

# *Current Awareness in Clinical Toxicology*

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

### **Quetiapine overdose: predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal**

**Isbister GK, Duffull SB. *Int Clin Psychopharmacol* 2009; 24: 174-80.**

#### ***Abstract***

To investigate factors that predict the probability and duration of mechanical ventilation in quetiapine overdose, and if cardiac toxicity occurs, this cohort study involved 176 patients presenting to a toxicology unit on 286 occasions with quetiapine overdose.

Patient demographics, dose, coingestants, single dose activated charcoal (SDAC) administration, requirement for and duration of mechanical ventilation and electrocardiogram parameters (heart rate, QT, QRS) were obtained. A fully Bayesian approach using logistic regression and time-to-event analysis was undertaken to investigate the relationship between predictor variables and the requirement for and duration of intubation. QT versus heart rate was plotted on a QT nomogram to investigate QT prolongation.

The commonest clinical effects were central nervous system depression on 136 occasions (48%) and tachycardia (67%). There were no malignant arrhythmias and an abnormal QT occurred in only 24 admissions (8.4%), all with tachycardia. Hypotension (systolic blood pressure <90 mmHg) occurred on 35 occasions (12%). The logistic regression model supported dose and SDAC (<2 h) influencing the probability of intubation, but not age, sex, therapeutic use of quetiapine or coingestants. The probability of intubation was 10% after 2 g, 22% after 5 g, 37% after 10 g and 55% after 20 g and SDAC resulted in a reduced probability of intubation of 7% for 2 g ingestion. The median duration of ventilation was 22 h (interquartile: 19-28 h), which was not affected by SDAC.

Ingested dose can inform early decision making about requirements for intensive care unit admission and intubation. SDAC seems to have only modest effects on outcomes but may be considered within 2 h for large ingestions. Electrocardiogram monitoring is unlikely to be necessary.

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## **Are calcium oxalate crystals involved in the mechanism of acute renal failure in ethylene glycol poisoning?**

**McMartin K. Clin Toxicol 2009; 47: 859-69.**

### ***Introduction***

Ethylene glycol (EG) poisoning often results in acute renal failure, particularly if treatment with fomepizole or ethanol is delayed because of late presentation or diagnosis. The mechanism has not been established but is thought to result from the production of a toxic metabolite.

### ***Methods***

A literature review utilizing PubMed identified papers dealing with renal toxicity and EG or oxalate. The list of papers was culled to those relevant to the mechanism and treatment of the renal toxicity associated with either compound. Role of metabolites. Although the "aldehyde" metabolites of EG, glycolaldehyde, and glyoxalate, have been suggested as the metabolites responsible, recent studies have shown definitively that the accumulation of calcium oxalate monohydrate (COM) crystals in kidney tissue produces renal tubular necrosis that leads to kidney failure. In vivo studies in EG-dosed rats have correlated the severity of renal damage with the total accumulation of COM crystals in kidney tissue. Studies in cultured kidney cells, including human proximal tubule (HPT) cells, have demonstrated that only COM crystals, not the oxalate ion, glycolaldehyde, or glyoxalate, produce a necrotic cell death at toxicologically relevant concentrations. COM crystal accumulation. In EG poisoning, COM crystals accumulate to high concentrations in the kidney through a process involving adherence to tubular cell membranes, followed by internalization of the crystals.

### ***Mechanism of toxicity***

COM crystals have been shown to alter membrane structure and function, to increase reactive oxygen species and to produce mitochondrial dysfunction. These processes are likely to be involved in the mechanism of cell death.

### ***Conclusions***

Accumulation of COM crystals in the kidney is responsible for producing the renal toxicity associated with EG poisoning. The development of a pharmacological approach to reduce COM crystal adherence to tubular cells and its cellular interactions would be valuable as this would decrease the renal toxicity not only in late treated cases of EG poisoning, but also in other hyperoxaluric diseases such as primary hyperoxaluria and kidney stone formation.

## **Comparative evaluation of Glasgow Coma Score and gag reflex in predicting aspiration pneumonitis in acute poisoning**

**Eizadi-Mood N, Saghaei M, Alfred S, Zargarzadeh AH, Huynh C, Gheshlaghi F, Yaraghi A, Saad YS. J Crit Care 2009; 24: 470.**

### ***Purpose***

The purpose of the study was to assess the incidence of aspiration pneumonitis (AP) and its association with gag reflex and Glasgow Coma Score (GCS).

### ***Materials and Methods***

In a retrospective analysis study after prospective data collection, 155 poisoned patients with GCS less than or equal to 12 were evaluated. An assessment of GCS and the quality of gag reflex was made on arrival and recorded. Intubation status before gastrointestinal decontamination was noted. All patients were subsequently followed for developing of AP.

### ***Results***

The incidence of AP was 15.5%, with significant variance among patients with respect to the gag reflex, GCS, and the performance of intubation. A logistic regression model for predicting AP contained the following predictors: GCS (odds ratio [OR], 0.43; 95% confidence interval [CI],

0.30-0.62), intubation (OR, 0.07; 95% CI, 0.01-0.49), organophosphate ingestion (OR, 1.39; 95% CI, 0.96-2.01), and gastric evacuation (OR, 4.29; 95% CI, 0.94-9.51). In patients with reduced gag reflex, variations in GCS were associated with AP (OR, 0.43; 95% CI, 0.20-0.90), whereas in patients with absent gag reflex, age was the most important predictor of AP (OR, 2.67; 95% CI, 0.99-7.22).

### **Conclusions**

A reduced GCS and a nonintubated trachea are associated with an increased incidence of AP.

## **Successful treatment of lithium toxicity with sodium polystyrene sulfonate: a retrospective cohort study**

**Ghannoum M, Lavergne V, Yue CS, Ayoub P, Perreault MM, Roy L. Clin Toxicol 2009; online early: doi: 10.3109/15563650903344785: 1-8.**

### **Context**

Lithium (Li) is a first-line treatment for bipolar disorder but has a narrow therapeutic index. Treatment of Li toxicity includes supportive measures and hemodialysis in severe cases, but this modality is not always immediately available. Sodium polystyrene sulfonate (SPS, Kayexalate), a cation exchanger, has been promising in animal models and human reports to reduce absorption and enhance elimination of Li.

### **Material and methods**

A retrospective cohort study was conducted. All cases of chronic Li intoxication were reviewed in two adult-care hospitals from 2000 to 2009. A group comparison and a within-patient comparison were performed to compare the effect of SPS on the median Li half-life ( $T_{1/2}$ ). For this study, at least three serum Li levels were required for  $T_{1/2}$  calculations.

### **Results**

Forty-eight patients met inclusion requirements, 12 of whom had taken SPS. Median Li  $T_{1/2}$  in the treated and control groups was 20.5 and 43.2 h, respectively ( $p = 0.0006$ ). In the 12 treated patients, Li  $T_{1/2}$  during SPS was on average 48.9% shorter than without SPS. Furthermore, in one subject in whom urinary Li data were available, Li clearance with SPS was superior to Li renal clearance. Prolonged constipation was noted in one patient whereas mild hypokalemia was noted in six patients treated with SPS.

### **Conclusion**

This study shows that SPS reduced Li  $T_{1/2}$  and suggests that SPS is capable of promoting Li elimination in chronic intoxications. These results warrant a prospective trial looking at the use of SPS in the treatment of Li overdose as an adjunct to supportive measures and hemodialysis.

## **Methemoglobinemia in critically ill patients during extended hemodialysis and simultaneous disinfection of the hospital water supply**

**Bek MJ, Laule S, Reichert-Junger C, Holtkamp R, Wiesner M, Keyl C. Crit Care 2009; 13: R162.**

### **Introduction**

To evaluate the cause of methemoglobinemia in patients undergoing extended daily hemodialysis/hemodiafiltration we analyzed the relationship between methemoglobinemia and the water disinfection schedule of the hospital.

### **Methods**

We reviewed all arterial blood gas analyses, obtained over a one-year period, in patients undergoing extended hemodialysis/hemodiafiltration, and compared the methemoglobin concentrations obtained on the days when the water supply was disinfected, using a hydrogen

peroxide/silver ion preparation, with data measured on disinfection-free days.

### **Results**

The evaluation of 706 measurements revealed a maximum methemoglobin fraction of 1.0 (0.8; 1.2)% (median and 25th; 75th percentiles) during hemodialysis/hemodiafiltration on the disinfection-free days. The methemoglobin fraction increased to 5.9 (1.3; 8.4)% with a maximal value of 12.2% on the days of water disinfection ( $p < 0.001$  compared to disinfection-free days). Spot checks on hydrogen peroxide concentrations in the water supply, the permeate, and the dialysate, using a semi-quantitative test, demonstrated levels between 10 and 25 mg/l during water disinfection.

### **Conclusions**

Our results demonstrate that even a regular hospital water disinfection technique can be associated with significant methemoglobinemia during extended hemodialysis. Clinicians should be aware of this potential hazard.

## **The association between drug related deaths and prior contact with hospital-based services**

**Thanacoody RHK, Jay J, Sherval J. Scott Med J 2009; 54: 7-10.**

### **Abstract**

Reducing drug related deaths has been identified as a health priority by the Scottish Executive

### **Aims**

This study investigates the association between drug related deaths in the Lothian region and prior contact with hospital-based services in the Edinburgh Royal Infirmary.

### **Design/setting**

Retrospective analysis of 90 drug related deaths in Lothian from 2003-2005. Hospital episodes within five years of death were identified by searching the electronic patient record system within the Edinburgh Royal Infirmary.

### **Findings**

Seventy-five of the 90 drug related deaths occurred in the hospital catchment area. Forty five of these 75 deaths (60%) occurred in patients who had used hospital-based services in the previous five years. The median time from hospital contact to deaths was five months and median number of hospital attendances/admissions was three (range 1-26).

### **Conclusion**

Liaison between emergency departments, clinical toxicology services and community based drug addiction services is important to identify drug misusers at high risk. A hospital-based nurse-led liaison service may be able to fulfil this role.

## **Trends in prescribing and self-poisoning in relation to UK regulatory authority warnings against use of SSRI antidepressants in under-18-year-olds**

**Bergen H, Hawton K, Murphy E, Cooper J, Kapur N, Stalker C, Waters K. Br J Clin Pharmacol 2009; 68: 618-29.**

### **Aims**

To assess the impact of the UK Medicines and Healthcare products Regulatory Authority (MHRA) warning in December 2003 not to prescribe selective serotonin reuptake inhibitor (SSRI) antidepressants, except fluoxetine, to under-18-year-olds.

### **Methods**

Interrupted time series analysis of prescriptions (UK) and general hospital presentations for

nonfatal self-poisoning (three centres in England) for 2000-2006.

### **Results**

Following the MHRA warning in December 2003 there were significant decreases in prescribing of SSRI antidepressants (conservative estimate 51%) to young people aged 12-19 years. Surprisingly, this decrease also affected fluoxetine (conservative estimate 20%) and tricyclics (conservative estimate 27%). Nonfatal self-poisoning in this age group following the warning also declined significantly for SSRIs (conservative estimate 44%), but not for fluoxetine, tricyclic antidepressants, or all drugs and other substances. Rates of nonfatal self-harm did not change significantly over the study period.

### **Conclusions**

The reduction in both prescribing and self-poisoning with SSRI antidepressants (except fluoxetine) following the MHRA warning is in keeping with reduced availability of these drugs. There was some evidence of substitution from other SSRIs to fluoxetine for use in self-poisoning. Importantly, overall rates of nonfatal self-harm and self-poisoning did not change, indicating no substitution of method or increases in self-injury.

## **Methamphetamine body stuffers: an observational case series**

West PL, Mckeown NJ, Hendrickson RG. *Ann Emerg Med* 2009; online early: doi: 10.1016/j.annemergmed.2009.08.005: 1-8.

### **Study objective**

We describe the demographics, characteristics, treatment, and clinical course of methamphetamine body stuffers. We also determine the clinical characteristics of methamphetamine body stuffers who have severe outcomes.

### **Methods**

A 6.5-year descriptive nonconcurrent observational case series evaluated methamphetamine body stuffers about whom the Oregon Poison Center was consulted by their primary physicians. Poison center charts were supplemented by completed hospital charts (for 95% of patients).

### **Results**

Six hundred forty-eight patients with methamphetamine exposure were identified and reviewed, and 55 charts met the criteria for "methamphetamine body stuffer." We found the following characteristics of methamphetamine body stuffers: mean age 29 years (range 16-57 years), men in 44 of 55 cases (80%), mean time to arrival 2.7 hours after ingestion, with a median of 1 h after ingestion. Ninety-seven percent (53/55) stuffed methamphetamine orally (2/55 rectally). Methamphetamine was most frequently swallowed in baggies, but 25% were unpackaged. The median dose ingested was 3.5 g of methamphetamine in 1 package. Outcome-based analysis revealed 29% (16/55) of patients had severe outcomes, as defined by end-organ toxicity, with agitation requiring intubation the most common severe outcome. There was 1 death reported. Toxicity did not appear to be related to the amount of methamphetamine or number of packets. Patients with severe outcomes had higher mean initial pulse rates and temperatures. Eighty-eight percent (14/16) of patients with severe outcomes had a presenting pulse rate greater than 120 beats/min or a temperature greater than 38°C versus 18% (7/39) patients with a benign outcome. Twenty-four radiographic studies were obtained; none detected packets.

### **Conclusion**

Methamphetamine body stuffers have similar demographics to those of body stuffers of other stimulants, but tended to ingest fewer baggies with larger masses, and had a higher percentage of severe outcomes (29%) than previously reported with other stimulants. Increases in presenting pulse rate and temperature (pulse rate >120 beats/min or >38.0°C) are common in patients who will develop end-organ damage.

## **Crotaline Fab antivenom appears to be effective in cases of severe North American pit viper envenomation: an integrative review**

**Lavonas EJ, Schaeffer TH, Kokko J, Mlynarchek SL, Bogdan GM. BMC Emerg Med 2009; 9:**

### ***Background***

In 2000, the United States Food and Drug Administration approved Crotalidae Polyvalent Immune Fab (Ovine) (hereafter, FabAV), "for the management of patients with minimal to moderate North American Crotalid envenomation." Because whole-IgG pit viper antivenom is no longer available in the United States, FabAV is currently the only specific treatment option available to United States clinicians treating snakebite victims of any severity. No clinical trial data are available concerning the effectiveness of FabAV for treatment of severe snakebite, but several published articles describe its use in this setting.

### ***Methods***

We performed a comprehensive review of the English-language medical literature to identify all publications (1996 to July, 2008) containing data about the administration of FabAV. Two trained reviewers separately extracted case-level data concerning the administration of FabAV to patients with severe envenomation by North American crotaline snakes to a standardized form. Descriptive statistics were used. In addition, we hand-searched the US National Poison Data System reports for the years 2000-2006 to identify and describe any reports of death that occurred after FabAV administration.

### ***Results***

The literature review found 147 unique publications regarding FabAV. Twenty-four evaluable cases of severe human envenomation treated with FabAV were identified in 19 publications. Seven cases were described in five cohort studies, and 17 cases were described in 14 single patient case reports or non-cohort case series. Sixty-five specific severe venom effects were reported in these 24 patients, of which 50 effects (77%) improved or resolved after FabAV therapy. Initial control of all severe venom effects was achieved in 12 patients (50%). The rate at which initial control was achieved was significantly higher among patients reported in the cohort series than in the case series and non-cohort reports (100% vs. 29%,  $P = 0.005$ ). The median dose of FabAV used to obtain initial control was 6 vials (range: 4-18 vials). Nine patients had severe venom effects that persisted despite FabAV therapy. Recurrent and/or delayed-onset severe defibrination syndrome occurred in 12 patients, most of whom did not receive recommended maintenance FabAV dosing. No patient developed systemic bleeding.

### ***Conclusion***

In this structured literature review, FabAV appears to be effective in the management of severe crotaline snake envenomation. Incomplete response to therapy, recurrence of venom effects, and delayed-onset venom effects were reported in case reports, but not reported in cohort studies.

## **An atropine and glycopyrrolate combination reduces mortality in organophosphate poisoning**

**Arendse R, Irusen E. Hum Exp Toxicol 2009; 28: 715-20.**

### ***Abstract***

Anticholinergics are the mainstay of the pharmacological management of organophosphate poisoning (OPP). Atropine has the potential to cause central toxicity which may complicate the management of this life-threatening condition. A combination of atropine and glycopyrrolate in equivalent dosages titrated to the peripheral muscarinic signs, theoretically reduces the central effect of the anticholinergics by 50% and thereby the risk of central toxicity, while it provides effective control of the peripheral manifestations of OPP.

This study reports the clinical morbidity and mortality associated with the management of OP with

this anticholinergic combination over a 4-year period, 2003 to 2006, at Tygerberg Academic Hospital (TAH). Two of the 53 patients treated for OPP died, with this mortality lower than that previously reported at TAH. Atropine toxicity was evident in 12 (22.5%) patients and responded to a temporary cessation of the combination infusion. The demographic profile, presenting symptoms, duration of stay and complications encountered were similar to previous reports from TAH.

Patients treated with the infusion of a combination of atropine and glycopyrrolate had a lower mortality rate compared with earlier reports from the same unit, but the occurrence of atropine toxicity was unchanged despite the hypothesized theoretical advantage.

## **Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants**

**Lennestal R, Otterblad Olausson P, Kallen B. Eur J Clin Pharmacol 2009; 65: 615-25.**

### ***Purpose***

To investigate the association between maternal use of antihypertensives in early pregnancy and delivery outcome, notably infant congenital malformations.

### ***Methods***

A cohort study of 1418 women who had used antihypertensive drugs in early pregnancy but had no diabetes diagnosis were identified from the Swedish Medical Birth Register.

### ***Results***

There was an excess risk for placental abruption, caesarean section, delivery induction, and post-delivery hemorrhage in women taking hypertensives. Infants were more often than expected born preterm, were small for gestational age, and had an excess of various neonatal symptoms. Cardiovascular defects occurred with an adjusted odds ratio of 2.59 (95% CI 1.92-3.51). The results were similar when the woman had used ACE inhibitors or other antihypertensives, notably beta blockers. Stillbirth rate was increased (risk ratio 1.87, 95% CI 1.02-3.02), again without any clear drug specificity.

### ***Conclusions***

There seems to be little drug specificity in the association between maternal use of antihypertensives and an increased risk for infant cardiovascular defects.

## **Recent advances in understanding the biomolecular basis of chronic beryllium disease: a review**

**McCleskey TM, Buchner V, Field RW, Scott BL. Rev Environ Health 2009; 24: 75-115.**

### ***Abstract***

In this review we summarize the work conducted over the past decade that has advanced our knowledge of pulmonary diseases associated with exposure to beryllium that has provided a molecular-based understanding of the chemistry, immunopathology, and immunogenetics of beryllium toxicity.

Beryllium is a strong and lightweight metal that generates and reflects neutrons, resists corrosion, is transparent to X-rays, and conducts electricity. Beryllium is one of the most toxic elements on the periodic table, eliciting in susceptible humans (a) an allergic immune response known as beryllium sensitization (BeS); (b) acute beryllium disease, an acutely toxic, pneumonitis-like lung condition resulting from exposure to high beryllium concentrations that are rarely seen in modern industry; and (c) chronic beryllium disease (CBD) following either high or very low levels of exposure. Because of its exceptional strength, stability, and heat-absorbing capability, beryllium is used in many important technologies in the modern world. In the early 1940s, beryllium was

recognized as posing an occupational hazard in manufacturing and production settings. Although acute beryllium disease is now rare, beryllium is an insidious poison with a latent toxicity and the risk of developing CBD persists. Chronic beryllium disease - a systemic granulomatous lung disorder caused by a specific delayed immune response to beryllium within a few months to several decades after exposure-has been called the "unrecognized epidemic". Although not a disease in itself, BeS, the innate immune response to beryllium identified by an abnormal beryllium lymphocyte proliferation test result, is a population-based predictor of CBD. Genetic susceptibility to CBD is associated with alleles of the major histocompatibility gene, human leukocyte antigen DP (HLA-DP) containing glutamic acid at the 69th position of the beta chain (HLA-DPbeta-E69). Other genes are likely to be involved in the disease process, and research on this issue is in progress.

The current Occupational Safety & Health Administration permissible exposure limit of  $2 \mu\text{g}/\text{m}^3$  has failed to protect workers from BeS/CBD. As a safe exposure limit that will not lead to BeS or CBD has not yet been determined, the realization that the risk of CBD persists has led to a renaissance in research on the effects of the metal on human health. Current data support further reductions in exposure levels to help minimize the incidence of CBD. Steps that would directly impact both the power of epidemiologic studies and the cost of surveillance would be to develop and validate improved screening and diagnostic tests, and to identify more genetic factors that affect either sensitization or disease process. The major focus of this review is the recent research on the cellular and molecular basis of beryllium sensitization and disease, using a multidisciplinary approach of bioinorganic chemistry and immunology. First we present a historical background of beryllium exposure and disease, followed by occurrence of beryllium in the environment, toxicokinetics, biological effects, beryllium lung disease, and other human health effects.

### **Acute effects of sulfur mustard injury - Munich experiences**

**Kehe K, Thiermann H, Balszuweit F, Eyer F, Steinritz D, Zilker T. Toxicology 2009; 263: 3-8.**

#### **Abstract**

Sulfur mustard (SM) is a strong vesicant agent which has been used in several military conflicts. Large stockpiles still exist to the present day. SM is believed to be a major threat to civilian populations because of the persistent asymmetric threat by non-state actors, such as terrorist groups, its easy synthesis and handling and the risk of theft from stockpiles. Following an asymptomatic interval of several hours, acute SM exposure produces subepidermal skin blisters, respiratory tract damage, eye lesions and bone marrow depression.

Iranian victims of SM exposure during the Iran-Iraq (1984-1988) war were treated at intensive care units of 3 Munich hospitals. All 12 patients were injured following aerial attacks with SM filled bombs, which exploded in a distance between 5 and 30 m. All patients soon noted an offensive smell of garlic, addle eggs or oil roasted vegetables. No individual protective equipment was used. Eye itching and skin blistering started 2 h after SM exposure. Some patients complained of nausea, dizziness and hoarseness. 4 h after exposure, most patients started vomiting. Eye symptoms worsened and most patients suffered from temporary blindness due to blepharospasm and lid oedema. Additionally, pulmonary symptoms such as productive cough occurred.

Patients were transferred to Munich 4-17 days after SM exposure. On admission all patients showed significant skin blistering and pigmentation. Conjunctivitis and photophobia were the major eye symptoms. Pulmonary symptoms, including productive cough were persistent. Bronchoscopy revealed massive inflammation of the trachea with signs of necrosis. 3 patients needed tracheotomy. Chest X-ray did not yield abnormal observations.

This presentation summarizes the experience of treating SM victims in Munich and discusses therapeutic implications.

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### Body packers

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