

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

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***September 2008***

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

### **Assessment of digoxin antibody use in patients with elevated serum digoxin following chronic or acute exposure**

**Lapostolle F, Borron SW, Verdier C, Arnaud F, Couvreur J, Mégarbane B, Baud F, Adnet F. *Intensive Care Med* 2008; 34: 1448-53.**

#### ***Objective***

To evaluate the use of antidotal therapy in patients with an elevated digitalis concentration following chronic or acute exposure.

#### ***Design and setting***

Retrospective review of patient records over 2 years in 20 city hospitals in France.

#### ***Patients***

Overall 838 patients with an elevated serum digitalis concentration (digoxin > 1.95 ng/ml or digitoxin > 23 ng/ml) were included in the study. Of these, 67 (8%) had received antidotal therapy with Fab fragments.

#### ***Measurements and results***

The relationships between previously reported prognostic criteria and use of antidotal therapy were investigated. We identified five independent factors that were associated with the use of antidotal therapy: acute overdose (OR 15.74), Fab fragment availability in the hospital (11.06), serum potassium (1.81), and heart rate (0.96). Mortality was significantly lower in Fab-treated (6%, 4/67) than untreated patients (15%, 117/770).

#### ***Conclusions***

Antidotal therapy is underused in patients with an elevated digitalis concentration especially in patients with chronic digitalis exposure. These patients in our series presented a higher mortality rate than patients with acute poisoning. Although they were older and tended to have a history of cardiac disease, they did not differ from patients with acute poisoning with regard to the main severity criteria and prognostic factors. The use of identical criteria for antidotal treatment after acute and chronic poisoning should help optimize outcomes. Fab fragment availability is insufficient in France but ranks only second after type of poisoning (acute or chronic) in the multivariate association with Fab treatment.

***Current Awareness in Clinical Toxicology* is produced monthly for the AACT  
by the Birmingham Unit of the UK National Poisons Information Service.  
The NPIS is commissioned by the Health Protection Agency.**



## **Pharmacokinetic/pharmacodynamic modeling of cardiac toxicity in human acute overdoses: utility and limitations**

**Mégarbane B, Aslani AA, Deye N, Baud FJ. Expert Opin Drug Metab Toxicol 2008; 4: 569-79.**

### ***Background***

Hypotension, cardiac failure, QT interval prolongation, dysrhythmias, and conduction disturbances are common complications of overdoses with cardiotoxicants. Pharmacokinetic/pharmacodynamic (PK/PD) relationships are useful to assess diagnosis, prognosis, and treatment efficacy in acute poisonings.

### ***Objective***

To review the utility and limits of PK/PD studies of cardiac toxicity.

### ***Methods***

Discussion of various models, mainly those obtained in digitalis, cyanide, venlafaxine and citalopram poisonings.

### ***Results/conclusions***

A sigmoidal Emax model appears adequate to represent the PK/PD relationships in cardiotoxic poisonings. PK/PD correlations investigate the discrepancies between the time course of the effect magnitude and its evolving concentrations. They may help in understanding the mechanisms of occurrence as well as disappearance of a cardiotoxic effect. When data are sparse, population-based PK/PD modeling using computer-intensive algorithms is helpful to estimate population mean values of PK parameters as well as their individual variability. Further PK/PD studies are needed in medical toxicology to allow understanding of the meaning of blood toxicant concentration in acute poisonings and thus improve management.

## **Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose**

**Myers RP, Shaheen AAM, Li B, Dean S, Quan H. Clin Gastroenterol Hepatol 2008; 6: 918-25.**

### ***Background & Aims***

Acetaminophen overdose is the most common cause of acute liver failure in the U.S. and other Western countries. Unintentional overdoses, alcohol abuse, and underlying liver disease might increase the risk of hepatotoxicity. In this population-based study, we examined outcomes of acetaminophen overdose, with particular attention to these risk factors.

### ***Methods***

Patients hospitalized for acetaminophen overdose between 1995 and 2004 were identified retrospectively by using administrative data. Comorbid conditions, suicidal intent, and hepatotoxicity were identified by using International Classification of Diseases-Ninth Revision-Clinical Modification and International Statistical Classification of Diseases and Health-Related Problems, 10th revision diagnostic codes.

### ***Results***

During the 10-year interval, 1543 patients were hospitalized for acetaminophen overdose; 34% were alcohol abusers, 3% had liver disease, and 13% overdosed unintentionally. Seventy patients (4.5%) developed hepatotoxicity. Unintentional overdoses (odds ratio [OR], 5.18; 95% confidence interval [CI], 3.00-8.95), alcohol abuse (OR, 2.21; 95% CI, 1.30-3.76), underlying liver disease (OR, 3.50; 95% CI, 1.57-7.77), and N-acetylcysteine treatment (OR, 6.75; 95% CI, 2.78-16.39) were independently associated with hepatotoxicity. Fifteen patients (1.0%) died in-hospital; risk factors included older age, unintentional overdoses, alcohol abuse, comorbidities including liver

disease, and hepatotoxicity (14% vs 0.3%;  $P < 0.0005$ ). During a median follow-up of 5.2 years (range, 1 day-11.0 years), 79 patients (5.1%) died. Approximately half of these deaths were due to preventable conditions including suicide, substance abuse, and trauma.

### **Conclusions**

In this population-based study, acetaminophen overdose had a relatively benign short-term course but was associated with substantial long-term mortality caused by preventable conditions. Acetaminophen-related hepatotoxicity is more common in patients with unintentional overdoses, alcohol abuse, and underlying liver disease.

## **Value of a systematic operative protocol for cocaine body packers**

**Veyrie N, Servajean S, Aissat A, Corigliano N, Angelakov C, Bouillot J-L. World J Surg 2008; 32: 1432-7.**

### **Background**

Internal concealment of illicit drugs during international drug traffic represents an important problem in developed countries. These drug traffickers are called "body packers." The aim of this study was to analyze retrospectively the surgical indications and complications for cocaine body packers and to describe our systematic operative protocol.

### **Methods**

From January 1997 to December 2005, 1181 cocaine body packers were admitted to our Medico-Judiciary Emergency Department. All patients had the same medical surveillance protocol. Nineteen patients required surgical procedure to remove drug packets.

### **Results**

Thirteen patients had obstruction or intestinal retention (68%). Suspicion of packet rupture or cocaine intoxication occurred in six patients (32%). Zero to three enterotomies were necessary during laparotomy. No deaths occurred. One pouch abscess required relaparotomy and one wound abscess was treated medically. The median hospital stay was 7 days (range: 5-30 days).

### **Conclusions**

Few cocaine body packers required a laparotomy. Our systematic operative protocol allowed intestinal clearance and caused acceptable morbidity rate.

## **Post-mortem clinical pharmacology**

**Ferner RE. Br J Clin Pharmacol 2008; online early: DOI:10.1111/j.1365-2125.2008.03231.x.**

### **Abstract**

Clinical pharmacology assumes that deductions can be made about the concentrations of drugs from a knowledge of the pharmacokinetic parameters in an individual; and that the effects are related to the measured concentration.

Post-mortem changes render the assumptions of clinical pharmacology largely invalid, and make the interpretation of concentrations measured in post-mortem samples difficult or impossible. Qualitative tests can show the presence of substances that were not present in life, and can fail to detect substances that led to death. Quantitative analysis is subject to error in itself, and because post-mortem concentrations vary in largely unpredictable ways with the site and time of sampling, as a result of the phenomenon of post-mortem redistribution. Consequently, compilations of "lethal concentrations" are misleading.

There is a lack of adequate studies of the true relationship between fatal events and the concentrations that can be measured subsequently, but without such studies, clinical pharmacologists and others should be wary of interpreting post-mortem measurements.

## **Oral fomepizole administration to treat ethylene glycol and methanol poisonings: advantages and limitations**

**Mégarbane B, Houzé P, Baud FJ. Clin Toxicol 2008; online early: doi:10.1080/15563650802310911: 1-2.**

### ***Abstract***

We report our experience with oral treatment of toxic alcohol poisonings, based on a 10-year retrospective analysis conducted in our intensive care unit in Paris, which aimed to evaluate fomepizole safety. Over this period, 18 ethylene glycol-poisoned patients [13 M/3 F: age, 31 years (27-51), median (25-75% percentiles)] were treated either orally [N = 7: serum ethylene glycol concentrations, 16 mg/dL (6-70); maximum concentration, 150 mg/dL], intravenously (N = 8) or both (N = 3), whereas nine methanol-poisoned patients [8 M/1 F: age, 46 years (38-55)] were treated either orally (N = 1: serum methanol concentration, 10 mg/dL) or intravenously (N = 8). Only two patients treated orally had positive prefomepizole plasma ethanol concentrations (60 and 73 mg/dL, respectively). Two different preparations containing either 4-methylpyrazole hydrochloride or sulfate were used in 22 and 78% of patients, respectively.

None of the poisoned patients treated with oral fomepizole developed further complications, including renal failure, blindness, or neurological sequelae, although oral route was preferentially used by the attending physicians in significantly less severe poisonings. Among the patients treated with oral fomepizole, three with serum ethylene glycol concentrations of >20 mg/dL and undetectable ethanol concentrations had uneventful outcome. Side-effects either possibly or definitely related to fomepizole were observed in five patients. Two patients treated with intravenous fomepizole suffered from painful inflammation at the injection site. Two orally treated patients developed mild transient eosinophilia (840 and 720/mm<sup>3</sup>) and one a generalized pruritus skin rash on day 2, whereas none reported an unpleasant taste in the mouth.

## **Occupational ototoxicity of *n*-hexane**

**Vyskocil A, Leroux T, Truchon G, Gendron M, El Majidi N, Viau C. Hum Exp Toxicol 2008; 27: 471-6.**

### ***Abstract***

The ability of chemicals to produce hearing loss themselves or to promote noise-induced hearing loss has been reported for some organic solvents. The objective of this study was to review the literature on the effects of low-level exposure to *n*-hexane on the auditory system and consider its relevance for occupational settings.

Both human and animal investigations were evaluated only for realistic exposure concentrations based on the permissible inhalation exposure limits. In Quebec, the time-weighted average exposure value (TWAEV) for 8 h is 50 ppm. In humans, the upper limit for considering ototoxicity data relevant to the occupational exposure situation was set at five times the TWAEV. Animal data were evaluated only for exposure concentrations up to 100 times the TWAEV. There is no convincing evidence of *n*-hexane-induced hearing loss in workers. In rats, *n*-hexane seems to affect auditory function; however, the site of these alterations cannot be determined from the present data.

Further studies with sufficient data on the exposure of workers to *n*-hexane are necessary to make a definitive conclusion. In the interim, we recommend considering *n*-hexane as a possibly ototoxic agent.

## **Protective effects of B vitamins and antioxidants on the risk of arsenic-related skin lesions in Bangladesh**

**Zablotska LB, Chen Y, Graziano JH, Parvez F, van Geen A, Howe GR, Ahsan H. Environ Health Perspect 2008; 116: 1056-62.**

### **Background**

An estimated 25-40 million of the 127 million people of Bangladesh have been exposed to high levels of naturally occurring arsenic from drinking groundwater. The mitigating effects of diet on arsenic-related premalignant skin lesions are largely unknown.

### **Objectives**

The purpose of this study was to clarify the effects of the vitamin B group (thiamin, riboflavin, niacin, pyridoxine, and cobalamin) and antioxidants (vitamins A, C, and E) on arsenic-related skin lesions.

### **Methods**

We performed a cross-sectional study using baseline data from the Health Effects of Arsenic Longitudinal Study (HEALS), 2000-2002, with individual-level, time-weighted measures of arsenic exposure from drinking water. A total of 14 828 individuals meeting a set of eligibility criteria were identified among 65 876 users of all 5 996 tube wells in the 25-km<sup>2</sup> area of Araihasar, Bangladesh; 11 746 were recruited into the study. This analysis is based on 10 628 subjects (90.5%) with non-missing dietary data. Skin lesions were identified according to a structured clinical protocol during screening and confirmed with further clinical review.

### **Results**

Riboflavin, pyridoxine, folic acid, and vitamins A, C, and E significantly modified risk of arsenic-related skin lesions. The deleterious effect of ingested arsenic, at a given exposure level, was significantly reduced (ranging from 46% reduction for pyridoxine to 68% for vitamin C) for persons in the highest quintiles of vitamin intake.

### **Conclusions**

Intakes of B-vitamins and antioxidants, at doses greater than the current recommended daily amounts for the country, may reduce the risk of arsenic-related skin lesions in Bangladesh.

## **Comparison of two commonly practiced atropinization regimens in acute organophosphorus and carbamate poisoning, doubling doses vs. *ad hoc*: a prospective observational study**

**Perera PMS, Shahmy S, Gawarammana I, Dawson AH. Hum Exp Toxicol 2008; 27: 513-8.**

### **Abstract**

There is a wide variation and lack of evidence in current recommendations for atropine dosing schedules leading to subsequent variation in clinical practice. Therefore, we sought to examine the safety and effectiveness of a titrated vs. *ad hoc* atropine treatment regimen in a cohort of patients with acute cholinesterase inhibitor pesticide poisoning.

A prospective cohort study was conducted in three district secondary referral hospitals in Sri Lanka using a structured data collection form that collected details of clinical symptoms and outcomes of cholinesterase inhibitor pesticide poisoning, atropine doses, and signs of atropinization. We compared two hospitals that used a titrated dosing protocol based on a structured monitoring sheet for atropine infusion with another hospital using an *ad hoc* regime. During the study, 272 symptomatic patients with anticholinesterase poisoning requiring atropine were admitted to the three hospitals. Outcomes of death and ventilation were analyzed for all patients, 226 patients were prospectively assessed for atropine toxicity. At baseline, patients in the titrated dose cohort had clinical signs consistent with greater toxicity. This in part may be due to ingestion of more toxic organophosphates. They received less pralidoxime and atropine, and

were less likely to develop features of atropine toxicity, such as delirium (1% vs. 17%), hallucinations (1% vs. 35%), or either (1% vs. 35%) and need for patient restraint (3% vs. 48%) compared with the *ad hoc* dose regime. After adjusting for the pesticides ingested, there was no difference in mortality and ventilatory rates between protocols.

*Ad hoc* high dose atropine regimens are associated with more frequent atropine toxicity without any obvious improvement in patient outcome compared with doses titrated to clinical effect. Atropine doses should be titrated against response and toxicity. Further education and the use of a structured monitoring sheet may assist in more appropriate atropine use in anticholinesterase pesticide poisoning.

## **Epidemiology of scorpionism: a global appraisal**

**Chippaux J-P, Goyffon M. Acta Trop 2008; 107: 71-9.**

### **Abstract**

The scorpionism is an actual public health problem in several parts of the world because, either incidence, or severity of envenomations is high and managed with difficulty by health services, or for these two reasons at the same time. The treatment of scorpion envenomation is complex and controversial, in particular regarding the utility of the antivenoms and symptomatic treatments that must be associated.

The authors reviewed the literature of last 30 years to discuss the epidemiologic importance of the scorpionism and to point out the principal therapeutic or preventive measures. According to the most recent studies, seven areas were identified as at risk: north-Saharan Africa, Sahelian Africa, South Africa, Near and Middle-East, South India, Mexico and South Latin America, east of the Andes. These involve 2.3 billion at risk population.

The annual number of scorpion stings exceeds 1.2 million leading to more than 3250 deaths (0.27%). Although adults are more often concerned, children experience more severe envenomations and among them, mortality is higher. Improvement of therapeutic management would reduce the lethality very significantly.

## **The "worldwide shortage" of anti-snake venom: is the only right answer "produce more" or is it also "use it smarter?"**

**Simpson ID. Wilderness Environ Med 2008; 19: 99-107.**

### **Abstract**

A frequent tenet of snakebite literature is what has been described as the "worldwide shortage of anti-snake venom" (ASV) and the demand for greater production. Anti-snake venom is the mainstay of snakebite management, and thus this principle of "shortage" can impact the view of policy makers when it comes to framing solutions to the problem.

This paper presents a model to enable policy makers to assess the amount and utilization of ASV in their areas. The model assesses ASV usage according to 2 criteria: risk and wastage. The actual usage of ASV is segmented in the model into the following main areas: (1) victims who receive too little ASV (high risk/low wastage); (2) victims who receive ASV either unnecessarily or in too great a quantity (low risk/high wastage); (3) victims who receive ASV that is not effective (high risk/high wastage); (4) victims who receive ASV according to effective local protocols (low risk/low wastage).

The current proposition about the "shortage" of ASV and the proposal to simply produce more addresses only a small part of the high-risk/low-wastage group and does not address the 2 high-wastage groups. Until the high-wastage groups are recognized and resolved with training and local protocols and moved into the low-risk/low-wastage group, the true requirement for ASV worldwide cannot be assessed.

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***Current Awareness in Clinical Toxicology* is produced monthly by the Birmingham Unit  
of the UK National Poisons Information Service.  
The NPIS is commissioned by the Health Protection Agency.**

