

Current Awareness in Clinical Toxicology

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CURRENT AWARENESS PAPERS OF THE MONTH

A randomised controlled trial of intramuscular vs. intravenous antivenom for latrodectism - the RAVE study

Isbister GK, Brown SGA, Miller M, Tankel A, MacDonald E, Stokes B, Ellis R, Nagree Y, Wilkes GJ, James R, Short A, Holdgate A. QJM 2008; online early: doi: 10.1093/qjmed/hcn048.

Background: Widow spider-bite causes latrodectism and is associated with significant morbidity worldwide. Antivenom is given by both the intravenous (IV) and intramuscular (IM) routes and it is unclear which is more effective.

Aim: To compare the effectiveness of IV vs. IM redback spider antivenom.

Design: Randomized controlled trial.

Methods: Patients with latrodectism were given either IV or IM antivenom according to a randomized double-dummy, double-blind protocol. The first antivenom treatment was followed by another identical treatment after two hours if required. The primary outcome was a clinically significant reduction in pain two hours after the last treatment. A fully Bayesian analysis was used to estimate the probability of the desired treatment effect, predetermined as an absolute difference of 20%.

Results: We randomly allocated 126 patients to receive antivenom IV (64) and IM (62). After antivenom treatment pain improved in 40/64(62%) in the IV group vs. 33/62(53%) in the IM group (+9%; 95% Credible Interval [CrI]: -8% to +26%). The probability of a difference greater than zero (IV superior) was 85% but the probability of a difference >20% was only 10%. In 55 patients with systemic effects, these improved in 58% after IV antivenom vs. 65% after IM antivenom (-8%; 95% CrI: -32% to +17%). Twenty-four hours after antivenom pain had improved in 84% in the IV group vs. 71% in the IM group (+13%; 95% CrI: -2% to +27%). A meta-analysis including data from a previous trial found no difference in the primary outcome between IV and IM administration.

Discussion: The difference between IV and IM routes of administration of widow spider antivenom is, at best, small and does not justify routinely choosing one route over the other. Furthermore, antivenom may provide no benefit over placebo.

Guidelines for the management of paracetamol poisoning in Australia and New Zealand - explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres

Daly FFS, Fountain JS, Murray L, Graudins A, Buckley NA. Med J Aust 2008; 188: 296-301.

Abstract: Paracetamol is involved in a large proportion of accidental paediatric exposures and

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deliberate self-poisoning cases, although subsequent hepatic failure and death are both uncommon outcomes.

The optimal management of most patients with paracetamol overdose is usually straightforward. However, several differing nomograms and varying recommendations regarding potential risk factors for hepatic injury introduce complexity.

In order to reconcile management advice with current Australasian clinical toxicology practice, revised guidelines have been developed by a panel of clinical toxicologists consulting to the poisons information centres in Australia and New Zealand using a workshop and consultative process.

This article summarises the rationale for the recommendations made in these new guidelines.

Coproxamol withdrawal has reduced suicide from drugs in Scotland

Sandilands EA, Bateman DN. Br J Clin Pharmacol 2008; online early: doi: 10.1111/j.1365-2125.2008.03206.x.

What is already known about this subject: Co-proxamol is associated with excess mortality in overdose. Legislative change in 2005 has led to a phased withdrawal of co-proxamol from the UK market.

What this study adds: Co-proxamol legislation resulted in a marked reduction in the number of prescriptions for co-proxamol within 6 months. This was followed by a major reduction in mortality associated with co-proxamol poisoning. Overall mortality from drug poisoning in Scotland has also fallen over the same period, suggesting an effect on total overdose mortality AIM To determine what effect the withdrawal of co-proxamol from the UK market has had on mortality from poisoning in Scotland.

Methods: This was a retrospective, observational study of mortality relating to poisoning by single agents in Scotland for the period 2000-2006. Mortality data were obtained from the General Register Office Scotland, and primary care prescribing data from the Information and Statistics Division of the Scottish Executive Health Department.

Results: A significant reduction in the proportion of poisoning deaths due to co-proxamol was observed following legislation [mean 2000-2004, 37 deaths (21.8% of total poisoning deaths); 2006, 10 (7.8%); $P < 0.0001$]. The most significant reduction was seen in male out-of-hospital deaths [mean 2000-2004, 17 (21.8%); 2006, two (2.9%); $P < 0.0001$]. This was associated with a decline in prescriptions by 60% within 6 months of legislation. The total number of poisoning deaths also fell, slightly earlier than the full impact on co-proxamol deaths (mean 2000-2004, 171.2; mean 2005-2006, 129.5; $P = 0.005$).

Conclusions: Legislation has resulted in a major reduction in the number of deaths associated with co-proxamol poisoning in Scotland, with no compensatory rise in mortality from poisonings from other common analgesics. We estimate from this study that a minimum of 300 lives across the UK will have been saved by the withdrawal of co-proxamol.

A five-year review of the medical outcome of heroin body stuffers

Jordan MT, Bryant SM, Aks SE, Wahl M. J Emerg Med 2008; online early: doi: 10.1016/j.jemermed.2007.06.022.

Abstract: The medical outcome of heroin body stuffers has rarely been described. This study was performed to illustrate the clinical course of heroin body stuffers. A retrospective chart analysis was performed on all cases of heroin body stuffers received by a metropolitan poison control center from 2000-2004. We identified 65 heroin body stuffers. Sixty-nine percent were men with a mean age of 35 years. The stated quantity of heroin containers ingested ranged from 1 to 30, with 65% reported as being wrapped in plastic. Six patients (9.2%) developed symptoms of opiate intoxication. All symptoms began within an hour after the ingestion. Three patients (4.6%)

needed naloxone. The mean length of observation was 24 h. Opiate intoxication from heroin stuffing is uncommon. Those patients that developed symptoms did so early in their course. These data indicate a benign clinical course in most heroin body stuffers.

Clinical assessment compared to laboratory screening in acutely poisoned patients

Heyerdahl F, Hovda KE, Bjornaas MA, Brørs O, Ekeberg O, Jacobsen D. Hum Exp Toxicol 2008; 27: 73-9.

Abstract: Acute poisonings may require identification of the toxic agents. It is impossible for routine laboratories to provide a full spectrum of toxicological analyses, and clinicians should know the reliability of the clinical diagnoses of toxic agents.

We performed a 1-year study of hospitalized acute poisonings to determine the agreement between the clinical assessment on admission and serum laboratory tests for eight common toxic agents. Blood samples were drawn in 665 (70%) of the 947 admissions.

The total number of laboratory found agents (967) exceeded the clinically suspected (871) by 11%. The agreement between the clinical assessment and laboratory analyses was good for ethanol and paracetamol ($\kappa = 0.70$ for both), whereas only moderate or fair for other agents ($\kappa = 0.22-0.51$). Sensitivities of the clinical assessments compared to the laboratory results were better for common than rare agents, and better for higher than lower serum concentrations. The four most common agents (ethanol, benzodiazepines, paracetamol, and opiates) had overall sensitivity of 82% for higher-than-median serum concentrations, whereas the other agents had sensitivities ranging from 14% to 71% for higher-than-median concentrations.

The reliability of the clinical diagnoses varied to such an extent that agents which are important to recognize for specific treatment, should be tested for.

Toxicity of buprenorphine overdoses in children

Hayes BD, Klein-Schwartz W, Doyon S. Pediatrics, 2008; 121: e782-e786.

Objective: There are few reports in children of overdoses of buprenorphine, a partial opioid agonist used in the treatment of opioid dependence and pain. The purpose of this study was to analyze buprenorphine overdoses in young children reported by US poison centers to the Researched Abuse, Diversion, and Addiction-Related Surveillance System.

Methods: A retrospective review of buprenorphine overdoses in children < 6 years of age reported to the Researched Abuse, Diversion, and Addiction-Related Surveillance System from November 2002 through December 2005 was performed. Patients lost to follow-up and those ingesting multiple substances were excluded.

Results: Eighty-six cases met inclusion criteria. In the 54 children who developed toxicity, the clinical effects included drowsiness or lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation or irritability (5%), pallor (3%), and coma (2%). There were no fatalities. The mean time to onset of effects was 64.2 minutes, with a range of 20 minutes to 3 hours. Duration of clinical effects was under 2 hours in 11%, 2 to 8 hours in 59%, 8 to 24 hours in 26%, and > 24 hours in 4%. Children who ingested ≥ 2 mg of buprenorphine were more likely to experience clinical effects, and all of the children who ingested > 4 mg experienced some effect. No child ingesting > 4 mg experienced a severe effect. Of the 22 children administered naloxone, 67% had at least a partial response.

Conclusions: Buprenorphine overdoses are generally well tolerated in children, with significant central nervous system and respiratory depression occurring in only 7%. Any child ingesting > 2 mg and children < 2 years of age ingesting more than a lick or taste should be referred to the emergency department for a minimum of 6 hours of observation. Naloxone can be used to reverse respiratory depression.

Biomarkers of low-level exposure to soman vapor: comparison of fluoride regeneration to acetylcholinesterase inhibition

Dabisch PA, Davis EA, Renner JA, Jakubowski EM, Mioduszewski RJ, Thomson SA. *Inhal Toxicol* 2008; 20: 149-56.

Abstract: The nerve agent O-pinacolyl methylphosphonofluoridate, also known as soman or by its military designation GD, is a highly toxic organophosphorus compound that exerts its effects through inhibition of the enzyme acetylcholinesterase (AChE).

In the present study, a fluoride ion based regeneration assay was developed to quantify the level of soman present in the blood of rats following a low-level whole-body inhalation exposure. It was hypothesized that the amount of regenerated nerve agent in the blood would be dose dependent in rats subjected to a whole-body inhalation exposure to a low-level dose of soman vapor, and that the fluoride ion-based regeneration method would be more sensitive for the detection of a low-level exposure to soman vapor than the measurement of whole blood AChE activity.

Regenerated soman was dose-dependently detected in both the red blood cells (RBCs) and plasma of exposed rats at all concentrations tested (0.033-0.280 mg/m³ for a 240-min exposure). Significant inhibition of whole blood AChE activity did not occur below a concentration of 0.101 mg/m³, and was only depressed by approximately 10-25% at concentrations ranging from 0.101 mg/m³ to 0.280 mg/m³.

This study is the first to utilize a fluoride ion-based regeneration assay to demonstrate the dose-dependent increases in soman in the blood following whole-body inhalation exposure to low levels of vapor. Additionally, the results of the present study demonstrate that the fluoride ion based regeneration assay was approximately threefold more sensitive than the measurement of AChE activity in the blood for the detection of exposure to soman, and also that miosis is a more sensitive marker of soman exposure than inhibition of AChE activity.

Inspiratory and expiratory high-resolution computed tomography (HRCT) in patients with chemical warfare agents exposure

Bakhtavar K, Sedighi N, Moradi Z. *Inhal Toxicol* 2008; 20: 507-11.

Abstract: Chemical warfare agents (CWA) including sulfur mustard (SM) were commonly used in Iran-Iraq war. Respiratory problems are the greatest cause of long-term disability among people who had combat exposure to SM. High-resolution computed tomography (HRCT) has been accepted as the imaging modality of choice in these patients.

We used expiratory HRCT findings in comparison to inspiratory HRCT for demonstration of pulmonary damage in these patients. HRCT in deep inspiration as well as full expiration was performed in 473 patients with a history of chemical gas exposure during the war and the results were compared. The study was prospective during 1 yr.

Of 473 patients, 366 (77.38%) showed normal HRCT in deep inspiration; however, on corresponding expiratory cuts, 263 (71.86%) had abnormalities. The most frequent abnormal finding in expiration was patchy air trapping (77.77%). We conclude that exposure to SM causes pulmonary complications resulting in disability in the affected patients; however, HRCT in inspiration is normal in most of the affected patients. Expiratory HRCT showed patchy air trapping as the most common finding, which is suggestive of small air way diseases such as bronchiolitis obliterans; therefore it is recommended to do HRCT both in deep inspiration and full expiration in patients with a history of CWA exposure.

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