

# ***Current Awareness in Clinical Toxicology***

***Editors: Sarah Cage MSc and Allister Vale MD***

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## ***CURRENT AWARENESS PAPERS OF THE MONTH***

### ***Pharmacokinetic considerations in clinical toxicology: clinical applications***

Roberts DM, Buckley NA. Clin Pharmacokinet 2007; 46: 897-939.

**Abstract:** Pharmacokinetic and pharmacodynamic principles should be regarded in the assessment and proper management of patients exposed to a poison. Clinicians must apply these principles to make rational clinical decisions regarding the significance of the poisoning (risk assessment) and to formulate an appropriate management plan. However, pharmacokinetic processes and parameters may be changed in the patient with acute poisoning. This may result from saturation of the capacity of a number of physiological processes due to the high dose, or the toxic effects of the poison may change these processes directly. For example, absorption kinetics may be altered because of increased gastrointestinal transit time (e.g. cholinergic receptor antagonists) or saturable absorption (e.g. methotrexate).

Saturation of protein binding may increase the volume of distribution and thereby increase the elimination half-life (e.g. salicylates). Alteration of the acid-base balance (poison-induced or iatrogenic) may also increase or decrease the distribution of a poison. Saturation of metabolism at high doses can prolong toxicity (e.g. phenytoin) or lead to other routes of metabolism that lead to increased toxicity (e.g. paracetamol (acetaminophen)).

Excretion may be reduced by saturation of active transporters or decreased renal blood flow. A better understanding of pharmacokinetic principles should improve the clinical care of patients. It should lead to more accurate interpretation of blood concentrations or biomarkers (e.g. ECG intervals or acetylcholinesterase activity) and how these relate to the time course for that poison, and better prediction of prognosis. This in turn, indicates the appropriate duration of observation and the requirement for some specific treatments.

Many specific poisoning treatments aim to favourably alter the pharmacokinetics of the poison. These include activated charcoal, whole bowel irrigation, extracorporeal elimination, chelating agents, antitoxins and urinary alkalinisation. The evidence supporting them, their indications and limitations can only be understood using pharmacokinetic principles. These principles also underpin the appropriate choice within the flexible dosage regimen for many antidotes. In particular, naloxone, flumazenil, methylene blue, atropine and pralidoxime all use variable doses and have an elimination half-life that is much shorter than many (but not all) of the poisons treated by these agents. A firm grounding in pharmacokinetics/toxicokinetics should be regarded as a core competency for all professionals involved in clinical care or undertaking research in clinical toxicology.

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## ***Psychiatric issues in toxic exposures***

Brown JS, Jr. Psychiatr Clin North Am 2007; 30: 837-54.

**Abstract:** Military, occupational, and environmental events can cause toxic injuries that require psychiatric diagnosis and treatment. This article reviews the psychiatric effects of neurotoxins, including nerve gases, ionizing radiation, insecticides, heavy metals, solvents, and other toxic agents. Diagnostic considerations and clinical tests for further evaluation of the numerous psychiatric conditions and symptoms caused by toxic exposures are discussed.

## ***Safety and efficacy of intravenous N-acetylcysteine for acetaminophen overdose: analysis of the Hunter Area Toxicology Service (HATS) database***

Whyte IM, Francis B, Dawson AH. Curr Med Res Opin 2007; 23: 2359-68.

**Background:** Acetaminophen (N-acetyl-p-aminophenyl; APAP) is the leading drug used in self-poisoning and frequently causes hepatotoxicity, including acute liver failure.

**Objective:** To provide descriptive data on the safety and efficacy of intravenous N-acetylcysteine (IV-NAC) in the treatment of APAP toxicity, based on information in the Hunter Area Toxicology Service (HATS) database involving residents of the Greater Newcastle Area of New South Wales, Australia.

**Methods:** This was a retrospective analysis of all APAP overdoses from January 1987 to January 2003. Data were collected prospectively according to a published protocol and included patient characteristics, exposures to APAP and other potential toxins, treatments, and outcomes. Primary safety/tolerability endpoints included the mortality rate and incidence of adverse drug reactions, while efficacy endpoints included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.

**Results:** Of 1749 patients, 399 (22.8%) were treated with IV-NAC. Of these, 37 (9.3%) had an adverse drug reaction to IV-NAC, of which seven (1.8% of total) were anaphylactoid. There were five deaths in hospital (mortality rate = 0.3%), including two attributed to APAP (0.1%) and none to IV-NAC. Of 64 patients who were treated with IV-NAC within 8 hours after APAP ingestion and had available ALT/AST data, two (3.1%) developed hepatotoxicity (AST/ALT > 1000 IU/L) compared with 32 (25%) of 128 patients receiving IV-NAC > 8 hours after APAP ingestion ( $p = 0.0002$ ). A total of 26 patients (15.6%) receiving IV-NAC treatment within 8 hours after APAP ingestion had hospitalization stays > 48 hours compared with 70 (33.3%) receiving IV-NAC > 8 hours after ingestion ( $p < 0.0001$ ).

**Conclusions:** For patients with APAP overdose seen in the HATS database of New South Wales, Australia, in-hospital death was infrequent (< 1%) and hepatotoxicity was significantly less likely when IV-NAC was administered within 8 hours after APAP ingestion compared with longer intervals ( $p < 0.01$ ). As a descriptive retrospective database analysis, this study could not exclude certain sources of bias, including temporal changes over the 16-year course of data collection in the use of IV-NAC and low ascertainment of mild, self-limiting reactions to IV-NAC.

## ***Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study***

Greene SL, Gawarammana I, Wood DM, Jones AL, Dargan PI. Intensive Care Med 2007; 33: 2019-24.

**Objective:** To examine the clinical safety of hyperinsulinaemia/euglycaemia therapy (HIET) in calcium channel blocker (CCB) poisoning.

**Design:** A prospective observational study examining biochemical and clinical outcomes of a HIET protocol administered under local poisons centre guidance.

**Setting:** Critical care settings.

**Patients:** Seven patients with significant CCB toxicity (systolic blood pressure (BP) < 90 mmHg)

treated with HIET. Interventions: HIET was commenced after correction of any pre-existing hypoglycaemia ((blood glucose) < 65 mg/dl) or hypokalaemia ( $K^+$  < 3.5 mmol/l). A quantity of 50 ml of 50% intravenous dextrose was followed by a loading dose (1 unit/kg) of intravenous short-acting insulin and an insulin maintenance infusion (0.5-2.0 units/kg/h). Euglycaemia was maintained using 5-10% dextrose infusions. Potassium was maintained within low normal range (3.8-4.0 mmol/l).

**Measurements and results:** Six patients survived. All patients received fluids, calcium, and conventional inotropes. Three patients (who all ingested diltiazem) received an insulin-loading dose; all experienced a significant sustained rise in systolic BP (> 10 mmHg) during the first hour of HIET. Systolic BP did not increase significantly in four patients who did not receive insulin loading. Single episodes of non-clinically significant biochemical hypoglycaemia and hypokalaemia were recorded in one and two patients respectively. Hypoglycaemia was not recorded in any patient administered HIET during the 24 h following CCB ingestion.

**Conclusions:** HIET used to treat CCB-induced cardiovascular toxicity is a safe intervention when administered in a critical care setting. Maximal HIET efficacy may be obtained when HIET is administered in conjunction with conventional therapy relatively early in the course of severe CCB poisoning when insulin resistance is high.

### ***Evaluation of centrally acting cholinesterase inhibitor exposures in adults***

McCain KR, Sawyer TS, Spiller HA. Ann Pharmacother 2007; 41: 1632-7.

**Background:** There are 4 centrally acting cholinesterase inhibitors (CA-ChEI) available in the US: tacrine, galantamine, rivastigmine, and donepezil. Documented clinical experience involving exposure to these agents is limited. The lack of information makes decisions involving excessive or unintended CA-ChEI exposure difficult.

**Objective:** To assess the effects, demographics, and outcomes of CA-ChEI exposures reported to US poison centers.

**Methods:** A retrospective review of the Toxic Exposure Surveillance System of the American Association of Poison Control Centers data of acute and acute-on-chronic exposures involving only a CA-ChEI in patients 19 years of age or older with documented medical outcomes from 2000-2005 was performed.

**Results:** There were 1026 records that met criteria for this study. Patients aged 70-89 years made up 73% of reports; 69% of the patients were female. Moderate (197) and major outcomes (20) accounted for 21% of exposures. There were no deaths. Clinical effects that occurred in 5% or more of patients included vomiting (34%), nausea (28%), diarrhea (12%), dizziness/vertigo (9.9%), drowsiness/lethargy (7.7%), diaphoresis (7.4%), tremor (5.2%), and bradycardia (5%). Patients were admitted to the hospital in 19% of all exposures. Of those patients, 42% were admitted to a critical care unit. The majority (65%) of exposures were attributed to unintentional therapeutic error. Patients received at least one form of therapy in 47% of exposures, including intravenous fluid (111), antiemetic (48), atropine (17), benzodiazepine (15), oxygen (14), antihypertensive (4), pralidoxime (4), intubation (3), antihistamine (2), antiarrhythmic (1), anticonvulsant (1), and pacemaker (1).

**Conclusions:** The majority of patients evaluated in this retrospective study experienced no or mild effect; however, significant or life-threatening effects were observed in a small group of patients and an appreciable number of patients were admitted to a healthcare facility.

### ***Hemodynamic effects of methadone and dihydrocodeine in overdose***

Afshari R, Maxwell SRJ, Bateman DN. Clin Toxicol 2007; 45: 763-72.

**Background:** Opioid overdose is an increasing health problem worldwide. The cardiovascular toxicity of opioids contributes to morbidity and mortality in overdose but the hemodynamic effects of opioids reported in animal and human studies are contradictory.

**Methods:** We performed a prospective observational study of patients admitted to hospital

following an overdose of methadone, dihydrocodeine, or low dose paracetamol (10 each). Basic cardiovascular indices including peripheral blood pressure, pulse rate, radial augmentation index and derived measures of aortic systolic, diastolic, pulse, and mean and end systolic pressures were measured every six hours for up to 18-23 hours after exposure or until hospital discharge.

**Results:** Dihydrocodeine and methadone significantly reduced peripheral and aortic systolic, mean and end systolic pressures. Both opioids significantly decreased peripheral pulse pressure, but only methadone decreased aortic blood pressure. Dihydrocodeine reduced systemic and aortic diastolic blood pressure, an effect not induced by methadone. Methadone significantly reduced peripheral pulse pressure. Augmentation index and heart rate, however, did not change. Both opioids decreased arterial oxygen saturation.

**Conclusion:** These results suggest that dihydrocodeine and methadone in overdose both have a significant effect on central and peripheral hemodynamics. These effects might be expected to reduce cardiac afterload, providing a pharmacological explanation for the apparent benefit of opioids in cardiovascular diseases.

### ***Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers***

Yassen A, Olofsen E, Van Dorp E, Sarton E, Teppema L, Danhof M, Dahan A. Clin Pharmacokinet 2007; 46: 965-80.

**Background and objective:** Respiratory depression is a potentially life-threatening adverse effect of opioid therapy. It has been postulated that the difficulty of reversing buprenorphine-induced respiratory depression is caused by slow receptor association- dissociation kinetics at the opioid ( $\mu$ ) receptor. The aim of this study was to characterise the pharmacodynamic interaction between buprenorphine and naloxone in healthy volunteers.

**Methods:** A competitive pharmacodynamic interaction model was proposed to describe and predict the time course of naloxone-induced reversal of respiratory depression. The model was identified using data from an adaptive naloxone dose-selection trial following intravenous administration of buprenorphine 0.2 mg/70 kg or 0.4 mg/70 kg.

**Results:** The pharmacokinetics of naloxone and buprenorphine were best described by a two-compartment model and a three-compartment model, respectively. A combined biophase equilibration-receptor association- dissociation pharmacodynamic model described the competitive interaction between buprenorphine and naloxone at the opioid ( $\mu$ ) receptor. For buprenorphine, the values of the rate constants of receptor association ( $k_{on}$ ) and dissociation ( $k_{off}$ ) were 0.203 mL/ng/min and 0.0172  $\text{min}^{-1}$ ), respectively. The value of the equilibrium dissociation constant ( $K(D)$ ) was 0.18 nmol/L. The half-life ( $t_{1/2}$ ) of biophase equilibration was 173 minutes. These estimates of the pharmacodynamic parameters are similar to values obtained in the absence of naloxone co-administration. For naloxone, the half-life of biophase distribution was 6.5 minutes.

**Conclusions:** Because of the slow receptor association-dissociation kinetics of buprenorphine in combination with the fast elimination kinetics of naloxone, naloxone is best administered as a continuous infusion for reversal of buprenorphine-induced respiratory depression.

### ***Comparative toxicology of fatal heroin overdose cases and morphine positive homicide victims***

Darke S, Duflou J, Kaye S. Addiction 2007; 102: 1793-7.

**Aims:** To compare the blood toxicology of heroin overdose cases and morphine positive homicide victims.

**Design:** Analysis of coronial cases. Setting: Sydney, Australia.

**Cases:** A total of 705 cases of death due to opioid toxicity and 28 morphine positive homicide cases (1 January 1998-31 December 2002).

**Findings:** There was no significant difference between the median morphine concentrations of the overdose and homicide groups (0.50 versus 0.45 mg/l). The overdose group was more likely to have blood alcohol (OR 3.21) present, but less likely to have methadone (OR 0.26) and cannabis (OR 0.04). There was a significant negative correlation between blood morphine and alcohol concentrations among the overdose group ( $\rho = -0.32$ ), but not among the homicide group ( $\rho = -0.03$ ). Independent predictors of a higher blood morphine concentration were a lower alcohol concentration and a higher methadone concentration.

**Conclusions:** Morphine concentrations per se are not diagnostic of overdose. The study confirms the salience of concomitant alcohol consumption in such events.

### ***Possible association between 3,4-methylenedioxy-methamphetamine abuse and valvular heart disease***

Droogmans S, Cosyns B, D'Haenen H, Creten E, Weytjens C, Franken PR, Scott B, Schoors D, Kemdem A, Close L, Vandenbossche JL, Bechet S, Van Camp G. Am J Cardiol 2007; 100: 1442-5.

**Abstract:** Valvular heart disease, inducing valvular regurgitation, has been described in users of drugs such as anorectic agents and ergot derivatives. 3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") also leads in vitro to the proliferation of cardiac valvular interstitial cells by activation of the 5-hydroxytryptamine 2B receptor. The aim of this study was to determine the occurrence of valvulopathy in young adults taking MDMA. Twenty-nine subjects using or having used MDMA and 29 gender- and age-matched controls were blindly evaluated with echocardiography. Eight subjects (28%) who took MDMA had abnormal echocardiographic results using the United States Food and Drug Administration's criteria for appetite suppressant-induced valvular heart disease, compared with none in the control group ( $p = 0.0045$ ). Six (21%) subjects had mitral regurgitation of 1/4 and 4 (14%) of  $\geq 2/4$ , compared with none in the control group ( $p = 0.002$ ). The mean mitral regurgitant area ratios (jet/atrium) were  $12 \pm 9.8\%$  and  $5 \pm 1.3\%$ , respectively ( $p = 0.007$ ). Tricuspid regurgitation  $\geq 2/4$  was present in 13 MDMA users (45%) and absent in controls ( $p < 0.001$ ). The mean tricuspid regurgitant area ratios were  $19 \pm 9.5\%$  and  $9 \pm 4.5\%$ , respectively ( $p < 0.001$ ). Four MDMA users (14%) had mild aortic regurgitation ( $p = 0.11$ ). Valvular "strands" were present in 6 MDMA users (21%) and in none of the controls ( $p = 0.02$ ). In conclusion, MDMA may lead to mild to moderate valvular heart disease and valvular strands.

### ***Methamphetamine detection in maternal and neonatal hair: implications for fetal safety***

Garcia-Bournissen F, Rokach B, Karaskov T, Koren G. Arch Dis Child Fetal Neonatal 2007; 92: F351-F355.

**Background:** Methamphetamine misuse is a serious health problem of epidemic proportions. Use of this drug, particularly during pregnancy, is difficult to ascertain. Sparse information is available on gestational exposure.

**Objectives:** To quantify methamphetamine accumulation in hair, identify the use of methamphetamine with other drugs of abuse and characterise correlations between concentrations of methamphetamine in maternal and neonatal hair.

**Subjects and methods:** Motherisk laboratory at the Hospital for Sick Children routinely carries out analysis of methamphetamine in hair. Mothers and infants with positive results for methamphetamine in hair were identified. Drugs present in hair were analysed by ELISA and positive results were confirmed by gas chromatography/mass spectrometry.

**Results:** 396 people positive for methamphetamine in their hair were identified from our database. Almost 85% of them were positive for at least one other drug of abuse, mostly cocaine. Eleven mother-baby pairs with hair positive for methamphetamine were identified. Methamphetamine levels in hair ranged between 0.13 and 51.97 ng/mg in the mothers and between 0 and 22.73 ng/mg in the neonates. Methamphetamine levels in mothers and neonates correlated significantly. One (9%) neonate was negative for methamphetamine even though the mother was positive.

**Conclusion:** To our knowledge, this is the first report on fetal exposure to methamphetamine during pregnancy, showing transplacental transfer of the drug, with accumulation in fetal hair. Hair measurement

for methamphetamine in neonates is a useful screening method to detect intra-uterine exposure to the drug. The data also indicate that positive exposure to methamphetamine strongly suggests that the person is a polydrug user, which may have important implications for fetal safety.

### ***Effects of prenatal cocaine exposure on growth: a longitudinal analysis***

Richardson GA, Goldschmidt L, Larkby C. Pediatrics, 2007; 120: e1017-e1027.

**Objective:** There has been a limited amount of research on the long-term effects of prenatal cocaine exposure on growth of the infant, and there has been no use of longitudinal growth models. We investigated the effects of prenatal cocaine exposure on offspring growth from 1 through 10 years of age by using a repeated-measures growth-curve model.

**Methods:** Women were enrolled from a prenatal clinic and interviewed at the end of each trimester of pregnancy about their cocaine, crack, alcohol, marijuana, tobacco, and other drug use. Fifty percent of the women were white, and 50% were black. Follow-up assessments occurred at 1, 3, 7, and 10 years of age.

**Results:** Cross-sectional analyses showed that children exposed to cocaine during the first trimester (n = 99) were smaller on all growth parameters at 7 and 10 years, but not at 1 or 3 years, than the children who were not exposed to cocaine during the first trimester (n = 125). The longitudinal analyses indicated that the growth curves for the 2 groups diverged over time: children who were prenatally exposed to cocaine grew at a slower rate than children who were not exposed. These analyses controlled for other factors associated with child growth.

**Conclusions:** To our knowledge, this is the first study of the long-term effects of prenatal cocaine exposure to conduct longitudinal growth-curve analyses using 4 time points in childhood. Children who were exposed to cocaine during the first trimester grew at a slower rate than those who were not exposed. These findings indicate that prenatal cocaine exposure has a lasting effect on child development.

### ***Public information needs after the poisoning of Alexander Litvinenko with polonium-210 in London: cross sectional telephone survey and qualitative analysis***

Rubin GJ, Page L, Morgan O, Pinder RJ, Riley P, Hatch S, Maguire H, Catchpole M, Simpson J, Wessely S. Br Med J 2007; 335: 1143-6.

**Objectives:** To identify public perceptions of the risk to health after the poisoning of Alexander Litvinenko with polonium-210 ( $^{210}\text{Po}$ ) in London and to assess the impact of public health communications.

**Design:** Cross sectional telephone survey and qualitative interviews.

**Setting:** London, United Kingdom.

**Participants:** 1000 people completed the cross sectional survey and 86 potentially exposed people completed the qualitative interviews.

**Main outcome measures:** Perception of risk to personal health after the  $^{210}\text{Po}$  incident. Qualitative interviews were analysed with an emphasis on information needs.

**Results:** 11.7% of the survey sample (n=117) perceived their health to be at risk. Aside from personal variables the main predictors of perceived risk to health were believing that the incident was related to terrorism (odds ratio 2.7, 95% confidence interval 1.5 to 4.6) rather than to espionage, that it was targeted at the wider public rather than one person (5.9, 3.2 to 10.9), and that it could affect people who had not been in the contaminated area (3.2, 2.1 to 5.1). Participants in the qualitative interviews were generally satisfied with the information they had received, although they would have preferred more information about their individual risk of exposure, the results of their urine tests, and the health implications of the incident.

**Conclusions:** Perceptions of the public that the  $^{210}\text{Po}$  incident in London in 2006 was related to espionage helped to reassure them that the risks to personal health were low. In the event of future incidents it is important to ensure that detailed, comprehensible information about the risks of any

exposure is available.

## ***Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies***

Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, Gamet-Payrastre L. Cancer Causes Control 2007; 18: 1209-26.

**Objective:** In this study we conducted a meta-analysis of 13 case-control studies that examined the occurrence of hematopoietic cancers in pesticide related occupations in order to undertake a qualitative and quantitative evaluation of a possible relationship.

**Methods:** Pubmed databases were searched for case-control studies published between 1990 and 2005 investigating the relation between hematopoietic cancers and occupational exposure to pesticides. Fixed and random effect meta-analysis models were used depending on the presence of heterogeneity between studies.

**Results:** The overall meta-odds ratio obtained after pooling 44 ORs from 13 studies was 1.3 (95% CI: 1.3-1.5). We realized stratified analysis on three different types of hematopoietic cancers (non-Hodgkin lymphoma (NHL), leukemia and multiple myeloma). A significant increased risk of NHL was found (OR = 1.35; 95% CI = 1.2-1.5). Moreover, increased risks of Leukemia (OR = 1.35; 95% CI = 0.9-2) and multiple myeloma (OR = 1.16; 95% CI = 0.99-1.36) were also detected but these results were not statistically significant. Significant heterogeneity existed among the different studies and a publication bias was detected. Therefore, a meta-regression was carried out. Our results showed that a long period of exposure (more than 10 years) provided an increase in the risk of all hematopoietic cancers and for NHL by fractions of 2.18 (95% CI = 1.43-3.35) and 1.65 (95% CI = 1.08-2.51), respectively.

**Conclusions:** The overall meta-odds ratio suggests that there is a significantly positive association between occupational exposure to pesticides and all hematopoietic cancers as well as NHL. A major limitation of our meta-analysis is the lack of sufficient data about exposure information and other risk factors for hematopoietic cancer (genetic predisposition, ethnic origin, immunodepression...). In addition, data concerning specific subtypes of hematopoietic cancers are often confusing. Thus, future epidemiological studies should undertake a major effort to assess the identity and the level of pesticides exposure and should control for the most likely potential confounders.

## ***Trial of low molecular weight heparin in the treatment of viper bites***

Paul V, Pudoor A, Earali J, John B, Anil Kumar CS, Anthony T. J Assoc Physicians India 2007; 55: 338-42.

**Aim of the study:** To study the efficacy of low molecular weight heparin (LMWH) in the treatment of viper envenomation to combat the haematotoxicity and disseminated intravascular coagulation (DIC).

**Methodology:** Eighty patients with viper bite and incoagulable blood were randomized into two groups of 40 each. One group (Test group) received LMWH, in addition to the antsnake venom (ASV) and other routine measures received by the other group (Control group). Efficacy was assessed by monitoring the bleeding time (BT), whole blood clotting time (CT), prothrombin time (PT), platelet count, fibrinogen, blood urea (BU), serum creatinine, development of complications and overall outcome.

**Results:** LMWH group showed favourable outcome in all the parameters except in the incidence of renal failure which was reversible in the majority of the cases. However the differences between the two groups were statistically not significant.

**Conclusion:** LMW heparin seems to have a beneficial role in the treatment of viper bites, but this needs to be confirmed by a larger trial using a higher dose of heparin.

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## Biomarkers

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