

# *Current Awareness in Clinical Toxicology*

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

### **Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning**

**Manini AF, Nelson LS, Skolnick AH, Slater W, Hoffman RS. J Med Toxicol 2010; online early: PM:20361362:**

#### ***Abstract***

Poisoning is the second leading cause of injury-related fatality in the USA and the leading cause of cardiac arrest in victims under 40 years of age. The study objective was to define the electrocardiographic (ECG) predictors of adverse cardiovascular events (ACVE) complicating suspected acute poisoning (SAP).

This was a case-control study in adults at three tertiary-care hospitals and one regional Poison Control Center. We compared 34 cases of SAP complicated by ACVE to 101 consecutive control patients with uncomplicated SAP. The initial ECG was analyzed for rhythm, intervals, QT dispersion, ischemia, and infarction. ECGs were interpreted by a cardiologist, blinded to study hypothesis and case data. Subjects were 48% male, with mean age  $42 \pm 19$  years. In addition to clinical suspicion of poisoning in 100% of patients, routine toxicology screens were positive in 77%, most commonly for benzodiazepines, opioids, and/or acetaminophen.

Neither the ventricular rate, the QRS duration, nor the presence of infarction predicted the risk of ACVE. However, the rhythm, QTc, QT dispersion, and presence of ischemia correlated with the risk of ACVE. Independent predictors of ACVE based on multivariable logistic regression were prolonged QTc, any non-sinus rhythm, ventricular ectopy, and ischemia. Recursive partitioning analysis identified very low risk criteria (94.1% sensitivity, 96.2% NPV) and high risk criteria (95% specificity).

Among patients with SAP, the presence of QTc prolongation, QT dispersion, ventricular ectopy, any non-sinus rhythm, and evidence of ischemia on the initial ECG are strongly associated with ACVE.

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## **Role of voltage-gated sodium, potassium and calcium channels in the development of cocaine-associated cardiac arrhythmias**

**O'Leary ME, Hancox JC. Br J Clin Pharmacol 2010; 69: 427-42.**

### ***Abstract***

Cocaine is a highly active stimulant that alters dopamine metabolism in the central nervous system resulting in a feeling of euphoria that with time can lead to addictive behaviours.

Cocaine has numerous deleterious effects in humans including seizures, vasoconstriction, ischaemia, increased heart rate and blood pressure, cardiac arrhythmias and sudden death. The cardiotoxic effects of cocaine are indirectly mediated by an increase in sympathomimetic stimulation to the heart and coronary vasculature and by a direct effect on the ion channels responsible for maintaining the electrical excitability of the heart. The direct and indirect effects of cocaine work in tandem to disrupt the coordinated electrical activity of the heart and have been associated with life-threatening cardiac arrhythmias.

This review focuses on the direct effects of cocaine on cardiac ion channels, with particular focus on sodium, potassium and calcium channels, and on the contributions of these channels to cocaine-induced arrhythmias.

## **Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside**

**Hoffman RS. Br J Clin Pharmacol 2010; 69: 448-57.**

### ***Abstract***

Widespread use of cocaine and its attendant toxicity has produced a wealth of benchwork studies and small animal investigations that evaluated the effects of cocaine on the cardiovascular system. Despite this wealth of knowledge, very little is known about the frequency or types of arrhythmias in patients with significant cocaine toxicity.

The likely aetiologies; catecholamine excess, sodium channel blockade, potassium channel blockade, calcium channel effects, or ischaemia may act alone or in concert to produce a vast array of clinical findings that are modulated by hyperthermia, acidosis, hypoxia and electrolyte abnormalities.

## **Putting cocaine use and cocaine-associated cardiac arrhythmias into epidemiological and clinical perspective**

**Wood DM, Dargan PI. Br J Clin Pharmacol 2010; 69: 443-7.**

### ***Abstract***

We will summarize the epidemiology of cocaine use across the world and in particular will focus on UK, Europe and US use prevalence data. We will discuss the acute cardiac and non-cardiac toxicity associated with cocaine and highlight the lack of data on the true UK prevalence of acute cocaine toxicity and on the incidence of cocaine-related cardiac arrhythmias.

## **Sulfonylurea intoxication at a tertiary care paediatric hospital**

**Glatstein M, Garcia-Bournissen F, Scolnik D, Koren G. Can J Clin Pharmacol 2010; 17: e51-e56.**

### ***Background***

Unintentional poisoning with sulfonylurea hypoglycaemic drugs is a serious danger to infants and children, as the ingestion of relatively small amounts can be fatal. Although the administration of octreotide is considered effective in patients that remain hypoglycaemic despite glucose administration, experience in children is limited.

### ***Methods***

A retrospective chart review of the clinical features of all children following sulfonylurea ingestion

presenting between April 2001 and November 2008 at the Hospital for Sick Children in Toronto.

### **Results**

Ten children were identified with sulfonylurea exposure; six were classified as suspected ingestion and four had confirmed signs of sulfonylurea overdoses (mean age: 8.2 years; range 1.5-15). All four patients with confirmed ingestion were exposed to glyburide and developed severe hypoglycaemia; two were toddlers and two teenagers. Ingestion was accidental in the case of the toddlers, and suicidal attempts in the case of the adolescents. All patients were initially treated with glucose infusions. Both toddlers also received octreotide with favourable response and no rebound hypoglycaemia. The two teenagers were treated only with prolonged glucose infusions; in both cases rebound hypoglycaemia and increased glucose requirements were observed.

### **Discussion**

Glyburide-induced hypoglycaemia was pronounced in all patients identified. Treatment with octreotide proved effective in the 2 infants treated, agreeing with the limited experience reported to date in the literature, and suggesting that octreotide should be considered the treatment of choice in children.

## **Escitalopram causes fewer seizures in human overdose than citalopram**

**Yilmaz Z, Ceschi A, Rauber-Lüthy C, Sauer O, Stedtler U, Prasa D, Seidel C, Hackl E, Hoffmann-Walbeck P, Gerber-Zupan G, Bauer K, Kupferschmidt H, Kullak-Ublick GA, Wilks M. Clin Toxicol 2010; 48: 207-12.**

### **Context**

Seizures are a recognized complication of acute overdose with the racemic (1:1 ratio of *R*- and *S*-enantiomers) selective serotonin reuptake inhibitor antidepressant citalopram.

### **Objective**

We tested the hypothesis that escitalopram (the therapeutically active *S*-enantiomer of citalopram) causes fewer seizures in overdose than citalopram at comparable doses of the *S*-enantiomer.

**Methods.** Multicenter retrospective review of cases with citalopram and escitalopram overdose reported to German, Austrian, and Swiss Poisons Centers between 1997 and 2006.

### **Results**

316 citalopram and 63 escitalopram cases were analyzed. Somnolence, nausea, vomiting, tachycardia, QT prolongation, and tremor occurred with similar frequency in both groups. There was a striking difference in the frequency of single and multiple seizures: 43 cases (13.5%) in the citalopram group and 1 case (1.6%) with a single seizure in the escitalopram group ( $p = 0.0065$ ).

### **Discussion and conclusions**

At comparable ingested doses of the *S*-enantiomer, the symptom profile for citalopram and escitalopram intoxications is similar except for seizures that occur more frequently in citalopram than in escitalopram poisoning.

## **Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol**

**Graudins A, Chiew A, Chan B. Intern Med J 2010; 40: 72-6.**

### **Abstract**

A modified-release formulation of paracetamol is currently available in Australasia and marketed under a number of different trade names. These include: Panadol Osteo, Panadol Extend Tablets, and Duatrol SR.

We report four cases of intentional overdose with this formulation resulting in delay to peak plasma paracetamol concentrations and prolonged paracetamol absorption. Physicians must be aware that a single plasma paracetamol estimation four or more hours post-ingestion may not be adequate in the risk assessment of patients requiring treatment with N-acetylcysteine (NAC).

Current Australasian guidelines for the management of modified-release paracetamol overdose advise empiric commencement of NAC if the suspected ingested dose is greater than 10 grams or 200 mg/kg (whichever is the least), an initial plasma paracetamol concentration should be assayed four or more hours post-ingestion and a second assay should be estimated four hours after the first. Treatment with NAC should continue if either concentration falls above the paracetamol treatment nomogram line.

With massive ingestions of this paracetamol formulation (>50 grams) plasma concentrations may be elevated for several days and prolonged treatment with NAC is recommended. When modified-release paracetamol overdose is suspected a clinical toxicologist or Poisons Information Centre should be consulted to help guide management decisions.

## Unintentional ingestion of bupropion in children

**Spiller HA, Bosse GM, Beuhler M, Gray T, Baker SD. J Emerg Med 2010; 38: 332-6.**

### *Background*

The incidence of seizures after unintentional bupropion ingestion in children aged < 6 years has been reported as 0.2%. However, in many poison centers, > 80% of these patients are referred to the Emergency Department (ED) for evaluation.

### *Objective*

To evaluate if all unintentional pediatric bupropion ingestions require referral to a health care facility (HCF), or what fraction of these could be managed safely at home.

### *Method*

A retrospective chart review was conducted of all bupropion ingestions in children aged < 6 years for 2000-2006 from four regional poison centers. Exclusion criteria were lack of follow-up or multiple drug ingestion.

### *Results*

Of 407 patients, 209 (51%) were male. Mean age was 2.2 y (SD  $\pm$  1.0). There were 329 patients (81%) seen in a HCF, of which 143 (35%) were hospitalized; 77 patients (19%) were observed at home. Symptoms occurred in 73 patients (18%): sinus tachycardia (n = 50), nausea/vomiting (n = 32), hyperactivity (n = 17), seizure (n = 3), hallucinations (n = 2), and hypertension (n = 2). The mean heart rate of patients with sinus tachycardia (n = 50, 12.3%) was 137 beats/min (SD  $\pm$  13), with a range of 112-172 beats/min. Mean dosage of those with tachycardia was 24 mg/kg. In the 2 patients with hypertension, the maximum recorded blood pressures were 145/80 mm Hg (2-year-old boy) and 137/90 mm Hg (2-year-old girl), with heart rates of 122 and 125 beats/min, respectively. Dose ingested and patient weight was known for 218 patients. Mean dosage ingested was 12.2 mg/kg, with a range of 2.6-64 mg/kg. Eighty-eight percent of patients with a known dosage ingested < 20 mg/kg.

### *Discussion*

A high percentage of children continue to be seen in a HCF. Concern from the higher incidence of severe effects seen with intentional adult exposures may be one of the reasons for this cautious approach.

### *Conclusion*

Unintentional pediatric bupropion ingestions resulted in clinical effects that rarely required any HCF intervention. Isolated unintentional bupropion ingestion of  $\leq$  10 mg/kg may not require referral to a health care facility.

## Elevated lactate in ethylene glycol poisoning: true or false?

**Meng QH, Adeli K, Zello GA, Porter WH, Krahn J. Clin Chim Acta 2010; 411: 601-4.**

### *Background*

There have been an increasing number of reports on false increase of lactate in ethylene glycol

poisoning. We recently encountered two cases of ethylene glycol poisoning with very high blood lactate concentrations on ABL blood gas analyzers.

### **Methods**

Patient plasma lactate concentrations were measured on different chemistry instruments in addition to ABL analyzer. Serum ethylene glycol and glycolic acid were also determined. Lactate values were determined from samples spiked with various amounts of glycolic acid.

### **Results**

In case 1, all the chemistry instruments produced similar lactate results compared to that by ABL analyzer whereas in case 2, the lactate on the ABL was dramatically elevated compared to that from all the chemistry analyzers. There was no glycolic acid detected in case 1 but high glycolic acid was obtained in case 2. Increased concentrations of glycolic acid resulted in a significant positive interference on lactate measurements on the ABL analyzer but none on other instruments.

### **Conclusions**

False increase of blood lactate by blood gas analyzers may occur but true increase of lactate can also be observed in ethylene glycol poisoning. Elevated lactate concentrations on blood gas analyzers should be confirmed by a chemistry analyzer in the differential diagnosis of ethylene glycol poisoning.

## **Household chemicals: management of intoxication and antidotes**

**Rauber-Lüthy C, Kupferschmidt H. EXS 2010; 100: 339-63.**

### **Abstract**

Exposure to household products is very common, but in industrialized countries severe or fatal poisoning with household products is rare today, due to the legal restriction of sale of hazardous household products. The big challenge for physicians, pharmacologists and toxicologists is to identify the few exceptional life-threatening situations where immediate intervention is needed.

Among thousands of innocuous products available for the household only very few are hazardous. Substances found in these products include detergents, corrosives, alcohols, hydrocarbons, and some of the essential oils. The ingestion of batteries and magnets and the exposure to cyanoacrylates (super glue) can cause complications in exceptional situations. Among the most dangerous substances still present in household products are ethylene glycol and methanol. These substances cause major toxicity only through their metabolites. Therefore, initial symptoms may be only mild or absent.

Treatment even in asymptomatic patients has to be initiated as early as possible to inhibit production of toxic metabolites. For all substances not only the compound itself but also the route of exposure is relevant for toxicity. Oral ingestion and inhalation generally lead to most pronounced symptoms, while dermal exposure is often limited to mild irritation. However, certain circumstances need special attention. Exposure to hydrofluoric acid may lead to fatal hypocalcemia, depending on the concentration, duration of exposure, and area of the affected skin. Accidents with hydrocarbon pressure injectors and spray guns are very serious events, which may lead to amputation of affected limbs. Button batteries normally pass the gastrointestinal tract without problems even in toddlers; in rare cases, however, they get lodged in the esophagus with the risk of localized tissue damage and esophageal perforation.

## **Caustic injury: can CT grading system enable prediction of esophageal stricture?**

**Ryu HH, Jeung KW, Lee BK, Uhm JH, Park YH, Shin MH, Kim HL, Heo T, Min YI. Clin Toxicol 2010; 48: 137-42.**

### **Background**

The aim of this study was to test the utility of our computed tomography (CT) grading system, compared with endoscopy, for association with the development of esophageal stricture in patients with caustic ingestion.

### **Methods**

This retrospective case series involved 49 patients with caustic ingestion from 1998 to 2009. The degree of esophageal damage was graded using a scoring system based on the extent of esophageal wall edema and the damage in adjacent tissue as seen on thoraco-abdominal CT scans. The presence of esophageal stricture was established by esophagography. Diagnostic performance was compared using receiver operating characteristic (ROC) analysis. Sensitivity and specificity were calculated for the grading system.

### **Results**

The CT grading score results showed that grade III was the most common injury (20 cases, 40.8%), followed by grade IV (14 cases, 28.6%), grade II (9 cases, 18.4%), and grade I (6 cases, 12.2%). In addition, damage to the esophagus was significantly correlated with esophageal stricture when the extent of damage approached grades III and IV ( $p < 0.001$ ). The CT grading system for esophageal stricture resulted in a slightly larger area under the receiver operating characteristic curve (0.90) compared with endoscopic grading system (0.79). The sensitivity and specificity of CT grading system were moderately higher than those of endoscopic grading system.

### **Conclusion**

Assessment of the degree of esophageal damage using CT, a noninvasive modality, in patients who visit the emergency department following caustic ingestion should be useful in estimating the occurrence of complications including esophageal stricture.

## **Pharmacologically-induced metabolic acidosis: a review**

**Liamis G, Milionis HJ, Elisaf M. Drug Saf 2010; 33: 371-91.**

### **Abstract**

Metabolic acidosis may occasionally develop in the course of treatment with drugs used in everyday clinical practice, as well as with the exposure to certain chemicals. Drug-induced metabolic acidosis, although usually mild, may well be life-threatening, as in cases of lactic acidosis complicating antiretroviral therapy or treatment with biguanides. Therefore, a detailed medical history, with special attention to the recent use of culprit medications, is essential in patients with acid-base derangements.

Effective clinical management can be handled through awareness of the adverse effect of certain pharmaceutical compounds on the acid-base status. In this review, we evaluate relevant literature with regard to metabolic acidosis associated with specific drug treatment, and discuss the clinical setting and underlying pathophysiological mechanisms.

These mechanisms involve renal inability to excrete the dietary  $H^+$  load (including types I and IV renal tubular acidoses), metabolic acidosis owing to increased  $H^+$  load (including lactic acidosis, ketoacidosis, ingestion of various substances, administration of hyperalimentation solutions and massive rhabdomyolysis) and metabolic acidosis due to  $HCO_3^-$  loss (including gastrointestinal loss and type II renal tubular acidosis). Determinations of arterial blood gases, the serum anion gap and, in some circumstances, the serum osmolar gap are helpful in delineating the pathogenesis of the acid-base disorder.

In all cases of drug-related metabolic acidosis, discontinuation of the culprit medications and avoidance of readministration is advised.

## **The value of brain CT findings in acute methanol toxicity**

**Taheri MS, Moghaddam HH, Moharamzad Y, Dadgari S, Nahvi V. Eur J Radiol 2010; 73: 211-4.**

### **Objective**

Due to depressant effects of methanol on the central nervous system, brain computed tomography (CT) scan has been introduced as a diagnostic device in methanol intoxication. The authors aimed to present brain CT findings in patients with acute methanol intoxication and to determine signs associated with death.

### **Materials and methods**

This cohort study involved 42 consecutive patients with acute methanol intoxication. Inclusion criteria were consisted of characteristic clinical presentation of methanol poisoning, and metabolic acidosis with increased anion and osmolar gaps. Brain CT scans without contrast medium were obtained. To determine the association between the CT findings and death, the chi-square test or the Fisher's exact test, odds ratio (OR) and its 95% confidence interval (95% CI) were calculated.

### **Results**

Twenty-eight patients (66.6%) had a total of 55 abnormal findings on brain CT, in which bilateral putaminal hypodense lesions was the most common manifestation (27 cases, 96.4%). Putaminal hemorrhage with varying degrees was observed in 7 patients (25%). Six patients (21.4%) had low attenuation lesions in the subcortical white matter of the insula. A significant association was observed between putaminal hemorrhage (OR = 8, 95% CI = 1.187-53.93, P = 0.018) and subcortical necrosis of the insula (OR = 11, 95% CI = 1.504-80.426, P = 0.007) with death.

### **Conclusion**

In addition to clinical and laboratory findings, presence of putaminal hemorrhage and insular subcortex white matter necrosis are associated with a poor clinical outcome in patients with methanol poisoning.

## **Acute human self-poisoning with bispyribac-containing herbicide Nominee: a prospective observational study**

**Gawarammana IB, Roberts DM, Mohamed F, Roberts MS, Medley G, Jayamanne S, Dawson A. Clin Toxicol 2010; 48: 198-202.**

### **Introduction**

Self-poisoning with herbicides is an important reason for hospital admission and death in Asia. Although some herbicides have a well-described toxicity profile in humans, many of the newer compounds rely on extrapolation from animal results as no published literature on clinical outcomes of human self-poisoning has been described. One example of these compounds is bispyribac, a selective herbicide used in rice and wheat cultivation that is marketed in two containers, one containing bispyribac 400 g/L with a solvent and the other the surfactant, polyethylene glycol. We present the first case series of acute human self-poisoning with an herbicide product containing bispyribac.

### **Methods**

Clinical data for all patients who presented with acute poisoning from a bispyribac-containing herbicide (Nominee) to two general hospitals in Sri Lanka from June 2002 to January 2009 were collected prospectively. Admission and serial blood samples were collected from consenting patients to confirm exposure and to study the toxicokinetics of bispyribac, respectively.

### **Results**

One hundred ten patients with a history of bispyribac ingestion presented after a median time of 4 h post-ingestion. There were three deaths at 15, 6, and 5 h post-ingestion because of asystolic cardiac arrest. All three patients had reduced Glasgow Coma Score (GCS) (3, 12, and 13, respectively) of whom the former two had co-ingested ethanol and developed tonic-clonic seizures. Admission blood sample was obtained from the former two of these patients but bispyribac was detected in only one of these patients. The other patient presented 2.5 h post-ingestion with a GCS of 12 but bispyribac was not detected. Excluding the patient with undetectable bispyribac, a conservative estimate of the case fatality ratio at 1.81% (95% confidence interval 0.32-5.8) can be made. The majority of the remaining patients had self-limiting upper gastrointestinal symptoms and eight patients had an abnormal GCS on presentation to hospital. The overall median hospital stay was 3 days. Bispyribac was not detectable on admission in 21 patients; in the remaining patients, the median plasma concentration was 50.55 microg/mL (interquartile range 1.28-116.5; n=32). The peak concentration was noted around 3 h post-ingestion and plasma bispyribac concentration did not predict the severity of poisoning.

### **Conclusion**

The majority of patients developed self-resolving symptoms and were successfully managed in rural general hospitals without transfer to larger tertiary hospitals. Patients who died developed significant poisoning within 6 h and plasma bispyribac concentrations did not appear to predict mortality. The lack of correlation between bispyribac outcomes and the available plasma concentrations may be because of exposure to non-bispyribac components or other undefined factors. Clinical outcomes from acute self-poisoning with bispyribac-containing herbicides appear to be relatively more favorable than other commonly used herbicides.

## **Residential pesticides and childhood leukemia: a systematic review and meta-analysis**

**Turner MC, Wigle DT, Krewski D. Environ Health Perspect 2010; 118: 33-41.**

### **Objective**

We conducted a systematic review and meta-analysis of previous observational epidemiologic studies examining the relationship between residential pesticide exposures during critical exposure time windows (preconception, pregnancy, and childhood) and childhood leukemia.

### **Data sources**

Searches of MEDLINE and other electronic databases were performed (1950-2009). Reports were included if they were original epidemiologic studies of childhood leukemia, followed a case-control or cohort design, and assessed at least one index of residential/household pesticide exposure/use. No language criteria were applied.

### **Data extraction**

Study selection, data abstraction, and quality assessment were performed by two independent reviewers. Random effects models were used to obtain summary odds ratios (ORs) and 95% confidence intervals (CIs).

### **Data synthesis**

Of the 17 identified studies, 15 were included in the meta-analysis. Exposures during pregnancy to unspecified residential pesticides (summary OR = 1.54; 95% CI, 1.13-2.11; I<sup>2</sup> = 66%), insecticides (OR = 2.05; 95% CI, 1.80-2.32; I<sup>2</sup> = 0%), and herbicides (OR = 1.61; 95% CI, 1.20-2.16; I<sup>2</sup> = 0%) were positively associated with childhood leukemia. Exposures during childhood to unspecified residential pesticides (OR = 1.38; 95% CI, 1.12-1.70; I<sup>2</sup> = 4%) and insecticides (OR = 1.61; 95% CI, 1.33-1.95; I<sup>2</sup> = 0%) were also positively associated with childhood leukemia, but there was no association with herbicides.

### **Conclusions**

Positive associations were observed between childhood leukemia and residential pesticide exposures. Further work is needed to confirm previous findings based on self-report, to examine potential exposure-response relationships, and to assess specific pesticides and toxicologically related subgroups of pesticides in more detail.

## **Delayed low-dose supplemental oxygen improves survival following phosgene-induced acute lung injury**

**Grainge C, Jugg BJ, Smith AJ, Brown RF, Jenner J, Parkhouse DA, Rice P. Inhal Toxicol 2010; online early: doi: 10.3109/08958370903571831:**

### **Abstract**

Phosgene is a chemical widely used in the plastics industry and has been used in warfare. It produces life-threatening pulmonary edema within hours of exposure; no antidote exists. This study examines pathophysiological changes seen following treatment with elevated inspired oxygen concentrations (Fio<sub>2</sub>), in a model of phosgene-induced acute lung injury.

Anesthetized pigs were exposed to phosgene (Ct 2500 mg min m<sup>-3</sup>) and ventilated (intermittent positive pressure ventilation, tidal volume 10 ml kg<sup>-1</sup>, positive end-expiratory pressure 3 cm H<sub>2</sub>O,

frequency 20 breaths min<sup>-1</sup>). The Fio<sub>2</sub> was varied: group 1, Fio<sub>2</sub> 0.30 (228 mm Hg) throughout; group 2, Fio<sub>2</sub> 0.80 (608 mm Hg) immediately post exposure, to end; group 3, Fio<sub>2</sub> 0.30 from 30 min post exposure, increased to 0.80 at 6 h post exposure; group 4, Fio<sub>2</sub> 0.30 from 30 min post exposure, increased to 0.40 (304 mm Hg) at 6 h post exposure. Group 5, Fio<sub>2</sub> 0.30 from 30 min post exposure, increased to 0.40 at 12 h post exposure.

The current results demonstrate that oxygen is beneficial, with improved survival, arterial oxygen saturation, shunt fraction, and reduced lung wet weight to body weight ratio in all treatment groups, and improved arterial oxygen partial pressure in groups 2 and 3, compared to phosgene controls (group 1) animals. The authors recommend that treatment of phosgene-induced acute lung injury with inspired oxygen is delayed until signs or symptoms of hypoxia are present or arterial blood oxygenation falls. The lowest concentration of oxygen that maintains normal arterial oxygen saturation and absence of clinical signs of hypoxia is recommended.

## **Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed substitute methadone in pregnancy**

**Hamilton R, McGlone L, MacKinnon JR, Russell HC, Bradnam MS, Mactier H. Br J Ophthalmol 2010; online early: PM:20410537:**

### ***Background and aims***

There are growing concerns regarding visual outcome of infants exposed to opiates (including substitute methadone) and/or benzodiazepines in utero. We describe the combined ophthalmology and visual electrophysiology findings in 20 infants and children who had been exposed to substitute methadone and other drugs of misuse in utero.

### ***Methods***

This was a descriptive case series of 20 patients, all of whom had been referred to a paediatric visual electrophysiology service because of concerns regarding visual function, and all of whom had been exposed to methadone in utero. All children underwent a full ophthalmic and orthoptic examination as well as visual electrophysiology testing deemed appropriate on an individual basis. A review was undertaken of paediatric case notes and of maternal antenatal urine toxicology.

### ***Results***

Ophthalmic abnormalities included reduced acuity (95%), nystagmus (70%), delayed visual maturation (50%), strabismus (30%), refractive errors (30%), and cerebral visual impairment (25%). Visual electrophysiology was abnormal in 60%. A quarter of the children had associated neurodevelopmental abnormalities. The majority of children with nystagmus (79%) had been treated for neonatal abstinence syndrome (NAS).

### ***Conclusion***

Infants born to drug-misusing mothers prescribed methadone in pregnancy are at risk of a range of visual problems, the underlying causes of which are not clear. Those infants with NAS severe enough to receive pharmaceutical treatment may be at particular risk of developing nystagmus. The inclusion of visual electrophysiology in comprehensive visual assessment of children exposed to substance misuse in utero may help clarify the underlying causes by differentiating abnormalities of retinal and cortical origin.

## **Congenital abnormalities in children of 43 pregnant women who attempted suicide with large doses of nitrazepam**

**Gidai J, Acs N, Banhidly F, Czeizel AE. Pharmacoepidemiol Drug Saf 2010; 19: 175-82.**

### ***Objective***

To evaluate the teratogenic effect of very large doses of nitrazepam in children born to pregnant women who attempted suicide and to check the feasibility of self-poisoning pregnant women

model.

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

Comparative analysis of exposed children and their unexposed sibs born to the same mothers who attempted suicide during the study pregnancy and admitted to the toxicological inpatients clinic, Budapest, 1960-1993.

### ***Study participants***

Of 1044 pregnant women who attempted suicide, 107 (10.3%) used large doses of nitrazepam alone or combination with other drugs, and 43 delivered live-born babies, these exposed children were evaluated.

### ***Main outcomes measures***

Structural birth defects, i.e., congenital abnormalities (CAs), pregnancy age at delivery, and birth weight.

### ***Results***

The mean dose of nitrazepam used for suicide attempt was 204 mg. Of 43 exposed children, 13 (30.2%) were affected with CAs, while of their 29 sib controls, 3 (10.3%) (OR with 95%CI: 3.8, 1.0-14.6). Most CAs in exposed children were mild and belonged to the deformation type. The mean pregnancy age was shorter.

### ***Conclusions***

The very large doses of nitrazepam used for suicide attempt during pregnancy resulted in a high rate of CAs which may be connected with the disruption of protein metabolism in fetal mesenchyma. The self-poisoning pregnant women model is feasible for the evaluation of teratogenic effect of drugs.

## **Low-dose exposure to *Veratrum album* in children causes mild effects - a case series**

**Rauber-Lüthy C, Halbsguth U, Kupferschmidt H, König N, Mégevand C, Zihlmann K, Ceschi A. Clin Toxicol 2010; 48: 234-7.**

### ***Introduction***

White or false hellebore (*Veratrum album*) has a toxicological relevance because of the potential for misidentification of this plant as yellow gentian (*Gentiana lutea*).

### ***Case series***

We report a retrospective case series of 11 children (8–12 years) with accidental intake of *V. album* at a youth camp where they had collected herbs for preparing fresh herb tea. Two children (18%) remained asymptomatic. Nine (82%) developed mild gastrointestinal symptoms, six (55%) presented neurological symptoms, and three (27%) showed bradycardia. All children recovered completely within 10 h of ingestion. The plant was identified at the emergency department; however, detection of veratridine and cevadine by means of high-performance liquid chromatography–Mass spectrometry from the blood of the child with the most severe symptoms was negative (limit 0.01 ng/mL).

### ***Discussion***

*Veratrum* species contain more than 200 different alkaloids, which are the principal toxins and are responsible for most clinical symptoms. There are likely multiple mechanisms of toxicity and some of them are only partially understood. The opening of voltage-gated sodium channels is probably one of the most relevant pathophysiological mechanisms.

### ***Conclusions***

*Veratrum album* intoxication in children demonstrated the same clinical course as observed in adults. Accidental ingestion of a low dose of the plant had a favorable outcome with supportive care.

## TOXICOLOGY

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