-limited disease beginning a few hours following exposure to zinc oxide fumes. The clinical picture is characterized by a large variety of symptoms: fatigue, fever, chills, myalgia, cough, dyspnea, leukocytosis, thirst, and metallic taste. This pattern is not specific to zinc oxide fumes and can also occur following exposure to fumes of numerous other metals (e.g. aluminum, nickel). The symptoms usually resolve within 1 or 2 days and no specific therapy is required. There is also no need for laboratory investigations and chest X-ray is usually irrelevant. Much more severe is the exposure to *zinc chloride* that has been described following the detonation of zinc chloride smoke bombs in a closed environment. Significant lung injuries have been observed leading to adult respiratory syndrome distress syndrome or death in some instances. Zinc has also been involved in poisoning cases by *ingestion* or exceptionally by intravenous injection. The severity of the clinical picture is related to the type of zinc salts: zinc sulfate produces emesis, while the toxicity of zinc phosphide is extremely serious due to the liberation of phosphine causing shock, metabolic acidosis and eventually death. Some zinc compounds are considered as extremely irritant and produce caustic lesions to the gastrointestinal tract. Zinc chloride poisoning may be particularly severe when the patient has ingested highly concentrated solutions.[2] Hypovolemic shock may occur due to diarrhea and extensive burns are observed in the oropharynx, the esophagus and the stomach. Immediate orotracheal intubation or tracheostomy may be required when upper airways are involved. The systemic effects of zinc excess are still debated. Zinc chloride is a soluble salt and zinc absorption is usually achieved in the second portion of the duodenum. Extremely high zinc plasma concentrations have been reported in some cases, but there is no clear correlation between these concentrations and the clinical manifestations.[2,3] The central nervous

system is a possible target organ, and lethargy and confusion have been noted mainly in children. Cardiogenic shock seems uncommon and hypertension has even been observed. Zinc may also accumulate in the pancreas with the possibility of acute pancreatitis and also delayed exocrine pancreatic insufficiency. Interference with gastrointestinal copper absorption has been described following the chronic excessive intake of zinc compounds and this mechanism has also been suggested following acute zinc poisoning.[3] Liver toxicity is uncommon. Renal failure with acute tubular necrosis can occur after ingestion. The treatment for the ingestion of zinc salts is mainly supportive. With zinc chloride, endoscopy should be performed to assess the severity of esophageal or gastric burns. Fluid and electrolyte disturbances should be corrected. There are few literature data concerning the usefulness of chelation for zinc systemic toxicity. Calcium disodium ethylenediaminetetracetate ($CaNa_2EDTA$) is the chelator of choice, dimercaprol (BAL) also being effective. Some authors noted an improvement of the neurological status following chelation therapy. In other observations, $CaNa_2EDTA$ or BAL increased urinary zinc excretion without significant clinical improvement. The decision to start chelation therapy should be guided by the severity of the clinical findings (lethargy, hypotension) rather than by zinc plasma level. References: [1]Barceloux DG. Zinc. *J Toxicol Clin Toxicol* 1999;**37:**279–292; [2]Hantson Ph, Lula F, Lievens M, Mahieu P. Extremely high plasma zinc following zinc chloride ingestion. *J Toxicol Clin Toxicol* 1998;**36:**375–377; [3]Hantson Ph, Lievens M, Mahieu P. Accidental ingestion of a zinc/copper sulfate preparation. *J Toxicol Clin Toxicol* 1996;**34:**725–730.

40 FEATURES AND MANAGEMENT OF ALUMINIUM (ALUMINUM) INTOXICATION

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Objective: To discuss the features and management of aluminium toxicity. Discussion: Aluminium is one of the commonest elements found in the earth's crust and human exposure is unavoidable. The commonest route of exposure is by ingestion with an average of 30-50 mg/day being taken of which 7 mg/day comes from the water supply. Most of aluminium is insoluble and not absorbed. There is controversy about the links between aluminium levels in drinking water and Alzheimer's disease though no clear relationship has been established. However both the pH of the drinking water and associate fluoride treatment may influence the amount of aluminium absorbed. Consequently it is difficult to establish an exposure-disease relationship. However accumulations of aluminium have been identified in the neurofibrillary tangle bearing neurons of cases of Alzheimer's as well as of Guam natives suffering from Parkinsonism, dementia and amyotrophic lateral sclerosis. Acute aluminium toxicity is rare. Chronic toxicity is usually found in patients with chronic renal failure or in occupational exposures. Patients with chronic renal failure are at the highest risk of developing aluminium toxicity from the aluminium in the dialysate fluids or from use of phosphate binders. The soluble forms of aluminium ($AlCl_3$, AlF, Al citrate) are more likely to cause toxicity than the insoluble forms (AlOH). The signs of aluminium toxicity in these patients are dialysis encephalopathy syndrome, microcytic anemia and aluminium-related bone disease. The features of dialysis encephalopathy syndrome include dysarthria, stammering, seizures, motor disturbances and dementia. This syndrome occurred originally in patients where there were high levels of aluminium in the dialysis fluid but now occurs secondary to the use of aluminium-containing phosphate binders. Aluminium-related bone disease is found in patients on long-term dialysis or who have had bilateral nephrectomy. Aluminium inhibits osteoblast formation leading to osteopenia and fractures. Occupational exposure to aluminium occurs at the electrolytic production of aluminium from Bauxite and in connection with remelting, milling, welding and production of aluminium compounds. Occupational exposure to aluminium-containing dust may cause pulmonary disease or systemic neurotoxicity. Combined exposure to aluminium and silica containing dust may cause pulmonary fibrosis known as Shaver's disease. In the clinical setting fatal encephalopathy has been described after a neurosurgical case where aluminium-containing cement was used. Aluminium toxicity is treated by stopping exposure and by using the chelating agent deferoxamine. Conclusion: Acute aluminium toxicity is rare. Chronic toxicity is found either in dialysis patients or in occupational exposures. The link between aluminium toxicity and Alzheimer's disease is controversial.

41 STUDY BY CEREBRAL MICRODIALYSIS OF THE KINETIC INTERACTION BETWEEN HIGH DOSES OF BUPRENORPHINE AND FLUNITRAZEPAM IN RATS

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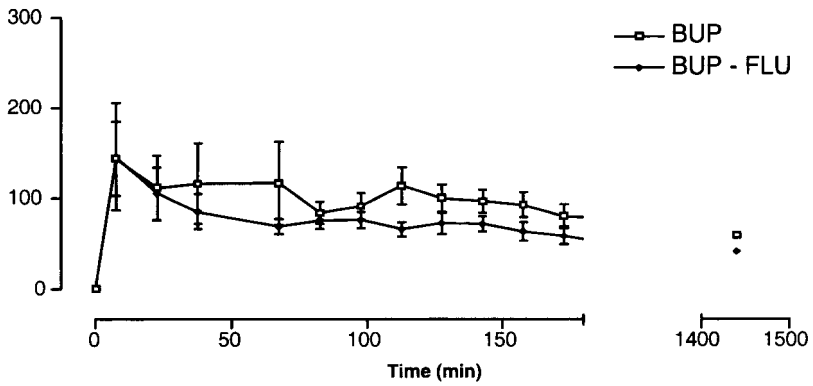
Objectives: Buprenorphine (BUP), a substitution treatment of opiate addiction, largely prescribed in France, may cause severe acute poisoning with coma and respiratory failures, in case of overdose, misuse or association with benzodiaze-

pines, including flunitrazepam (FLU)[1]. We tested the hypothesis of a pharmacokinetic interaction in brain between BUP and FLU, using an intracerebral microdialysis procedure in rats. Methods: BUP was measured by high-performance liquid chromatography with electrochemical detection. We compared 2 randomized groups of Male Sprague-Dawley rats treated IV with BUP 30 mg/kg (N = 10) and BUP 30 mg/kg + FLU 40 mg/kg (N = 10). Results: Kinetics of BUP in the striatal dialysates show a rapid initial increase corresponding to diffusion into the brain, followed by a sustained plateau and then a slow elimination phase. This distribution kinetic might result from 3 non-exclusive mechanisms: 1) an equilibrium between blood and brain tissue; 2) continuous diffusion between the cerebral intra- and extracellular compartments or 3) the saturation of BUP metabolism, related to the high dose used in this present study. BUP



concentrations in dialysates are not significantly different between the 2 groups. Moreover, there is no significant difference in the other kinetic parameters: maximal striatal concentration (Cmax), time to reach Cmax (Tmax), area under curve, plateau value, time to reach plateau, mean residence time and elimination half-life. Conclusion: Our study does not support the hypothesis of a kinetic interaction between BUP and FLU in rat brain. Synergy in the effects of these two psychotropics may result from a pulmonary local interaction or be relevant of a toxicodynamic mechanism. Reference: [1]Tracqui A. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol* 1998;**22**:430–434.

42 PRETREATMENT WITH 4-METHYLPYRAZOLE BLOCKS THE DELAYED AND POTENTIATED TOXICITY OF CONCOMITANT ALCOHOL AND 1,4-BUTANEDIOL POISONING IN CD-1 MICE

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Objective: 1,4-butanediol (BD) is the dihydroxy precursor of gamma-hydroxybutyrate (GHB), a popular recreational drug that has been banned by the FDA and controlled as a federal Schedule I drug. Like GHB, BD is abused at nightclubs and dance "raves" for its purported effects as a "natural" euphoriant, psychedelic, and sexual enhancer. BD is enzymatically converted to GHB *in vivo* by alcohol dehydrogenase (ADH), and overdoses can result in life-threatening coma, respiratory depression, bradycardia, hypotension, and seizures. Moreover, ethanol (ETOH) coingestion with BD may lead to potentially dangerous pharmacodynamic interactions due to competition for ADH. In fact, animal models with ETOH and BD poisoning resulted in potentiated and prolonged toxicity. Clinically, delayed BD toxicity was recently reported in a patient who had preingested ETOH. This study investigated if pretreatment with the ADH antagonist, 4-methylpyrazole (4-MP), can decrease the potentiated and delayed toxicity of concomitant ETOH and BD poisoning. Methods: Twenty male CD-1 mice were administered intraperitoneal (i.p.) 4-MP 25 mg/kg as a pretreatment (n = 10) or i.p. deionized, distilled water as control injections (n = 10). Five minutes later, mice in both groups were administered i.p. ETOH 2 g/kg followed another 5 minutes later by i.p. BD 600 mg/kg. Toxicity was then assessed at 10 minute intervals by the righting reflex and the rotorod test (ability of the mouse to log roll on a 1 inch diameter rod revolving at 6 RPM) until recovery. Results: The righting reflex was not lost in any pretreated or control animals. Control animals failed the rotorod test after 10 minutes but recovered it by 60 minutes. However, after an apparent lucid period of 50 minutes (regained rotorod test), toxicity recrudesced with re-failure of the rotorod test for the next 200 minutes. Con-

versely, all pretreated animals failed the rotorod test after 10 minutes but regained it by 60 minutes without recrudescence of toxicity. Conclusion: Concomitant poisoning of CD-1 mice with 2 g/kg ETOH followed by 600 mg/kg BD resulted in initial toxicity that was interrupted by a brief lucid period. Toxicity then recrudesced. ETOH appeared to delay onset of BD toxicity, presumably because of a greater affinity for ADH. However, 4-MP pretreatment significantly reduced the potentiated toxicity of ETOH and BD and prevented recrudescence of toxicity, presumably by blocking ADH biotransformation of BD to GHB.

43 RECOVERY OF CYTOCHROME c OXIDASE ACTIVITY IN CHRONIC SMOKERS AFTER CESSATION OF TOBACCO CONSUMPTION

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Background: Recently, we demonstrated that chronic smoking is associated with a 23% of decrease in cytochrome *c* oxidase (COX) activity with respect to non-smoking individuals matched by gender, age and physical activity[1]. Since this enzyme is the latest step (complex IV) of mitochondrial respiratory chain (MRC), we hypothesised that this inhibition could contribute to the pathogenesis of diverse diseases associated with tobacco consumption. However, it is not known if this inhibition is reversed when smokers became abstinent. Objective: To assess if the cessation in smoking is associated with a recovery of COX activity. Patients and Methods: We studied MRC from peripheral lymphocytes of 8 healthy, smoking individuals (age 43 ± 7; 50% men) before (t_0) and seven days after (t_1) cessation of tobacco consumption. At both times, carboxyhemoglobin was determined in blood samples by CO-oximetry, and carbon monoxide concentration in exhaled breath of participants by an electrochemical transducer. Lymphocytes were isolated by Ficoll's gradient, protein content was determined by Bradford's methodology, and MRC function was studied using two techniques First, individual enzyme activities of complex II, III and IV of MRC were assessed spectrophotometrically. Second, oxygen consumption was polarographically measured in permeabilized lymphocytes using pyruvate, succinate and glycerol-3-phosphate as complex I, II and III substrates, respectively. This later methodology ascertains if eventual dysfunction of any MRC complex has some effect on the whole mitochondrial respiratory capacity. The paired t test was used to compare measurements at t_0 and t_1. Results: All patients remained abstinent, as judged by a decrease in both, carboxyhemoglobin levels from 4.74% ± 1.6 to 0.66% ± 0.38 ($p < 0.001$), and carbon monoxide exhalation from 24 ± 6 ppm to 4 ± 2 ppm ($p < 0.001$). Stopping the tobacco consumption was associated with a recovery in COX activity from 36.63 ± 14.33 nmol/min/mg of protein to 48.89 ± 13.21 nmol/min/mg of protein ($p < 0.005$). No other changes in enzyme activities of the rest of MRC complexes assayed were found. Similarly, oxygen consumption was found to be similar at t_0 and t_1. Conclusion: COX inhibition associated with chronic smoking disappears after cessation of smoking. References: [1]*Carcinogenesis* 1999;**20**:1331–1336. (Supported by FIPSE 3102/00, FIS 00/0927, DGCYT PM99-0038, SGR 1999/00279 and Premi Fi de Residència 1998 of HCP).

44 MECHANISMS AND MANAGEMENT OF ACID/BASE BALANCE DISORDERS IN ACUTE POISONING

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Introduction: Many acute poisonings can induce acid/base balance disturbances. The primary acid/base balance disorders discerned are metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. Generally, in an early stage of an intoxication one of the primary acid/base disorders can be observed. In a later phase combined acid-base balance disorders may be present. This may be induced by multiple causes of the acid/base balance disorder or by physiological compensation mechanisms. Metabolic acidosis can be caused as a result of the intoxicating compound itself (e.g. salicylates) or by its metabolites (e.g. methanol, ethylene glycol). Metabolic acidosis with an elevated lactate level can be caused by increased production of lactate by changes in metabolism (e.g. some oral hypoglycemic agents), tissue hypoxemia (e.g. poisoning induced seizures, hypoventilation, or shock) or decreased lactate clearance (poisoning induced liver failure). Metabolic acidosis can also be caused by poisoning-induced renal failure (e.g. nonsteroidal anti-inflammatory agents, toluene) or severe diarrhoea. In the case of metabolic acidosis it is very important to determine the anion gap. In cases of an increased anion gap it is more likely that an intoxication is present and further assessment is needed to find the cause of the intoxication. Respiratory acidosis can be, e.g., the result of airway obstruction (e.g. severe inhalation injury, aspiration of caustic agents), acute pulmonary oedema (e.g. opiates), CNS and respira-

tory depression (e.g. sedative-hypnotics) or muscle weakness (e.g. cholinesterase inhibitors). Metabolic alkalosis can be observed, e.g., following protracted vomiting or diuretic therapy. Respiratory alkalosis can be caused, for example, by over-stimulation of the respiratory centre in the medulla oblongata (e.g. salicylates). Therapeutic interventions such as mechanical ventilation that is not well-tuned to the patient's need can also induce acid/base disturbances like respiratory alkalosis or acidosis. Management: It is very important for the treating physician to be aware of the differential diagnosis associated with acid/base balance disorders. Judgements must be based on general medical and toxicological histories and clinical presentation. Careful evaluation of the blood gas analysis is needed to determine if this disorder is a primary or combined disorder. Severe acid/base imbalances may be associated with severe vital organ dysfunction (severe acidosis, pH <7.10, can irreversibly damage heart or brain tissue; severe alkalosis, pH >7.60, may cause seizures, cardiac arrhythmias or respiratory dysfunction). Correction of the acid/base balance disorder itself may be the first initial treatment in order to prevent secondary damage. The aetiology of each component has then to be determined. In most cases, treatment will be restrained to the elimination of the underlying cause of the acid/base balance disorder. Evaluation of the anion gap, in the context of acute poisoning, is an essential step in the work up of an acid-base balance disorder, because immediate intervention may be needed in order to prevent irreversible tissue damage (e.g. brain damage caused by methanol and ethylene glycol metabolites). Furthermore, attention should be paid to circumstances that may cause prolongation of the acid/base balance disorder (e.g. metformin induced lactate acidosis in renal failure). Conclusion: It is very important to assess the primary cause of the acid/base balance disorder and to evaluate any contributing factors that may prolong the existence of the disorder. By this work up the treating physician will be guided to the correct therapeutic regimen needed to cure the patient and to prevent unnecessary secondary tissue damage.

45 SEVERE LACTIC ACIDOSIS WITH MULTIORGAN FAILURE SECONDARY TO ANTIRETROVIRAL THERAPY

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Objectives: Toxicity of antiretroviral therapies is an increasingly important issue in the treatment of HIV-infected patients. Several cases of severe lactic acidosis with multiorgan failure have been reported, with an estimated incidence of 1.3/1000/year. Elevation of serum lactate results from nucleoside reverse-transcriptase inhibitors (NRTIs)-associated mitochondrial respiratory chain dysfunction. NRTIs are known to produce an *in vitro* inhibition of mitochondrial DNA polymerase gamma and may therefore alter the *in vivo* hepatic clearance of lactate. The aim of this study is to describe the clinical features, means of diagnosis and management of severe lactic acidosis. Methods: Retrospective collection of clinical, biological and outcome data from all published cases of NRTIs-associated severe lactic acidosis, by a systematic review of Medline from 1995–1999. Results: Forty HIV-infected patients (40 [0-68] years (median [extremes]); sex ratio M/F: 1.2; 48% homosexuals; 43% without prior opportunistic infection; CD4+ T lymphocytes: 130 /mm^3 [0-556]) were included in this study. Patients were admitted for the onset of dyspnea (58%), vomiting (53%), weight loss (43%), general fatigue (43%), abdominal pain (35%) or diarrhea (8%). Incriminated NRTIs were zidovudine (n = 26), stavudine (n = 7), didanosine (n = 4), lamivudine (n = 3) and zalcitabine (n = 1), mainly in associations. A delay between symptom onset and therapy initiation was 14 weeks [3-55]. No particular predisposing factor could be identified. Physical findings were generally not contributive, but hepatomegaly was constantly noted. Clinical chemistry revealed severe metabolic acidosis (arterial pH: 7.26 [6.9-7.42]; serum bicarbonate: 7.7 mmol/L [1.6-19]; anion gap: 26 mmol/L [14-37]) with increased serum lactate: 13.8 mmol/L [6.3-43]. Elevation of lactate/pyruvate (10) and acetoacetate/gb-hydroxybutyrate (5) ratios highlights mitochondrial dysfunction. Moderate alteration of serum hepatic (80%) or pancreatic (20%) enzymes was present. Echotomography and CT scan showed fatty liver (79%), with macrovesicular (80%), mixed (15%), or microvesicular steatosis (5%) on liver biopsy. Outcome led in the majority of cases to multiorgan failure and death (60%) within a short time (5 days [2-28]). Supportive treatments (mechanical ventilation, bicarbonate infusion, hemodialysis and catecholamines) were generally ineffective to reverse acidosis and stop fatal outcome. Several agents, including thiamine, compound Q, L-carnitine, thiamine and riboflavine were used with no definitively demonstrated benefit. In one patient, spectrophotometry assay showed a decrease of the respiratory chain proteins encoded by mitochondrial DNA, assessing the *in vivo* inhibition of mitochondrial DNA polymerase. Conclusion: Mitochondrial toxicity is an important adverse effect of antiretroviral therapies and may lead to severe lactic acidosis with multiorgan failure in HIV-infected patients. Early cessation of the causative NRTI represents the most important point in management.

46 LACTIC ACIDOSIS IN CYANIDE POISONING: PATHOPHYSIOLOGY AND CLINICAL CONSIDERATIONS

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Background: Cyanide quickly binds to the ferric ion of cytochrome aa_3 inducing a noncompetitive inhibition of the mitochondrial cytochrome c oxidase activity. The inactivation of cytochrome c oxidase results in a shift of aerobic to anaerobic metabolism eventually leading to cellular ATP depletion and lactic acidosis. Due to the shift from aerobic to anaerobic metabolism, significant cyanide poisoning is invariably associated with lactic acidosis. Methods: Retrospective study in a university hospital ICU. Repeated blood samples were simultaneously collected for blood cyanide and plasma lactate determination in acute cyanide poisonings, excluding fire victims. The correlations were studied using the Spearman test. Results: Eleven patients were studied. Before antidotal treatment (hydroxocobalamin ± thiosulfate), the median plasma lactate concentration was 18.6 mmol/L, the median blood cyanide concentration was 156 µmol/L (4.0 mg/L). There was a significant correlation between plasma lactate and blood cyanide concentrations ($r = 0.745$, $p = 0.0174$). There were significant inverse correlations between plasma lactate concentrations and systolic blood pressure ($r = -0.875$, $p = 0.0016$), spontaneous respiratory rate ($r = -0.867$, $p = 0.0123$), and arterial pH ($r = -0.870$, $p = 0.0045$). There was a significant positive correlation between plasma lactate concentrations and anion gap ($r = 0.833$, $p = 0.0083$). The correlation with blood glucose concentration did not reach the level of statistical significance ($p = 0.0589$). There was no significant correlation of plasma lactate concentrations with heart rate, Glasgow coma score, $PaCO_2$ or PaO_2. Before antidotal treatment, there were significant inverse correlations of blood cyanide concentrations with systolic blood pressure ($r = -0.717$, $p = 0.0234$), and arterial pH ($r = -0.912$, $p = 0.0013$). There was a significant positive correlation with anion gap ($r = 0.767$, $p = 0.0214$), and blood glucose concentration ($r = 0.783$, $p = 0.0172$). There was no significant correlation of blood cyanide concentration with pulse rate, respiratory rate, Glasgow coma score, PaO_2 or $PaCO_2$. During the course of cyanide poisonings, a plasma lactate concentration ≥8 mmol/L was sensitive (94%) and moderately specific (70%) for a toxic blood cyanide concentration (≥40 µmol/L or 1.0 mg/L). The specificity was substantially improved in patients not receiving catecholamines (85%). Interpretation: Several factors may contribute to the onset of lactic acidosis in cyanide poisoning including mitochondrial inhibition, cardiovascular collapse, respiratory depression, and catecholamine rush while seizures seems rare. The serial measurement of plasma lactate concentrations is useful in assessing the severity of cyanide poisoning.

47 EFFECTS OF RESPIRATORY ACIDOSIS AND ALKALOSIS ON THE DISTRIBUTION OF CYANIDE INTO THE RAT BRAIN

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Objective: The question to be addressed is whether respiratory acidosis favors the cerebral distribution of cyanide, and conversely, if respiratory alkalosis limits its distribution. Methods: The pharmacokinetics of a non-toxic dose of cyanide were first studied in a group of 7 rats in order to determine the distribution phase. The pharmacokinetics were found to best fit a three-compartment model with very rapid distribution ($T_{1/2\alpha} = 21.6 \pm 3.3$ s). Then, the effects of the modulation of arterial pH on the distribution of a non-toxic dose of intravenously administered cyanide into the brain of rats were studied by means of the determination of the permeability-area product (PA). The modulation of arterial blood pH was performed by variation of $PaCO_2$ in 3 groups of 8 anaesthetized mechanically ventilated rats. Results: The mean arterial pH measured 20 min after the start of mechanical ventilation in the acidotic, physiologic, and alkalotic groups were 7.07 ± 0.03, 7.41 ± 0.01, and 7.58 ± 0.01, respectively. The mean PAs in the acidotic, physiologic, and alkalotic groups, determined 30 s after the intravenous administration of cyanide, were 0.015 ± 0.002, 0.011 ± 0.001, and 0.008 ± 0.001 s^{-1}, respectively (one-way ANOVA $p < 0.0087$). At alkalotic pH the mean permeability-area product was 43% of that measured at acidotic pH. This effect of pH on the rapidity of cyanide distribution does not appear to be limited to specific areas of the brain. Conclusion: We conclude that modulation of arterial pH by altering $PaCO_2$ may induce significant effects on the brain uptake of cyanide.

Pharmacokinetics of a Nontoxic Dose of ^{14}C Labeled Cyanide Administered as a Bolus Dose in Seven Rats

	Cmax (nmol/L)	T1/2α (s)	T1/2β (s)	T1/2γ (min)	Vd (L/kg)	Cltot (mL/min/kg)
1	983	13	40	40	0.65	11.3
2	749	12	132	61	0.84	11.5
3	879	38	293	69	0.84	8.5
4	604	22	125	120	0.87	5.0
5	837	21	74	212	1.01	3.3
6	1204	25	207	61	0.79	8.9
7	830	20	137	49	0.81	11.3
Mean ± SEM	869 ± 71	21.6 ± 3.3	144.0 ± 31.8	87.4 ± 22.9	0.83 ± 0.04	8.5 ± 1.2

48 THE VALUE OF SERUM BICARBONATE AND BASE DEFICIT IN THE DIAGNOSIS OF ETHYLENE GLYCOL TOXICITY. A SYSTEMATIC REVIEW

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Objective: Serum ethylene glycol (EG) levels are not readily available in most hospitals in the United States. In these cases, the development of a metabolic acidosis may indicate an occult toxic EG ingestion. This concept has never been validated using an evidence-based approach. We utilized the medical literature, to test the hypothesis that all patients who ingest EG will develop a significant metabolic acidosis (serum $HCO_3 \leq 20$ mEq/L or base deficit ≥ 4) unless the resulting serum EG < 20 mg/dL. Methods: A systematic analysis was performed using a predefined search procedure of the following electronic databases: MEDLINE, EMBASE, CINAHL, Best Evidence and the Cochrane Databases of Systematic Reviews. Using the Ovid search engine, all English and non-English language articles regarding human ethylene glycol ingestion from 1960–1999 were reviewed. Bibliographies, personal files, poison center physician consults from 1997–1999, and extensive communications with authors identified additional cases. Structured data collection extracted time of ingestion, EG levels, serum HCO_3, base deficit and ethanol levels. Results: 262 articles (413 patients), 11 consults, and 23 unpublished cases were reviewed; 52 review articles were excluded as they provided no patient information. A total of 447 patients were analyzed, of which, 213 (48%) were excluded due to lack of patient data on acidosis and EG levels. Of the remaining 234 patients, 213 (91%) were acidotic and 21 (9%) were not acidotic at presentation. Therefore, most patients would have been detected due to an abnormal serum bicarbonate level or base deficit. Of the 21 patients without acidosis, 12 had ingested ethanol (thereby blocking alcohol dehydrogenase), 8 presented within 4 hours of the ingestion (before acidosis would be expected to develop), and one patient was treated with a $NaHCO_3$ infusion prior to assessment. Kappa scores for intra-rater and inter-rater reliability were 0.95 and 0.93 respectively. Conclusion: Although this study is limited by its retrospective nature, all untreated patients with significant EG ingestion manifested acidosis unless alcohol dehydrogenase was blocked or they presented prior to 4 hours of the ingestion. Decreasing HCO_3 levels or increasing base deficits at least 4 hours after ingestion may be a sensitive indicator of significant EG ingestion when serum EG levels are not available.

49 INTOXICATION INDUCED LIVER DYSFUNCTION AND ITS CONSEQUENCES FOR METABOLIC DISTURBANCES

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Background: The liver is the major detoxification organ of the body and represents the major target organ for numerous drugs, environmental toxins and other xenobiotic substances. Recent reports of fatal liver injury from newly marketed drugs, drugs of abuse and environmental toxins illustrate that continuous efforts are required to early detect potential hepatotoxins, to study the mechanisms of their hepatotoxicity and to develop more effective strategies to prevent and treat drug- and toxin-induced liver injury. Objectives: To summarize the risk factors, pathophysiology, clinical features and therapeutic options for some relevant forms of drug- and toxin-induced (*a*) hepatocellular necrosis, (*b*) hepatitis, (*c*) steatosis and steatohepatitis, and (*d*) cholestasis. Discussion: *A*) Acute hepatocellular necrosis without significant

hepatitis is a typical feature of intrinsic hepatotoxins (e.g. paracetamol, halothane, CCl4, chloroform, Amanita phalloides toxin, microcystins) and/or their toxic biotransformation products (e.g. CYP2E1 dependent formation of *N*-acetyl-p-benzoquinone imine (NAPQI) from paracetamol). Typical signs are increased serum transaminases (i.e. ALT, AST) and in severe cases abnormal blood coagulation tests (i.e. prolonged INR). The risk of hepatotoxicity can be increased by induction of CYP2E1 and/or a preexistent decrease of intracellular reduced glutathione (GSH) as it occurs for example in chronic alcoholics. Interestingly, autoprotection against hepatocellular necrosis has been reported in chronic paracetamol overdose by selective down-regulation of CYP2E1/1A2 and GSH rebound through hepatocyte proliferation. *N*-acetylcysteine has been established as an effective therapeutic agent for paracetamol hepatotoxicity, but not (or less so) for other forms of hepatocellular necrosis. Cocaine and ecstasy induced hepatic necrosis is frequently associated with rhabdomyolysis, hyperthermia and/or renal failure. *B*) Nonspecific hepatitis is typical of many types of drug-induced hepatotoxicity (e.g. phenytoin, carbamazepine, sulfonamides, diclofenac, nimesulide, isoniazid, herbal medicines). In addition to jaundice and elevated ALT, AST in serum, signs of hypersensitivity such as rash, fever, lymphoadenopathy and eosinophilia may be present. Most forms of toxic hepatitis resolve after resolution of the intoxication, although progression to terminal liver failure may require liver transplantation in some patients. *C*) Hepatocellular micro- or macrovesicular steatosis is a hallmark of toxic mitochondrial damage either due to inhibition of fatty acid β-oxidation (e.g. aspirin, valproic acid, tetracyclines, Bacillus cereus toxin) or to inhibition of mitochondrial DNA synthesis (e.g. antiviral nucleoside analogs). Patients at risk are very young children (valproic acid), children with viral infections (aspirin; Reye's syndrome), patients treated concomitantly with cytochrome P450 inducers (e.g. phenytoin, carbamazepine) and patients with inherited disorders of mitochondrial β-oxidation of fatty acids and/or urea cycle enzymes. Serum transaminases are initially low despite an acute "energy crisis" within liver cells as evidenced by a marked increase of conjugated bilirubin and ammonia in serum, decreased synthetic liver functions (e.g. prolonged INR) and the development of systemic lactic acidosis. The risk for development of terminal liver failure with hepatic encephalopathy is high unless the toxic exposure is stopped as soon as prodromes such as lethargy, nausea, vomiting and jaundice develop. *D*) Cholestasis means decreased bile formation and accumulation of toxic bile components (e.g. bile salts) within hepatocytes and in serum. It can be induced by many drugs including anabolic and contraceptive steroids, chlorpromazine, erythromycin estolate, flucloxacillin, amoxicillin/clavulanic acid and cyclosporine A. Increases in alkaline phosphatase, bile salts and conjugated bilirubin in serum dominate over serum transaminases. Metabolic liver functions are relatively well maintained, but secondary biliary cirrhosis can develop with prolonged cholestasis. The pathogenesis of many forms of drug- and toxin-induced cholestasis can now be explained by selective inhibition of hepatobiliary transport mechanisms at the canalicular membrane of hepatocytes. Ursodeoxycholic acid and/or cholestyramine can improve symptoms (e.g. pruritis, fatigue) and cholestatic serum parameters in some patients.–The therapeutic significance of the recently developed extracorporeal albumin dialysis system MARS® (Molecular Adsorbents Recirculating System; TERAKLIN) in drug- and toxin-induced liver injury is currently under investigation and remains to be further evaluated in future clinical trials.

50 MECHANISMS AND MANAGEMENT OF POTASSIUM DISTURBANCES IN THE INTOXICATED PATIENT

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Introduction: Potassium plays a key role in cardiovascular and neuromuscular physiology. Variations of the kalemia outside the normal values (3.5–5 mmol/L) may induce rapidly life-threatening cardiovascular disturbances. Plasma potassium levels are determined by the balance between absorption and excretion and by internal shifts between the extracellular fluids and cells. Mechanisms: Dyskalemia may result from changes in potassium intake or excretion or from potassium transcellular shifts. In the poisoned patient, the mechanisms of dyskalemia may not be specific of a poison. Hyperkalemia may result from an increase of potassium intake or administration, from a decrease of renal excretion due to renal failure, or from a transcellular shift due to acidosis, rhabdomyolysis, hemolysis and malignant hyperthermia. Hypokalemia may result from an increase in potassium losses by gastrointestinal route (vomiting and/or diarrhea) or by renal route (osmotic diuresis) or from a transcellular shift due to alkalosis. Some poisons induce potassium disturbances that are related to a specific toxic effect. Hyperkalemia may be due to drugs which decrease renal excretion of potassium (NSAI drugs, angiotensin-converting enzyme inhibitors, ciclosporin, K^+-sparing diuretics) or which increase the extracellular shift of K^+ (succinylcholine, digoxin, beta blockers, fluoride). Hypokalemia may occur with drugs increasing the renal K^+ elimination (diuretics, glycyrrhizic acid) or increasing the intracellular shift

of K^+ (beta- adrenergic drugs, theophylline, barium, chloroquine, insulin). In these cases changes in potassium level are a criteria of severity of the poisoning: e.g. hyperkalemia in acute digoxin poisoning, hypokalemia in chloroquine poisoning. Diagnosis: apart from the plasma potassium level, the most relevant features are the changes in the ECG and the occurrence of dysrhythmias. Hypokalemia induces tachycardia and ventricular tachyarrhythmias especially *torsades de pointes*. Hyperkalemia is associated with bradycardia, atrioventricular block and widening of the QRS complex. A widening of the QRS is not specific of hyperkalemia and may also be seen in poisonings by class I antiarrhythmic drugs, tricyclic antidepressants and chloroquine. Management: Dyskalemias need a close monitoring of blood pressure and ECG because dysrhythmias or severe hypotension and cardiac arrest may occur suddenly. Treatment of hypokalemia includes potassium replacement and correction of other electrolytes abnormalities especially hypomagnesemia. The rate of potassium replacement depends on the potassium level and the presence of ECG abnormalities. In the case of ventricular dysrhythmias, antiarrhythmic drugs are contraindicated. *Torsades de pointes* may require the administration of beta-mimetic drugs or an overdrive by cardiac pacing. Irrespective of the cause, the primary goals of the treatment of hyperkalemia are reduction of plasma potassium toward the safe range and myocardial protection. Immediate treatment of cardiac failure includes inotropic agents such as catecholamines and calcium salts. The most rapid way to decrease the potassium level is by increasing the cellular shift of potassium with sodium bicarbonate and glucose-insulin infusions. Elimination of potassium can be increased by administration of loop diuretics in patients with normal renal function. In patients where these methods fail or in those with renal failure, rapid hemodialysis is indicated. In some poisonings, management of dyskalemias needs a specific approach. In poisonings by membrane stabilizing agents, hypokalemia should be corrected very cautiously, especially when cardiac conduction disturbances are present. In severe chloroquine poisoning, an important hypokalemia is present at the initial phase. A rapid correction may be followed by a sudden hyperkalemia when the toxic effects of chloroquine have disappeared. In acute digoxin poisoning, hyperkalemia reflects the severity of the Na^+-K^+ ATPase inhibition and is corrected by the administration of antidigoxin Fab fragments. Conclusion: In the intoxicated patient, potassium disturbances may induce rapid life threatening cardiac disturbances. Apart from the general treatment of hypo- and hyperkalemia, management of potassium disturbances needs sometimes a specific approach depending on the mechanism of action of the poison.

51 FEATURES AND MANAGEMENT OF MAGNESIUM AND CALCIUM IN THE INTOXICATED PATIENT

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Calcium and magnesium metabolism: The evolutionary reasons that led to selection of magnesium (and phosphorus) as major cytoplasmic components are poorly understood. The solubility of magnesium salts, and the greater abundance of magnesium than of calcium in ocean water, may help to explain why magnesium evolved as the principal cytoplasmic divalent cation. In humans, calcium and magnesium are mainly in the bones and teeth (Table 1).

Table 1

Distribution of Calcium and Magnesium

Compartment	Calcium	Magnesium
Bones and teeth	99%	54%
Extracellular fluid	0.1%	1%
Cells	0.9%	45%

Plasma calcium participates in multiple processes, including proteolysis, regulation of plasma membrane potential, exocytosis. Its normal concentration in plasma is 2.2 to 2.6 mmol/L. Normal plasma concentrations of magnesium are 0.8 to 1.2 mmol/L. Only the ionized fraction of calcium participates directly in most biological reactions. Albumin accounts for 70% of the protein binding of calcium in serum. Proportional binding increases with the rise in pH such that ionized calcium concentration decreases. A small part of circulating calcium is in the form of complexes with

bicarbonate, phosphate, citrate and other anions. Complexed calcium increases during renal failure or during infusion of calcium chelators such as EDTA. When complexed calcium increases hypocalcemia occurs. The proportional distribution of magnesium as ionized, protein bound and complexed is similar to that of calcium. (Table 2).

Table 2

States of Calcium and Magnesium in Human Plasma

State	Calcium	Magnesium
Protein bound	47%	29%
Complexed	10%	8%
Ionized	43%	63%

Large amounts of calcium and magnesium continuously enter and leave plasma via intestine, kidney and bone. Each of the organs contributes to regulation of plasma concentrations of these ions. Calcium concentration is maintained by means of the balance between dietary intake and renal elimination. Vitamin D, parathyroid hormone and calcitonin are main determinants of calcium metabolism. Magnesium homeostasis is maintained through dietary intake and losses (renal and gastrointestinal). Xenobiotic-induced hypocalcemia can occur very quickly in hydrofluoric acid poisoning due to the direct complexation with fluoride ion. Other agents (ethanol, ethylene glycol, phosphate, etc) produce hypocalcemia with very different mechanisms such as decreased absorption, enhanced renal elimination and redistribution. The clinical picture of hypocalcemia is characterized by neurological findings: paresthesiae, muscular cramps, spasms, tetany and convulsions. Cardiac dysrhythmias are possible but they are not life-threatening. The focal point of treatment is calcium replacement. Calcium replacement does not work if hypomagnesemia or hyperphosphatemia is present. Xenobiotic-induced hypercalcemia is less common than hypocalcemia; it can be caused by different mechanisms: i) increase of calcium release from bone (cholecalciferol); ii) decrease of calcium elimination (thiazides, cholecalciferol); iii) increase of gastrointestinal absorption of calcium (cholecalciferol); iiii) increase of calcium in the diet (antacids). The clinical picture of hypercalcemia consists in nausea, vomiting, constipation, muscle weakness, lethargy and cardiac dysrhythmias. Treatment of xenobiotic-induced hypercalcemia includes gastrointestinal decontamination and enhancing elimination. Xenobiotic-induced hypomagnesemia is rarely a life-threatening situation. It can be caused by different mechanisms: i) complexation (fluoride, hyperphosphatemia); ii) gastrointestinal losses (ethanol); iii) renal losses (loop diuretics). Because the same causes can produce other ion abnormalities, when hypomagnesemia is present other electrolyte abnormalities are usually present. The symptoms of hypomagnesemia include tremor, hyperreflexia, nausea, vomiting, muscular weakness, lethargy and cardiac dysrhythmias. Treatment is based on magnesium replacement. Xenobiotic-induced hypermagnesemia is rarely a significant clinical situation in absence of renal failure with the exception of massive parenteral infusions of magnesium salts (inadvertent intravenous infusion, urological procedures, ingestion of large amount of magnesium-containing cathartics) The clinical picture of hypermagnesemia include nausea, vomiting, muscular weakness, flush. As magnesium levels increase more severe symptoms and signs appear: bradycardia, hypotension, hypoventilation, muscle paralysis and ventricular dysrhythmias. Hypermagnesemia is rare but it is a life-threatening situation: calcium can reverse magnesium toxicity; further therapy includes forced diuresis and haemodialysis when renal function is not good. Summary: Calcium and magnesium play a fundamental role in intracellular and extracellular homeostasis. The evaluation of electrolyte status is a key point in the management of the intoxicated patient.

52 GLUCOSE DISTURBANCE IN THE INTOXICATED PATIENT

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Background: In normal patients the glucose concentration in blood is closely maintained between fixed levels (3.5–6.5 mmol/L). Glucose is essential for normal functioning of body cells, particularly the central nervous system. Homeostatic processes normally control glucose levels. Insulin appears to be the only hormone that reduces blood glucose whereas glucose can be increased by the action of a number of hormones including, in particular, glucagon, catecholamines and glucocorticoids. Sugars are normally absorbed from the gastrointestinal tract and, in part due to the release of insulin,

converted in the liver to glycogen for storage. Glycogen is also used in muscles as an energy source. Insulin promotes glycogenesis and also promotes the storage of energy in fat. Under conditions of stress catecholamines promote glycogen breakdown and increase the availability of sugars in muscle. In toxicological terms alterations in blood sugar can occur at a variety of sites. Hypoglycaemia may be due to excess insulin, either iatrogenic by use of insulin injection, or following ingestion of drugs that increase insulin release, such as sulfonylureas or quinine. In patients with serious liver damage, for example severe paracetamol poisoning, liver production of glucose may be impaired and sugar levels may fall. Ethanol is a further cause of hypoglycaemia and this may be particularly relevant in children. Beta-blockers prevent the actions of catecholamines in raising blood sugar and may be associated with hypoglycaemia in overdose. Hyperglycaemia, which in itself is less hazardous than hypoglycaemia, may be caused by many agents. These range from agents: i) which are directly toxic to the insulin producing cells in the pancreas, such as streptozosin and diazoxide, ii) compounds which prevent insulin release including thiazide diuretics, iii) compounds such as which act peripherally to stimulate glucose release (catecholamines, beta-receptor agonists such as salbutamol, and the adenosine agonist theophylline). Maintenance of glucose homeostasis may be complicated if these changes occur in patients who also have underlying metabolic disorders. Patients who have access to hypoglycaemic agents usually have diabetes mellitus and the potential interactions between a hypoglycaemic stimulus from a drug and a hyperglycemic tendency due to diabetes need to be carefully managed. Clinical features of hypoglycaemia are in part related to catecholamine release that is associated with this phenomenon. Catecholamine release should normally reverse the hypoglycaemia. Thus tachycardia and sweating are normal components of an early hypoglycaemic attack. These are followed by confusion, agitation, aggression and ultimately coma as the brain becomes increasingly starved of glucose. Management of hypoglycaemia is a medical emergency and all patients who are in a coma should have an urgent blood sugar estimated. The appropriate treatment is reversal of hypoglycaemia either by use of intravenous glucose (usually 10 or 20% solution initially) or if this is not readily available the use of glucagon by intramuscular injection. Glucagon itself causes glucose release from the liver by promoting glycogen breakdown. This allows a window of opportunity in which appropriate management of glucose, in mild cases perhaps given orally but in more severe cases intravenously, needs to be instituted. If in doubt glucose should be given, as it is unlikely to cause harm. In patients in whom insulin release is occurring due to effects of drugs that act on the pancreas directly, e.g. sulfonylureas, antagonism may be possible by administration of a somatostatin analogue, e.g. octreotide. It is important to remember that the duration of action of hypoglycaemic agents may be prolonged. Patients need to be observed in hospital until they are fully recovered from such ingestions. A high degree of suspicion is required in patients who present with hypoglycaemic episodes. Measurement of C-peptide and insulin levels independently is one way in which covert insulin administration may be detected. Hyperglycaemia is rarely clinically important in its right, but may be a useful indicator of toxicity, for example in theophylline poisoning. Only in diabetics is it necessary usually to intervene therapeutically (with insulin) and here a standard infusion of dextrose and insulin can be used to titrate plasma glucose into the normal range. Hyperglycaemia may produce an osmotic diuresis, and in this circumstance appropriate fluid replacement is necessary. The occurrence of hyperglycaemia in a patient in whom diabetes is not suspected should alert the physician to the possibility of ingestion of a toxin.

53 METHEMOGLOBINEMIA AND INTOXICATIONS

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The dominant clinical symptoms of methemoglobinemia are a brownish cyanosis and signs of hypoxemia. The human organism is able to reduce oxidized methemoglobin to hemoglobin by two reductase systems. Under normal conditions, most of the naturally occurring methemoglobin is reduced by a NADH–dependent methemoglobin reductase (NADH-MR) system. A very small part, not needed under normal conditions, is reduced by a NADPH-MR system that is only active if the pentose-phosphate-shunt with the key enzyme G-6-PD is intact. All the drugs used for the treatment of toxic methemoglobinemia work this way. Hereditary methemoglobinemias are rare. They only happen if there is a lack of NADH-MR. These patients are accustomed to high methemoglobin levels without severe symptoms. Patients with a lack of NADPH–MR show no increase in methemoglobin. Toxic methemoglobinemia is also a rare event. We have treated about 20 cases in 30 years. The exact molecular mechanism of the formation of methemoglobinemia is still not known. Many different chemicals and drugs can induce methemoglobinemia. There is a great difference between different species in their MR activity which makes it difficult to transfer the results of animal experiences to man. One can differentiate between three types of methemoglobin-inducing substances. Directly oxidizing poisons, poisons that oxi-

dize hemoglobin only in the presence of oxygen, and indirectly oxidizing agents that only oxidize hemoglobin to methemoglobin *in vivo* and not *in vitro*, due to some metabolism of these chemicals in the body. The first group consists of H_2O_2, copper, hydroxylamine, chromate, chlorate, nitrites, organic nitrites and nitrates and quinones. The second group includes all aminophenols. To the third group belong aniline and aniline derivates, N-alcylated aromatic amino-compounds which only act after deacylation has happened. For the diagnosis, treatment and prognosis of the intoxication syndrome by these substances it is necessary to take into consideration all mechanism of actions besides the production of methemoglobin such as hemolysis, cardiotoxicity, nephrotoxicity and hepatotoxicity. The high lethality, for example, of chlorate intoxication is certainly due to other mechanisms than to the creation of methemoglobin. Treatment of methemoglobinemia in these cases is inappropriate due to hemolysis that is enhanced by inducing methemoglobin reduction. Very often in poisoning by these agents kidney failure is predominant. This may be caused by a direct toxic effect of the chemical, by hemolysis induced by the agent or by methemoglobin itself. The treatment of these toxic methemoglobinemias by thiazine dyes is pharmacologically and in some cases clinically very effective. Toluidine blue is the most efficient and fastest acting drug, followed by methylene blue, for this purpose. The ad hoc administration of one of these drugs may be life saving. Even if organ failure is already present, improvement in the oxygenation of the organism and restoration of vital functions may be achieved. An exact dosing is of utmost importance since an overdose of these antidotes may produce methemoglobinemia itself. In poisonings with indirect oxidizing compounds, the reduction induced by these drugs has to be repeated as the toxic agent is creating methemoglobin as long as it is present in the system. The repetitive administration of reducing dyes is only appropriate if no or little hemolysis is present as can be monitored by LDH, ASAT and bilirubin. The dosage regime for toluidine blue is 2–4 mg/kg body weight in a 4%. solution. Children need 2 mg/kg body weight. Methylene blue is given in a 1% solution in a dose of 1–2 mg/kg body weight. If thionine is used 10–20 mL of a 0.2% solution is recommended. The measurement of oxygen saturation by pulse oxymetry gives wrong results if methemoglobin or the dyes are present. If methemoglobin persists, it is likely that methemoglobin-induced lysis has happened. This can be seen by the detection of methemoglobin in the urine. In these cases blood exchange or HBO seems to be reasonable. The poisonings in which we have seen methemoglobinemia in clinical practice were sodium nitrate (50% died), nitrous gases (1 by exhaust gas from a diesel engine), amyl nitrite, aniline, p-bromaniline, p-toluidine, phenacetin, dapsone, 4-DMAP as cyanide antidote, chlorate (50% died), chromate (very mild) and two cases of methemoglobin of unknown origin. There is a rough correlation between the percentage of methemoglobinemia and the severity of the poisoning. The only clinical sign when 10–20% methemoglobinemia develops is cyanosis. More than 30% MetHb shows a brown skin colour, tachycardia, tachypnea, headache, vertigo, nausea and abdominal pain. More than 80% leads to coma and circulatory failure. It is of importance that even more than 80% methemoglobinemia can be survived if the poison does not induce severe organ damage and is rapidly reduced.

54 RISKS AND REMEDIES—THE AMBIGUITIES OF TRADITIONAL MEDICINE

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Introduction: In many developing countries traditional or herbal medicines are often the only accessible form of medicine–the WHO has estimated that 80% of the worlds' population are dependent on traditional systems of health care[1]. In Europe, Australia and the US, herbal and other traditional medicines have become increasingly popular and are used alongside or sometimes as a replacement for western allopathic medicines. Surveys suggest that use of complementary medicine ranges from around 60% in Germany, 50% Australia and France to 20% in the UK. Discussion: There has been considerable debate in the medical literature about the safety and efficacy of traditional and herbal medicines. Attitudes are often at the opposite extremes–they are either viewed as toxic and ineffective or on the other hand as totally safe and effective. Neither view is totally correct and a balanced perspective is needed. Some traditional medicines are part of highly developed medical systems and may be used alongside western allopathic medicines. The Indian Ministry of Health has announced a new initiative to promote their traditional systems of medicine (ISM) and to integrate these into mainstream health care, with GMP standards for the production of traditional medicines[2,3]. China has an integrated health care system and western allopathic medicine may be practiced alongside traditional Chinese medicine. However in other countries, traditional medicine is less well developed and concerns have been expressed about toxicity of some of the plants and other items of materia medica used. Perceived safety of some herbal medicines may be based on traditional use with no reports of toxicity. This depends on associating the health effect with the medicine and also an effective reporting system. Adverse health effects often mimic other diseases, and the association between the use

of a traditional medicine and an adverse health effect may not be obvious. It has only been over the last ten years that consistent reports have emerged on the hepatotoxicity (eg *Teucrium chaemydris*) and renal toxicity (eg *Aristolochia* spp) of some commonly used herbs. Changing use may also result in unexpected side effects–the pharmacological properties of a herb used as a tea may be very different compared with use as a selective concentrated extract. The Uppsala Monitoring Centre takes reports on herbal ADRs from all collaborating countries, but generally there are few effective reporting systems for herbal and traditional medicine[4]. Absence of reports of side effects is not the same as evidence of safety. The Medical Toxicology Unit has reviewed the adverse health effects from these remedies identified from enquiries to the National Poisons Information Service (London). Although these remedies were found to be relatively safe there were a number of areas of concern[5]. A primary area is the use of toxic heavy metals such as lead, arsenic or mercury in prepared medicines from Asia. In some cases this is based on philosophical differences and for this reason imported products need careful review. Issues of safety are not only associated with the direct toxicity of the herbs or other materia medica. Self-prescribed herbal medicines may be used incorrectly, inappropriately, in chronic overdose, or with other pharmaceutical medications. Poor quality control may result in the use of incorrect plants where botanical identity is not checked, plants may be incorrectly or poorly processed and stored, or contaminated with pesticides or herbicides. The transfer of traditional medical systems between countries may lead to other problems. Especially where cross cultural use occurs these systems may be used out of context and without the regulations and knowledge base support of the originating country. Lack of this knowledge may leave these systems open to abuse by unscrupulous individuals. Unexpected adverse health effects may result from differences in genetics, lifestyle, diet or other population differences. Conclusion: Herbal and traditional medicines may be effective but appropriate monitoring systems are needed. With increased globalization, individual herbs or traditional medicines are constantly being introduced into new communities. It is becoming increasingly important that knowledge and information on traditional medicines is more widely available. With cross-country usage, the monitoring systems for adverse health effects have to be more broadly based. Improved research and regulation is also needed–to identify toxicity and safety issues and ensure the safest use of those that may contribute to health care systems. Over the past six months there have been developments within the EU and also internationally aimed at addressing the issues of safety and regulation of traditional medicine. It is hoped that these will start to introduce the much-needed international approach to the safe and effective use of these medicines. References: [1]Wagner H, Farnsworth N, eds. *Economic and Medicinal Plant Research*, Vol 4, London Academic Press, 1990. [2]Sharma D. *Lancet* 2000;**356**:9242. [3]Sharma. *Lancet* 2000;**356**:231. [4]Farah M, et al. *Pharmacoepidemiology and Drug Safety* 2000;**9**:105–112. [5]Shaw D, et al. *Drug Safety* 1997;**17**:342–356.

55 ADVERSE EVENTS IN CHINESE HERBAL MEDICINE AND THE DEVELOPMENT OF A TOXICITY DATABASE

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Background and Objectives: In 1996 an Australian Chinese medicine survey revealed a significant number of adverse events related to the practice of Chinese herbal medicine (CHM), including direct toxicity, allergic reactions and inappropriate prescribing. Furthermore, one third of patients who use CHM do so in conjunction with pharmaceutical drugs.[1] In response to the increased consumption of Chinese herbs and the changing manner in which they are used (in conjunction with pharmaceuticals), a Chinese herbal toxicity database is being developed. The objectives of the database are to evaluate original English and Chinese literature, to provide a toxicity grading based on an assessment of the quality of evidence for individual Chinese herbs and, by doing so, to facilitate safe use of CHM. Methods: Systematic search methods were developed by collaborating centers in Australia and China to retrieve all relevant published primary English and Chinese research literature. Supplementary searches for Korean and Japanese research literature were carried out by a Korean center. A new grading system for the toxicity of herbs has been developed and applied to a variety of Chinese herbs including those with copious or few adverse reaction reports. A system for grading the quality of the evidence has also been devised and applied to retrieved literature. Professional translations from key Chinese texts have been completed and standard English texts also searched for relevant data. A database has been designed to allow searching for multiple herbs, herb pseudonyms, and adverse reactions. Results: It is possible to construct a toxicity grading which considers the strength of evidence for each Chinese herb, and these have been completed for the initial herbs. However, the development of methods and collection of data have proved to be extensive and laborious processes. Summary monographs have been developed for each of the completed herbs. The volume and quality of evidence varies

dramatically from herb to herb. In some cases no relevant literature is available in English. The Chinese research literature appears to provide important data not otherwise available in the English language literature. Conclusion: There appears to be value in drawing together the English and Chinese literature and evaluating both to grade the toxicity of individual Chinese herbs. It is anticipated that the database, while still requiring expansion to include other Chinese herbs, will provide an important and valuable resource for clinicians, poisons and drugs information centers, government agencies and industry. References: [1]Bensoussan A, Myers SP, Carlton AL. Risks presented by the practice of Chinese herbal medicine: an Australian study. *Arch Fam Med* 2000;**9**(10):1071–1078.

56 ADVERSE REACTIONS AND TOXICITY ASSOCIATED WITH THE USE OF SOUTH AFRICAN MEDICINAL HERBS

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Traditional medicines, mainly of plant origin, are regularly taken in South Africa by 60–80% of the population. Traditional healers and the use of traditional medicines are part of ancient cultural practices amongst the Zulu, Xhosa, Sotho and Tswana peoples. The *material medica* that underpins this tradition is drawn from natural stands of vegetation in the northern and eastern provinces of South Africa. Approximately 500 plant species, comprising mainly barks and subterranean organs (bulbs, rhizomes, roots) are in common use. In the southern and western part of the country, originally the home of San and Khoi-khoi peoples, the modern use of traditional herbal medicines is not by prescription from a traditional healer but mainly by self-medication. The plant material used, comprising mainly leaf and stem samples, is also obtained entirely from the wild and includes an additional 200 species, indigenous to the floristically rich Cape Floral Kingdom (CFK). There is little overlap between the species used in the CFK and those used in other parts of South Africa. Traditional medicines are at present neither regulated nor subjected to formal quality control measures. The results of available epidemiological studies suggest that most traditional medicines are safe and that their consumption seldom gives rise to serious adverse events. Some 30 species have however been implicated in cases of acute poisoning and the mortality rate in such cases is high (25%). Gastro-intestinal symptoms and signs predominate, but hepatorenal and CNS effects are also seen. Toxicity is due to a number of plant secondary chemicals e.g. cardiac glycosides, alkaloids and diterpenes. Acute poisoning may arise following accidental overdosage, exacerbation of an existing medical problem or inappropriate procedures. Examples are given of each category. The majority of deaths (80%) following acute poisoning with traditional medicines is in the pediatric age group, mostly below the age of 3. Treatment is symptomatic and includes support and maintenance of vital functions and prevention of complications.

57 DEVELOPMENT OF THE TOXICOLOGY SECTION OF THE AMERICAN HEART ASSOCIATION'S (AHA) GUIDELINES 2000 FOR CARDIOPULMONARY RESUSCITATION AND EMERGENCY CARDIOVASCULAR CARE (ECC)

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Background: The evidence- and consensus-based development of these published guidelines for poisoned patients will be reviewed.[1] The scarcity of RCT on these topics made an exclusively evidence-based evaluation impossible. This work highlights the need for properly designed clinical studies in developing medical toxicology treatment guidelines. The following topics, evidence overview and recommendations will be discussed. Use of alpha- and beta-adrenergic receptor antagonists in the management of cocaine-associated, acute coronary syndrome (Coc-ACS): The reviewed evidence consisted of 2 randomized clinical trials (RCT) of very good quality, 1 prospective study and 4 cath lab studies of very good to excellent quality, three case series of poor to fair quality and 4 animal studies of good to excellent quality. Recommendations: First line therapies of Coc-ACS include nitrates and benzodiazepines. The use of an alpha-adrenergic receptor antagonist (i.e. phentolamine) should be considered in Coc-ACS patients refractory to vigorous nitrate and benzodiazepine therapy. The use of non-selective beta-adrenergic receptor blockers (i.e. propranolol) is contraindicated in Coc-ACS. Non-selective beta-adrenergic receptor blockers may worsen cocaine induced hypertension and/or coronary vasoconstriction. The use of selective beta-adrenergic receptor blockers (i.e. esmolol and metoprolol) and mixed alpha/beta-adrenergic receptor blockers (i.e. labetalol) are not recommended in Coc-ACS. Use of bicarbonate, lidocaine, propranolol and epinephrine in cocaine-associated, ventricular tachycardia or fibrillation (Coc-VT/VF): For bicarbonate in Coc-VT, two very small case series of good quality and 7 animal studies of fair to good quality were

reviewed with most addressing the electrophysiological effects and only one specifically addressing Coc-VT. For lidocaine in Coc-VT, one retrospective clinical study of good quality and 5 animal studies of fair to good quality were reviewed with most addressing the electrophysiological effects and only one specifically addressing Coc-VT. On the safety of lidocaine when given in cocaine toxicity, three animal studies were reviewed. For propranolol in Coc-VT/VF, 2 animal studies of good quality were reviewed with both addressing ventricular arrhythmias. There were no studies of the efficacy of epinephrine in Coc-VF. Recommendations: First-line drug therapies for hemodynamically stable Coc-VT or refractory Coc-VF are sodium bicarbonate and lidocaine. The use of non-selective beta-adrenergic receptor blockers (i.e. propranolol) is contraindicated in Coc-VT. Use of calcium in calcium channel blocker (CCB) and beta-blocker (BB) poisoning: Evidence evaluated included 2 case series of fair to very good quality, 10 animal studies of good to excellent quality and numerous case reports concerning the use of calcium in CCB poisoning. There are more than 130 published case reports on the use of calcium in calcium channel blocker poisoning. Because multiple treatments were usually attempted and severity of poisoning quite varied, it was impossible to reach definitive conclusions from them. Recommendations: First-line drug therapy for calcium channel blocker CCB drug-induced shock (DI shock) remains catecholamine type vasopressors. Calcium chloride infusions (1–3 gm slow IV push) are recommended in CCB-induced shock refractory to conventional catecholamine vasopressor therapy. Additional calcium infusions via bolus or constant infusion would be warranted in patients demonstrating a beneficial hemodynamic response to the initial calcium infusions. Calcium infusions may be beneficial in other types of drug induced (DI) shock but cannot be recommended because of limited supportive data. Use of insulin euglycemia in CCB and BB poisoning: Evidence reviewed included 1 small case series of fair quality and 8 animal studies that were of very good to excellent quality. Recommendation: Insulin-euglycemia "-pump or –clamp" therapy may be beneficial in CCB-DI shock and BB-DI shock but cannot be recommended because of limited supportive data. Timing of assisted ventilation and dose of naloxone in opiate-induced respiratory failure: There were no articles, which compared the safety and efficacy of naloxone reversal of opioid overdose before or after the initiation of artificial ventilation. The impact of naloxone therapy on blood catecholamine levels was evaluated in two prospective human trials of good quality and four animal studies of good to very good quality. Four cases series of good to very good quality were reviewed for data on efficacy and safety of opioid reversal in ECC. Recommendation: Assisted ventilation and reversal with an opioid antagonist, such as naloxone, should be attempted as soon as possible and prior to intubation in patients with a palpable pulse. Naloxone therapy need not be withheld until assisted ventilations have begun. In opioid dependent patients, a lower initial dose of naloxone (i.e. 0.1–0.2 mg IV, repeated until 0.4 mg) is preferable to a larger initial dose (i.e. 2.0 mg IV). When an opioid overdose is suspected, one should not conclude that the patient was unresponsive until a total naloxone dose of 4–6 mg has been given. Systemic alkalosis in tricyclic antidepressant (TCA) poisoning: The evidence supporting the proposal consisted of four case series (n = 3, 4, 5 and 91) that were of good quality and 24 animal or in vitro studies that were of good to excellent quality. There was one small case report (n = 2) of fair quality with questionable opposing evidence. The numerous published individual cases reporting beneficial effects of systemic alkalosis in TCA poisoning were not included in this review. Recommendation: Sodium bicarbonate is the drug of choice for ventricular dysrhythmias and/or shock due to tricyclic antidepressant (TCA) poisoning. The beneficial effects of sodium bicarbonate result from systemic alkalosis and hypertonic sodium effects. More rapid systemic alkalosis may be achieved via hyperventilation but further benefit often results from the hypertonic sodium. In cases of serious TCA-induced CV toxicity, the goal is a systemic pH of 7.50–7.55. Intermittent bolus sodium bicarbonate administration is preferable to a constant infusion until the desired pH is attained. Procainamide for TCA-induced ventricular dysrhythmias: The panel members could find very little evidence on the use of procainamide in TCA-induced VT/VF. Reports of use in one dog and two rabbits and two case reports were reviewed. Recommendation: When TCA-VT/VF is resistant to sodium bicarbonate, lidocaine is the antiarrhythmic of choice. The use of procainamide for TCA-VT/VF is contraindicated. Because both procainamide and TCA have class Ia antiarrhythmic properties, procainamide would be expected to worsen TCA CV toxicity. Use of high dose vasopressors in DI shock in cases refractory to conventional therapy: Evidence supporting high dose vasopressors consisted 9 case reports of very good quality. Two animal that were either neutral or opposing were of good quality.Recommendation: In DI-shock refractory to conventional therapy, high dose vasopressors may be life saving. While most patients with refractory DI shock have a very low systemic vascular resistance (SVR), some patients have a very high SVR. Therefore, central hemodynamic monitoring should be implemented in patients with DI shock refractory to high dose vasopressors. In most cases vasopressors may be rapidly titrated until shock is adequately treated or recurrent ventricular dysrhythmias, signs of severe peripheral vasoconstriction or an excessively high

SVR is observed. Use of circulatory assist devices (IABP or emergency bypass) in DI-shock refractory to maximal medical therapy: Evidence supporting the use of cardiopulmonary bypass consisted of 6 animal studies of very good quality and more than 30 case reports. Evidence supporting the use of the intra-aortic balloon pump consisted of 1 animal study of fair quality and more than 10 case reports. Recommendation: Circulatory assist devices may be live saving in DI-shock refractory to *maximal* medical therapy. If these heroic measures are to be effective, they must be implemented before the stage of irreversible shock has been reached. Early implementation usually requires advanced planning and approval from multiple disciplines including cardiology, cardiothoracic surgery and cardiopulmonary perfusion. Reference: [1]*Circ* 2000;**102**(suppl I):223–228.

58 THE T40-MS AXIS AS A PROGNOSTIC FACTOR IN TRICYCLIC ANTIDEPRESSANTS OVERDOSE

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Tricyclic antidepressant (TCA) overdose is the most common cause of death from prescription drugs. Clinical presentation of overdose includes cardiac arrhythmias, hypotension, seizures, coma and anticholinergic signs such as hyperthermia, flushing and intestinal ileus. The highly toxic level (>1,000 ng/mL) is manifested on electrocardiograms as prolongation of the QRS interval to 100 milliseconds or more. Objective: describe the changes over time of the QRS interval and terminal 40-msec QRS frontal axis (T40-ms) in patients with acute tricyclic antidepressant poisoning, identify clinical factors and treatment associated with these changes, define the prognostic factors related to T40-ms changes; TCA poisoning has been reported to cause a right-axis deviation of 130 degrees to 270 degrees in the T40-ms axis. Methods: 60 patients were divided into two groups: TCA overdose (40 p.) and non-TCA overdose (20 p.). The T40 ms-axis was significantly more rightward in the TCA overdose group (>120 degrees). The QRS interval and T40 ms-axis were manually measured in all 60 ECGs. We calculated and compared the T40 ms-axis, QRS, QTc and PR intervals and evaluated ECG modifications, correlating presented symptoms. Results: The mean T40-ms axes were 150 +/− 112 degrees. A T40-ms between 120 and 270 degrees had a sensitivity of 38% and a specificity of 74%. Conclusions: These characteristics could demonstrate that T40 ms-axis is a better marker of TCA toxicity than the QRS interval and a significant prognostic factor if related to symptomatology.

59 THE EFFECT OF L-NAME ON AMITRIPTYLINE-INDUCED HYPOTENSION IN RATS

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Objective: Tricyclic antidepressant-induced hypotension is known as multifactorial. Nitric oxide (NO) production catalyzed by nitric oxide synthase (NOS) was reported to aggravate the tricyclic antidepressant-induced hypotension in rats. Our study was aimed to evaluate the role of NO in amitriptyline-induced hypotension using L-NAME, a NOS inhibitor, and SIN-1, a NO donor, in anesthetized rats. Methods: Amitriptyline intoxication was induced by the infusion of amitriptyline 0.625 mg/kg/min throughout the experiment in anesthetized rats. Fifteen and 25 minutes after amitriptyline infusion, two bolus doses of 10 mg/kg of L-NAME (n = 8) or an equivalent volume of 5% dextrose solution (n = 8) was administered in each rat (Protocol 1). To investigate whether the effect of L-NAME on blood pressure is reversed by SIN-1, after the same protocol of amitriptyline infusion and five minutes after L-NAME bolus, a bolus of 3000 nmol/kg of SIN-1 was administered (n = 8) in each rat (Protocol 2). To investigate the effect of L-NAME on SIN-1 induced hypotension, a group of rats received an infusion of 0.54 mg/kg/h of SIN-1 until 50% reduction was observed in mean arterial pressure (MAP) followed by a bolus dose of 10 mg/kg of L-NAME (n = 6) or 5% dextrose solution (n = 6) (Protocol 3). Outcome measures included MAP, heart rate (HR) and QRS interval. Student's t test and survival analysis were used for selected comparisons. Results: For all parameters, no significant difference was noted between treatment groups during the baseline or post-amitriptyline periods before therapy was rendered. In protocol 1, administration of amitriptyline caused a significant reduction in MAP ($p < 0.01$) and prolongation in QRS ($p < 0.01$) after 15 minutes. L-NAME significantly increased MAP when compared to control animals in 5, 10 and 15 minutes (72 ± 7.8%, 74.2 ± 8.4, 77.9 ± 8.5 of baseline, $p < 0.01$, respectively). Although the prolongation in QRS tended to continue with time, there were no significant differences between L-NAME and control groups. Survival time was increased by L-NAME (19.9 ± 2.7 vs. 33.4 ± 4.1, $p < 0.01$). In protocol 2, SIN-I reversed L-NAME-induced increase in MAP ($p < 0.01$). In both protocols, there was a significant decrease in HR during amitriptyline infusion but no significant differences were found between treatment and control groups. In protocol 3, L-NAME bolus reversed SIN-1-induced

hypotension when compared with those of dextrose-administered rats ($p < 0.001$). Conclusion: L-NAME is found to be effective in improving hypotension temporarily and prolonged survival time. Because this effect was antagonized by SIN-I, NO production appears to contribute to the pathophysiology of amitriptyline-induced hypotension.

60 RELATIVE TOXICITY OF VENLAFAXINE AND SEROTONIN SPECIFIC REUPTAKE INHIBITORS IN OVERDOSE

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Objective: To assess the toxicity in overdose of venlafaxine and serotonin specific reuptake inhibitors (SSRIs) compared to tricyclic antidepressants (TCAs). Methods: Cohort study of consecutive patients admitted with antidepressant poisoning to the Hunter Area Toxicology Service, Newcastle, Australia. We studied 456 admissions with antidepressant poisoning involving venlafaxine (51), tricyclic antidepressant excluding dothiepin (172) or a serotonin specific reuptake inhibitor (233). A further group of dothiepin overdose (81) was also studied for seizure activity. Main outcome measures were presence of seizures, arrhythmias, coma, serotonin toxicity, intensive care unit admission and QRS duration. Results: The odds ratio (OR) for seizures with dothiepin versus other TCAs was 3.4 (95% CI 1.0–12.0, $p = 0.04$). The OR for seizures with venlafaxine versus other TCAs was 4.4 (1.2–16.6, $p = 0.02$) while the OR for SSRIs versus other TCAs was 0.4 (0.1–1.7, $p = 0.25$). Arrhythmias were not more or less likely than with other TCAs for venlafaxine (0.0, 0.0–5.1, $p = 0.70$) or SSRIs (0.2, 0.0–1.9, $p = 0.21$). Venlafaxine (0.1, 0.0–0.6, $p = 0.005$) and SSRIs (0.1, 0.0–0.2, $p < 0.0001$) were much less likely to cause coma than TCAs. When compared to other TCAs, SSRIs (0.3, 0.2 - 0.6, $p < 0.30001$) but not venlafaxine (0.6, 0.3–1.4, $p = 0.31$) were more likely to prolong the QRS to 100 ms. Compared to TCAs, admission to ICU was less likely for SSRIs (0.1, 0.1–0.2, $p < 0.0001$) and nearly so for venlafaxine (0.5, 0.2–1.0, $p = 0.051$). Serotonin toxicity was much more common with venlafaxine (35.4, 7.6 - 325.3, $p < 0.0001$) and SSRIs (20.4, 5.2–174.9, $p < 0.0001$) than with TCAs. Conclusions: Dothiepin in overdose is pro-convulsant. Venlafaxine in overdose seems also to be pro-convulsant. It is much more likely to cause serotonin toxicity but is less likely to cause coma than TCAs. SSRIs are much less likely to cause coma, require ICU admission or prolong the QRS but are much more likely to cause serotonin toxicity than TCAs. Antidepressants other than dothiepin or venlafaxine should be considered in patients at risk of seizure or suicide.

61 CHLORAL HYDRATE OVERDOSE: COMEBACK OF AN OLD SUBSTANCE

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Objective: Chloral hydrate is still widely used in Switzerland as a sedative and hypnotic drug. In recent years an increasing number of chloral hydrate poisonings have been reported to the Swiss Toxicological Information Centre. The aim of this study was to analyze the cases with chloral hydrate mono-intoxications in regard to severity, dose dependent toxicity and effects of early decontamination. Methods: We retrospectively analyzed all feedback reports from physicians on patients with chloral hydrate poisoning between January 1980 and December 1999. Only cases with oral chloral hydrate mono-intoxication containing clinical detailed information regarding the severity of symptoms were included. Severity was assessed according to the EAPCCT/EC/IPCS Poisoning Severity Score. Results: Among a total number of 402 cases with chloral hydrate overdose, 95 patients (86 adults, 9 children) with clinically well-documented mono-intoxications could be included in the study. 88 chloral hydrate poisonings were intentional and 4 accidental. In 3 cases the circumstances of intoxication were unknown. Nine (9.5%) individuals remained asymptomatic. 59 (62%) patients developed minor symptoms such as somnolence (52) and/or mild tachycardia (9). 17 (18%) patients showed moderate symptoms including sopor (9), agitation (5), moderate cardiac disturbances (2), single convulsion (1), gastric ulcer (1) and rhabdomyolysis (1). Eight (8.5%) patients were severely intoxicated with deep coma (6), ectopic ventricular beats (1), ventricular tachycardia (1), asystole (2) and respiratory insufficiency (2). Two (2%) patients died because of septic-toxic shock after aspiration pneumonia and cardiac arrest. Ingested doses (±10%) were known in 50 cases (4 asymptomatic, 34 mild, 9 moderate, 3 severe) and ranged between 0.6 g and 30 g. Moderate and severe symptoms where observed only above ingested doses of 2.4 g and 7.5 g chloral hydrate, respectively. While late primary decontamination (gastric lavage and/or activated charcoal) after one hour of intoxication had no influence on the dose-dependent severity of poisoning, early (<1 hour) primary decontamination (14 patients, ingested doses between 3 g and 30 g) prevented the development of severe symptoms and increased the dose-limit for moderate symptoms to 6 g. Conclusions:

Chloral hydrate is an important cause of moderate and severe acute poisoning in Switzerland. Patients who have ingested doses above 2.4 g should receive primary decontamination with activated charcoal within one hour after intoxication in order to prevent the development of moderate and severe symptoms. Primary decontamination after one hour of intoxication appears to be ineffective, and the patients should be transferred to an intensive care unit for monitoring and rapid therapy of potentially life-threatening symptoms.

62 PRINCIPLES OF OXIME TREATMENT AND ITS LIMITATIONS: FROM CASE REPORTS TO AN ASSESSMENT OF OXIME EFFECTIVENESS

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Objectives: Reactivation of inhibited acetylcholinesterase (AChE) with oximes is a causal approach for therapy of intoxication with organophosphorus compounds (OPs). Maximal oxime effects are expected when appropriate doses of oxime are administered as soon as possible and as long as reactivation can be anticipated. The proof of oxime effectiveness in intoxicated patients, however, is difficult due to atropinization, sedation, and artificial ventilation during the life-threatening phase of cholinergic crisis. Additionally, differences of individual courses during the acute phase of intoxication (e.g. amount and type of OP, time elapsing to first symptoms and treatment) result in different toxicokinetics and -dynamics (toxication and elimination of the poison as well as ageing). All these variables are obscure a clear look on oxime effectiveness. To unravel the characteristic oxime effect we analyzed the reactivation of AChE using red blood cells (RBC) as an accessible enzyme source that reflects synaptic AChE. To foster the appropriateness of this approach, neuromuscular function was monitored following nerve stimulation. Based on these considerations a clinical trial was initiated according to ICH-GCP guidelines. 18 OP-intoxicated patients with life-threatening cholinergic crisis were included and received as specific treatment atropine at low dosage and obidoxime by continuous infusion. Methods: Obidoxime, 250 mg IV as bolus, followed by 750 mg/24h, was administered as long as reactivation was possible. Neuromuscular transmission was estimated after stimulation of the N. ulnaris by recording the compound muscle action potential of the M. abductor dig. V. RBC-AChE and plasma-BChE were determined by a modified Ellman procedure. Reactivatability was checked by incubating patient's RBC with obidoxime in vitro. Inhibitory activity as measure of poison load was assessed by incubation of donor RBC with patient's plasma. Plasma concentrations of obidoxime were determined by HPLC and of atropine with a radioreceptor assay. Results: Reactivation by about 10 μM obidoxime was possible for about one week after intoxication with OPs leading to diethylphosphoryl-AChE. In contrast, due to fast ageing of dimethylphosphoryl-AChE, its reactivation was restricted to the first two days after intoxication. In both types, high poison load may result in faster reinhibition than reactivation of AChE, thereby preventing net reactivation. Irrespective of the OP used, increase of inhibited RBC-AChE activity to values above 20 per cent of normal correlated with normal neuromuscular function and with reduced atropine demand. In cases with lethal outcome, death occurred several days after subsidence of cholinergic crisis, mostly due to preclinical complications (late resuscitation, aspiration followed by ARDS) and problems arising from long-lasting intensive therapy (e.g. cardiac infarction, lung emboli). Conclusions: To assess effectiveness of treatment with enzyme reactivators an exact individual judgment is necessary. The therapeutic effect of oximes can be clearly evaluated using neuromuscular function and cholinesterase status. In cases where an increase of RBC-AChE activity by more than 20% was observed an improvement of neuromuscular function occurred indicating therapeutic benefit. Oxime administration may be reasonable for up to one week in poisoning with diethyl-OPs, whereas oximes should be subsided on the second day after intoxication with dimethyl-OPs. Moreover, oximes should be administered as long as reactivation is possible. We feel that lethality alone, if not properly specified, is a poor parameter to judge effectiveness of oxime treatment.

63 EXPERIENCES IN RUNNING AN ORGANOPHOSPHATE EXPOSURE CLINIC

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Although the toxicology of organophosphate compounds when taken in large doses is well documented–a cholinergic syndrome,[1] a polyneuropathy[2] and an intermediate syndrome,[3] the association between chronic low dose exposure and neurological damage has been difficult to confirm.[4] However, a number of farmers and other agricultural workers in

Northern Ireland and elsewhere are convinced that their symptoms are due to previous low dose exposure. Objectives: This study outlines the clinical findings obtained while assessing a group of patients with chronic ill health that they attributed to previous exposure to organophosphate insecticides. Methods: A detailed history relating to the type of compound, the amount and frequency of pesticide exposure and the principal symptoms of which they complained, was obtained. Full clinical examination was undertaken with particular attention to the signs of peripheral neuropathy and impaired cognitive function and where appropriate patients were referred for more detailed neurophysiological (30%) and neuropsychological (87%) assessments. A battery of blood tests was also obtained in all patients to measure cholinesterase activity and exclude other diseases in line with the Joint Guidelines of the Royal Colleges of Physicians and Psychiatrists. Results: A total of 39 patients were assessed. Most patients (54%) were exposed to organophosphates for 20–40 hours per year with a maximum exposure of 240 hours and in most individuals (82%) it was the result of sheep dipping. The principal symptoms were fatigue (86%), musculoskeletal pains (86%) and memory problems (80%), although chest pain, mood disturbances, chemical sensitivity, shortness of breath, tingling of the extremities, visual problems, unsteadiness, abdominal swelling and nausea were also experienced. Pre-existing diagnoses were depression (8), chronic fatigue syndrome (5), asthma (3) and other (9), including cardiomyopathy and osteoporosis. Overall 66% had non-specific features that could not be classified. In 18% the pre-existing diagnosis offered the best diagnosis. In 8% a new diagnosis was made and in the remaining 8% the possible diagnosis was organophosphate toxicity based on the symptoms at the time of exposure, evidence of neuropathy and possible cognitive defects. References: [1]Minton NA, Murray VSG. A review of organophosphate poisoning. *Med Toxicol* 1988;**3**:350–375. [2]Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994;**84**:731–736. [3]Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorous insecticides. An intermediate syndrome. *N Engl J Med* 1987;**316**:761–763. [4]Bateman DN. Are there long-term sequelae from repeated low dose organophosphorous insecticide exposures? *J Toxicol Clin Toxicol* 1999;**37**:368–369.

64 CLINICAL COURSE AND ANALYTICAL DATA OF NINETEEN ORGANOPHOSPHATE INTOXICATIONS

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Objectives: The treatment of suicidal attempts with ingestion of multiple lethal doses of organophosphate compounds is still a major problem in clinical toxicology. This report describes the clinical course and analytical data of 19 cases of severe organophosphate intoxications. Case Series: In 19 cases (age 25 to 80) of severe organophosphate pesticide poisoning (OP) following suicide attempts, obidoxime was given as an IV bolus 250 mg followed by continuous infusion at 750 mg/d. The serum concentrations of organophosphates and the clinical course were monitored in each case. We divided the patients into 5 groups of different OPs. There were 7 cases of parathion intoxication, 6 cases of oxydemeton-methyl intoxication, 4 cases of dimethoate intoxication and 1 case of malathion and 1 case of methamidophos intoxication. The lethality was 57.1% (4 out of 7) in the parathion group and 16.7% (1 out of 6) in the oxydemeton-methyl group. Death occurred in one case (oxydemeton-methyl) on day 8 and in four cases between day 17 to 22 (mean 19.8). The reason was multiorgan failure in 3 cases and complications like pulmonary thromboembolism and peritonitis. The duration at ICU in the surviving group was between 5 and 46 days (mean of parathion group 23.3 days; oxydemeton-methyl 19.8; dimethoate 19.6). Mechanical ventilation was performed from day 2 to 45 (mean 13.6). The most common complications of all groups were pneumonia (16 cases), acute renal failure (16) and circulation insufficiency (14), hyperlipasemia in (14), elevation of liver enzymes (9), arrhythmias (8), cholestasis (5) and 5 cases with ARDS. All complications were reversible in the surviving group. We treated the patients with obidoxime ranging from 0.8 g to 8.9 g (mean 2.8 g) during 1 to 12 (mean 4.5) days as long as reactivation of the erythrocyte-AChE could be observed. The serum concentrations of OP in the parathion group ranged from 0.025 mg/L to 22.11 mg/L, in the oxydemeton-methyl group it varied from 0.024 mg/L to 2.49 mg/L. In two cases of mega-dose parathion intoxication serum OP levels remained high until death (up to 17 and 22 days, half life of parathion in the serum 57 and 99 hours). Conclusion: The lethality of parathion intoxication is much higher than in oxydemeton-methyl intoxication. In parathion poisoning patients survived with serum OP levels under 0.1 mg/L; in oxydemeton-methyl poisoning patients survived serum levels under 2 mg/L. The most frequent complications of OP poisoning during ICU stay were pneumonia, acute renal failure and circulatory insufficiency.

65 PROGNOSTIC VALUE OF PLASMA COLCHICINE CONCENTRATIONS IN ACUTE POISONINGS

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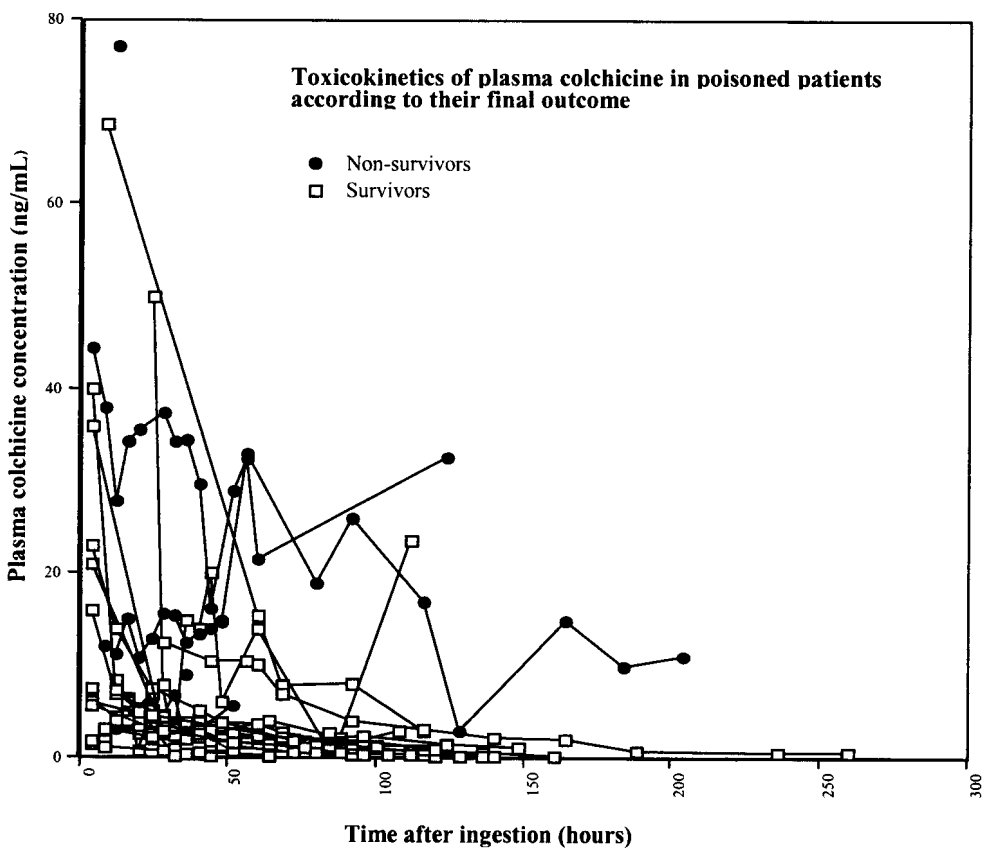
Objectives: Colchicine toxicity is dose-dependent with multiorgan involvement and delayed onset. Failure to appreciate the potential for serious toxic effects could be a major pitfall in managing acute poisoned patients. Recognized prognostic factors include the supposed ingested dose (SID), a decrease in prothrombin time (PT) = 20% of normal values and an elevation in white blood cell (WBC) count = 18.10^9/L in the 24 hours and the onset of cardiogenic shock in the 72 hours following admission. The aim of our study was to assess the prognostic value of colchicine plasma concentrations on admission and plasma kinetics from date of ingestion. Methods: Retrospective collection of clinical, biological data and outcome of all patients hospitalized in two Intensive Care Units (ICU) for acute colchicine overdose; analysis of plasma kinetics, obtained by radio-immunological assay; comparison of survivors and non-survivors groups using Chi-2 and Mann-Whitney tests. Results: Twenty-four patients, admitted from 1993–1999 in ICU for colchicine acute poisoning were included: 12 F/12 M, 36 years [15-70] (median, [extremes]), with SID of 20 mg [5-94]. 6/24 (25%) died in ICU, 4/24 (17%) developed multiorgan failure, 5/24 (21%) acute respiratory distress syndrome, 6/24 (25%) cardiogenic shock and 7/24 (29%) hematological toxicity. There was no significant difference (p = 0.09) of colchicine plasma concentrations on admission between survivors (4.1 ng/mL [0.7-68.5]) and non-survivors (13.6 ng/mL [3.2-77.0]). Only PT significantly (p = 0.03) differs on admission between these two subgroups, while SID (p = 0.6), and WBC count (p = 0.5) did not. However, despite a limited number of patients, there was an interesting difference in plasma kinetics of colchicine considered from time of ingestion, regarding the final outcome. Conclusion: The prognosis of colchicine-poisoned patients admitted in ICU is severe with a mortality rate of 25%. It seems more correlated to plasma toxicokinetics of colchicine than to the plasma concentration measured on admission. However, our results should be confirmed by a larger multi-center study.



66 IDENTIFYING FREQUENTLY OCCURING SUBSTANCES WITH LOW TOXICITY– PRIMARY PREVENTION WITHIN THE EUROPEAN COMMON MARKET

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Introduction: In Germany an estimated 100,000 accidental childhood ingestions occur every year. In 10,000 of these cases (10%) symptoms of poisoning are observed, the number of severe poisonings ranges below 500 (0,5% of all accidental ingestions). The death rate of poisonings in this age group lies between 20 to 40 per year. From these data it is obvious, that rapid, low threshold telephone advice by poison centers is essential and highly effective in sorting out the 90% of cases, where no further medical treatment is necessary[1]. Besides the knowledge accumulated in these poison centers about substances with low toxicity or definite atoxic amounts of potentially harmful substances helps to achieve primary prevention by targeted public campaigns. Within the national and international cooperation of poison centers throughout Europe such lists form the basic denominator for further harmonization and standardization of poison centers work and at the same time reduce the workload within each poison center. Results: We have developed a list of 24 substances or group of substances (pharmaceuticals, household products and plants) out of a retrospective analysis of 401,000 childhood ingestions between 1989 and 1999 that occur frequently and have low inherent toxicity or cause no harm due to the maximum amount ingested[2]. A preliminary list had been published in the 1995, 3rd edition of our textbook for use in all German childrens hospitals and by other German speaking poison centers. The consequent use of this list in everyday counseling at Berlin poison center applies to over 30% of all requests from lay people and medical personal likewise. The list will be explained in detail. By this way we could reduce the time for documentation and counseling in 12,000 out of 36,000 annual requests concerning childhood accidental ingestions and focus our attention on the detection of new risks and follow-up of relevant intoxications. Conclusion: Because regional and national differences exist in consumer habits, plant toxicity and use of remedies and household products we propose to compile a European list of substances with low inherent toxicity as a common denominator for the basic harmonization of poison center counseling throughout Europe. Together with medical advice as to the deleterious effects of table-salt induced vomiting in children this list could be made available to the general public in our effort for primary prevention on the EAPCCT homepage, a workgroup within EAPCCT being responsible for the peer reviewed biannual actualization of this list. References: [1]Krenzelock EP. The use of poison prevention and education strategies to enhance the awareness of the poison information center and to prevent accidental pediatric poisonings. *J Toxicol Clin Toxicol* 1995;**33**(6):663–667. [2]Lovejoy FH, Robertson WO, Woolfe AD. Poison centers, poison prevention, and the pediatrician. *Pediatrics* 1994;**94**(2):220–224.

67 ARE THERE RISK POPULATIONS FOR "ENVIRONMENTAL ILLNESS"?

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Objective: The etiology of symptoms attributed to widely used chemicals in low doses remains unclear. Despite the lack of scientific evidence the phenomenon has already been given a variety of more or less suggestive names, e.g. Multiple Chemical Sensitivity. Some authors postulate risk populations such as workers using solvents. We compared patients of our Environmental Clinic and a group of workers in the semiconductor industry. Methods: We studied 117 outpatients complaining of symptoms attributed to environmental toxins. Using a standardized questionnaire, the SOMS and the SCL-90R we collected data on their psychosocial, professional and environmental situation. We compared these data to those of 59 workers in the semiconductor industry with a known exposure to metals and solvents in low doses. Biomonitoring was carried out the patient group according to the substances they suspected to be harmed by. In the control group solvents and metals were screened routinely. Results: Both groups were similar in age and sex distribution. Major social differences consisted of the fact that patients lived less often with a partner or children, had a higher socioeconomic level and were predominantly employees. The percentage of patients carrying dental amalgam, smoking, drinking and living near highways was identical in both samples. There was a tendency towards patients living in more rural and less industrialized areas. Food intolerances were more common among patients, as well as self-reported allergies. The majority of patients had clear ideas about the harmful substance, mainly amalgam, other metals, solvents or a combination. Every third control person reported physical symptoms; every fifth considered environmental or occupational hazards as a possible cause, but no worker felt ill from metals or solvents. Biomonitoring was adjudged normal in 96% of patients and in 81% of controls. 10% of the workers had high counts of urine arsenic, up to 23 fold than normal, single cases of increased levels of chrome, aluminum, toluol, xylol and trichloroethanol were also found. Bio-

monitoring of patients revealed abnormalities in 8 of 182 analyses with relatively high levels of aluminum (2 patients), β-HCH, γ-HCH, DDE, PCB, trichloroethanol, or cadmium. In neither group did the results of the biomonitoring correlate with the number of symptoms. Patients scored significantly higher on almost all dimensions of the SCL-90R symptom checklist. Conclusion: We found no evidence that workers in the semiconductor industry define a risk population for illness caused by commonly used chemicals in small doses. There was a discrepancy between reported symptoms and biomonitoring results, suggesting no toxicological relation. Obviously, "environmental illness" tends to affect a different socioeconomic group with a different psychological profile than the assumed risk population.

68 CONTROVERSIES IN THE INTERPRETATION OF PEDIATRIC POISONING OUTCOME STUDIES

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Problem: Pediatric poisoning outcome studies are designed to allow physicians to use past experience in "pediatric poisonings" to predict whether a child in a future situation is at risk for serious toxicity. Children exposed to poisons are managed differently in different regions because of differences of opinion about the utility and applicability of various pediatric studies. Issues: The single most important factor limiting conclusions from pediatric poisoning studies is the lack of consistent proof that biological absorption actually occurred and that the entire "estimated dose" was absorbed. Controversy arises when experience with a product is large but difficult to interpret. The actual dose ingested may be far lower than the estimated dose based upon incorrect history or decontamination. Reports of "good outcome" in these situations may represent low toxicity of the drug at an estimated dose, overestimation of the amount ingested with low toxicity at the dose actually ingested (and consequent risk if another child actually ingested the whole estimated dose) or no effect because ingestion did not occur. Reports of good outcome that attempt to generate a "safe" mg/kg dose based upon small numbers of patients who may have ingested one or two tablets of a new drug are particularly suspect. A second major difficulty resulting in controversy in applying the results of pediatric studies is the source of the data. Most studies come from retrospective reviews of passively collected, phone based, poison center data. Difficulties with this form of data collection include the following: passive (biased) enrollment, incomplete reporting (presence of symptom/lab results may be significant but absence is not), inconsistent reporting (similar studies may not have been done on all patients), data of interest may not have been collected, not reported or incorrectly transmitted/recorded (with no access to primary record to confirm), poor time fixation of symptoms and lab results, inability to differentiate related symptoms from iatrogenic symptoms (e.g., "bleeding" after brodifacoum may be traumatic nosebleed related to NG administration of activated charcoal), follow up to final outcome is biased (more severe get more effort at follow up) and incomplete (lost phone follow up). Even prospective poison center studies cannot alleviate many of these difficulties. The third major source of controversy concerns the collection and use of an appropriate outcome measure. All toxicologists want to craft a management strategy that uses societal resources efficiently to prevent dangerous outcomes. Toxicologists, like others, vary in their relative degree of risk aversion. However, significant arguments develop over whether the appropriate outcome has been studied and applied in the cost/benefit assessment. This is particularly important in considering a very rare but preventable severe outcome that may not have warning symptoms. When considering the cost/benefit of referring children to the ED for evaluation after brodifacoum ingestion, is the appropriate outcome measure the frequency of an unexpected CNS bleed or the more commonly occurring mildly abnormal PT INR? When choosing a referral dose for paracetamol is the appropriate measure the frequency of hospitalization for severe hepatic injury or of a serum paracetamol concentration in the "possible toxicity" portion on the Rumack-Matthew nomogram? Disagreement on these kinds of issues leads to rejection of studies by various experts and inconsistent recommendations within nations. Two other factors also contribute to controversy. Not all experts accept management strategies based upon patients who have received decontamination even if they are only to be applied to patients receiving decontamination. The reduction of absorption that occurs in a population has a distribution of effect around the mean, often including no effect. Thus, it is difficult to apply such data to an individual situation, particularly at the margin of the "safe dose if decontaminated." Also, toxic doses derived from retrospective studies of patients with bad outcome may be misleading. They are based upon recall and may not reveal key associated features that set severely affected patients apart from others who may have ingested the same dose but escaped identification because they suffered no effects. Proposal: Toxicologists must explicitly recognize these factors when they design

studies and dialogue about differences in management. Multi-center, prospective agreements must exist between poison centers and pediatric institutions. These agreements must include IRB approved general ingestion studies, covering a broad range of substances that allow collection of biological specimens on enrolled patients and mutual access to complete data. Studies of specific drugs with single tablet ingestion (clonidine, glipizide, verapamil SR) or multi-tablet ingestion (paracetamol, multivitamins) may provide models to assess the validity of "estimates" and the frequency of non-ingestion. Such data will allow proper planning of studies using pediatric patients.

69 PEDIATRIC PARACETAMOL (ACETAMINOPHEN) POISONING: THE 150 MG/KG MYTH

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The commonly accepted dose of concern for acetaminophen in children is 150 mg/kg, often referred to as "the toxic dose." However, hepatotoxicity due to a single ingestion of acetaminophen in a child is a rare event. It is difficult to find more than two reports with one of them being an en passant mention of a few examples. Therefore, this value is at best, an extrapolation from adult data. Recently, an Australian report recommended raising the bar to 250 mg/kg based upon pharmacokinetic modeling of pediatric data.[1] Children are considered to be relatively resistant to the development of toxicity from acetaminophen overdose. This is unrelated to the well-known difference in the metabolism of this drug. The sulfation pathway is proportionally greater in children than in adults. However, this is a compensation for their relative inability to glucuronidate. The capacity of phase II metabolism of acetaminophen has not been shown to differ between children and adults. Therefore this difference regarding the relative amounts of sulfation and glucuronidation is not a credible explanation for children being relatively resistant to acetaminophen toxicity. Nevertheless it is reasonable to expect that on a mg/kg basis, a young child should tolerate a larger acetaminophen dose than adults. This is because young children clear drugs more efficiently. They require larger mg/kg doses of many drugs to maintain therapeutic serum concentrations. A few examples are phenobarbital, phenytoin and gentamicin. There is a simple anatomic reason for this. Their livers and kidneys are relatively larger. Data compiled from several sources by Maxwell[2] describe the proportion of organ weight to total body weight. Selected hepatic values are 4.0% for a one year old, 3.6% for a two year old, 3.0% for a five year old and 2.4% at age 18. Renal data for these ages are 0.70%, 0.74%, 0.66% and 0.42% respectively. Thus a one-year-old child's liver is larger than an adult's liver by a factor of 1.67 when expressed as a percentage of body weight. Multiplying 150 mg/kg, the dose of concern derived from adult data by 1.67 produces the value of 250 mg/kg. Perhaps not coincidentally, this is Anderson et al. recommended pediatric dose of concern.[1] The same calculations for a five year old results in a ratio of 1.25 and a dose of concern of 187.5 mg/kg. Thus 150 mg/kg is too low for all children less than six years old but to a much greater extent for the very young members of this group. The commonly accepted acetaminophen dose of concern of 150 mg/kg in a child is indeed a myth. Raising the bar will result in fewer patients receiving gastrointestinal decontamination and serum concentration determinations. The benefits are obvious. References: [1]Anderson BJ, Holford NHG, Armishaw JC, Aicken R. Predicting concentrations in children presenting with acetaminophen overdose. *J Pediatr* 1999;**135:**290–295; [2]Maxwell GM. *Principles of Pediatric Pharmacology*. New York: Oxford University Press; 1984:96.

70 CHILDREN VERSUS ADULTS: DIFFERENCES AND SIMILARITIES IN RESPONSE TO ENVIRONMENTAL POLLUTANTS AND CHEMICAL/DRUG POISONS

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Objective: Minimal published data are available to evaluate quantitatively risk of exposure and response of infants and children to environmental pollutants and some chemical/drug poisons. Biologic differences in infants and children compared to adults allow possible prediction in some cases of potentially increased or potentially decreased toxicity risks to some environmental chemicals. Results: These biologic/physiologic differences include: as much as a 2.7 fold greater skin surface area:body mass ratio, proportionally larger brain size, rapid brain growth, greater cerebral blood flow per unit mass of brain weight, developmental changes in brain neurotransmitters, a 40-fold to 60-fold greater lung respiratory minute ventilation rate per square meter of lung surface area, decreased but later increased (compared to adults) liver hydroxylation, glucuronidation and other metabolism, developmental ontogeny of cytochrome P450 isozymes, decreased renal glomerular filtration and tubular secretion, protein binding to albumin/alpha-1-glycoprotein and

tissue binding, and increased intracellular glutathione. Known examples from the available database will be discussed including hexachlorophene and benzyl alcohol brain stem cell necrosis, lead (Pb) poisoning, acrodynia, acetaminophen hepatotoxicity, chloramphenicol gray-baby syndrome, gentamicin nephrotoxicity and ototoxicity, dystonic adverse drug reactions, nitrate-induced methemoglobinemia, fetal alcohol syndrome, retinoid embryopathy, neural tube birth defects, breast milk environmental pollutant exposure, ozone air pollution, passive cigarette smoke exposure, and environmental endocrine disruptors. Conclusion: All of these differences have potential implications for toxicological risk for infants and children, in some cases greater risk and in some cases lesser risk than adults.

71 UNIQUE ASPECTS IN PEDIATRIC POISONINGS

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Background: Clonidine ingestions (A) and gastrointestinal decontamination (B) in children deserve special consideration. Case Series A: Clinically, clonidine toxicity mimics opiate overdose. Therefore, it is not surprising that naloxone has been administered in an attempt to reverse clonidine-induced hypotension, bradycardia, coma, and apnea. Case reports reveal inconsistent reversal of central nervous system (CNS) and cardiovascular (CV) effects following the administration of naloxone to toddlers who have ingested clonidine. There are multiple variables in these case reports. Varying doses of naloxone, frequently determined by weight, were administered. Varying degrees of coma, hypotension, and bradycardia were present at the time that naloxone was administered. Cardiovascular response was not differentiated from CNS response. Discussion: Animal research indicates that clonidine causes hypotension by inhibiting the imidazoline-preferring receptors in the ventrolateral medulla oblongata but clonidine causes sedation by inhibiting the alpha-2 adrenoreceptors in the locus cereleus. Large doses of clonidine are required to inhibit the metabolic activity of catecholaminergic neurons within the locus cereleus. Therefore the clinical picture (sedation) is partially determined by ingested dose of clonidine. Central alpha-2 receptor agonists such as clonidine may cause release of beta-endorphin. Both sympathetic tone and adrenoreceptors in the locus cereleus are inhibited by beta-endorphin. A genetic predisposition may determine the resting tone of the sympathetic nervous system as well as the release of endogenous opiates in response to clonidine. There may be genetically predetermined "responders" and "nonresponders." Clinical presentation at the time of administration of naloxone, genetic predisposition and individual response to the actions of naloxone contribute to the inconsistent reversal of CV and CNS toxicity. The clinical question that has not yet been answered is whether there is a dose of naloxone that would reverse the toxic effects of clonidine in all patients. There is very little evidence that large doses of naloxone would be harmful in these patients. Hypertension myth: The myth of hypertension following naloxone administration can be clarified by analysis of the three case reports supporting this myth. Administration of atropine and paralytic agents prior to the administration of naloxone contribute to the hypertension that occurred following naloxone administration. Yet many practicing pediatricians do not use naloxone in the setting of clonidine intoxication due to the concern of subsequent hypertension. The lack of evidence for naloxone-induced hypertension in the setting of clonidine intoxication needs to be disseminated to practicing clinicians. Receptor physiology: Receptor physiology may be different in children and adults. One of the clinical aspects to be considered is whether children should be treated with larger doses of drugs that affect receptors. Case Series B: Certain aspects of gastrointestinal decontamination require special consideration in children. Aspects include: conflicting opinions regarding the indications for syrup of Ipecac administration, reasons that gastric lavage is seldom, if ever, indicated in children, the risk:benefit ratio of administering single-dose activated charcoal (SDAC) to children, multiple-dose activated charcoal (MDAC) and the misconception regarding the dangers of administering charcoal with sorbitol to children. Conclusion: The risk:benefit ratio of administration of syrup of Ipecac, gastric lavage, SDAC and MDAC may be different in children than in adults. Some poisons, such as cellular toxins, require special consideration.

72 PEDIATRIC TRICYCLIC POISONING—IS QRS DURATION AN INDICATOR OF IMPENDING TOXICITY?

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Objectives: ECG criteria, particularly QRS duration, have been shown to be a useful determinant of outcome in adults with tricyclic antidepressant (TCA) poisoning. There is, however, limited published data on whether such criteria are