Articles You Might Have Missed

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Spiller HA, Bosse GM, and Beuhler M. et al. Unintentional ingestion of bupropion in children. *J Emerg Med* 2010;38(3):332–336.

Background: The incidence of seizure after unintentional bupropion ingestion in children less than 6 years of age has been reported as 0.2%, yet poison centers refer the majority of children reported to have ingested bupropion to emergency departments for evaluation.

Research Question: Do all unintentional pediatric bupropion ingestions require referral to healthcare facilities?

Methods: A retrospective chart review was performed regarding unintentional bupropion ingestions in children less than 6 years old from four regional poison centers. Polysubstance ingestions and cases with lack of follow-up were excluded.

Results: Four hundred seven patients were identified, 77 of which were observed at home. Three hundred twenty-nine were seen in a healthcare facility, and 143 were subsequently hospitalized.

Seventy-three patients developed symptoms that included sinus tachycardia ($n=50$), nausea/vomiting ($n=32$), hyperactivity ($n=17$), seizure ($n=3$), hallucinations ($n=2$), and hypertension ($n=2$). QT prolongation occurred in one case, which was also complicated by a single seizure. All children

who seized exhibited a prodrome of hyperactivity and vomiting.

The dosage was known in 218 cases and averaged 12.2 mg/kg (mean) with 88% ingesting less than 20 mg/kg. The mean dosage in patients who experienced seizures was 22.5 mg/kg, 24 mg/kg in those with sinus tachycardia, and 33.4 mg/kg in patients who developed hyperactivity. No significant symptoms occurred when the reported amount of bupropion was less than 10 mg/kg.

Conclusion: Unintentional pediatric bupropion ingestions resulted in clinical effects that rarely required intervention. Isolated, unintentional bupropion ingestion of less than or equal to 10 mg/kg may not require referral to a healthcare facility.

Critique: Limitations of poison center studies include possible bias in under- or overreporting of dose as well as a lack of laboratory confirmation. Given these limitations, this well-done retrospective review of poison center data sheds light upon a relatively common ingestion and provides further evidence that can enhance poison center management of unintentional bupropion ingestions.

Implications for Toxicologists: Isolated, unintentional bupropion ingestion of less than or equal to 10 mg/kg in children may be safely observed at home.

Bebarta VS, Tanen DA, Lairet J. et al. Hydroxocobalamin and sodium thiosulfate versus sodium nitrite and sodium thiosulfate in the treatment of acute cyanide toxicity in a swine (*Sus scrofa*) model. *Ann Emerg Med*. 2010;55(4):345–351.

Background: No study has directly compared hydroxocobalamin with sodium nitrate/sodium thiosulfate in cyanide toxicity.

Research Question: What is the relative efficacy of hydroxocobalamin versus sodium nitrate (both combined

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with sodium thiosulfate) in reversing cyanide-induced hypotension and preventing mortality?

Methods: Twenty-four swine were instrumented and then poisoned with cyanide until hypotensive (MAP less than 50% baseline). They were randomly divided into two treatment arms: IV hydroxocobalamin (150 mg/kg)+sodium thiosulfate (413 mg/kg) or sodium nitrite (10 mg/kg)+sodium thiosulfate (413 mg/kg). Hemodynamics, acid–base status, and survival were monitored for 40 min after initiation of antidotal therapy.

Results: One animal in the hydroxocobalamin and two in the sodium nitrite group died during antidote administration. Early in the study, hydroxocobalamin improved blood pressure. At 10 min, mean arterial pressure in the hydroxocobalamin group was 133% of the baseline value compared with 68% for sodium nitrite. No statistically significant difference was detected between groups for mortality, lactate levels, cyanide levels, cardiac output, pulse rate, and systemic vascular resistance during treatment.

Conclusion: Hydroxocobalamin/sodium thiosulfate led to a faster return to baseline mean arterial pressure compared with sodium nitrate/sodium thiosulfate; however, there was no statistically significant difference between the two groups in serum acidosis, serum lactate, or overall mortality.

Critique: This interesting animal study is the first to compare directly the new versus standard antidotes for cyanide toxicity. Limitations to an otherwise well-designed trial included a lack of hydroxocobalamin only treatment group and a relatively short duration of treatment (40 min). The authors report more rapid blood pressure improvement in the hydroxocobalamin + thiosulfate group, but this was based on only one significant value between treatment groups. There were three deaths and no differences between groups, but perhaps, the study was not powered to detect a difference in mortality.

Implication for Toxicologists: This study provides a modicum of evidence for hydroxocobalamin's noninferiority to sodium nitrite/sodium thiosulfate for use in cyanide toxicity.

Page CB, Calver LA, Isbister GK et al. Risperidone overdose causes extrapyramidal effects but not cardiac toxicity. *J Clin Psychopharmacol* 2010;30: 387–390.

Background: Risperidone is an atypical antipsychotic with published reports of akathisia, tachycardia, hypotension, lethargy, respiratory depression, QRS widening, QT prolongation, coma, and death following overdose. However, it is difficult to assign causation to risperidone due to the presence of coingestants.

Research Question: What are the clinical features of patients who overdose on risperidone alone compared to cases with coingestants?

Methods: A retrospective chart review was done of admissions to a regional toxicology service from the years 1995–2008. Historical data included demographics, amount of risperidone ingested, time of ingestion, length of stay, and coingestants. Clinical data included GCS, vital signs, QRS and QT intervals, dystonia, and outcomes.

Results: One hundred seven patients presented for 157 admissions. Of these, 38 ingested risperidone alone for a total of 45 admissions, and 78 patients ingested risperidone with a coingestant for a total of 112 admissions.

Of the risperidone alone patients, the dose was known for 44 of the 45 patients with a median ingestion of 33 mg (interquartile range 15–75). Median length of stay was 16 h (interquartile range 8–18) with no patient intubated or admitted to the ICU. All of these patients essentially had a normal GCS, and there were no instances of seizures, neuroleptic malignant syndrome, delirium, or death. There were five dystonic reactions (11%). The only cardiovascular effect noted was tachycardia on 26 admissions (58%), with no episodes of hypotension or dysrhythmias. EKGs were available for 41 of the 45 risperidone alone patients with a median QRS of 80 ms (interquartile range 80–80; range 40–120).

Those who ingested risperidone with a coingestant had known ingestion amounts in 99 out of the 112 presentations, with a median ingestion of 25 mg (interquartile range 14–60). Median length of stay was 16 h (interquartile range 7–22). Half of these patients were tachycardic. GCS was less than 15 in 29 admissions (26%), with 14 (13%) of these being admitted to the ICU, and 7 (6%) requiring ventilator support. Three (3%) had dystonic reactions, 1 (1%) had a seizure, and 3 (3%) became delirious.

Conclusion: Risperidone-only overdoses cause minimal effects with the main clinical features of tachycardia and dystonic reactions. Significant cardiac and neurologic features are more likely to occur due to coingestants.

Critique: This retrospective review sheds light upon a relatively common ingestion. The strength of the study can be seen in its relative size and hands-on clinical information that is systematically entered into a database. Previous studies were much smaller and had conflicting results concerning observed cardiotoxicity. The major limitation associated with the report is lack of laboratory confirmation of the ingested substances. Additionally, the authors do not include details regarding intent, and this omission could influence conclusions. Interestingly, the authors applied their patient data to a recently published QT-heart rate nomogram (QJM 2007;100:609–615). Four of 38 isolated ingestions had abnormal QT-heart rate values, but none developed torsades.

Implications for Toxicologists: This study provides evidence toward the safety of risperidone in overdose. This suggests that if clinical manifestations arise, then it may benefit the toxicologist to consider coingestants.

Waring WS, Jamie H, Leggett GE. Delayed onset of acute renal failure after significant paracetamol overdose: a case series. *Human and Experimental Toxicology* 2010;29(1):63–68.

Background: Acute renal failure is a recognized manifestation of paracetamol (acetaminophen) overdose that receives little attention. It is unknown if current clinical management of practice is sufficiently sensitive enough to detect acute renal failure.

Research Question: What are the prevalence, time course, and severity of acute renal failure after paracetamol overdose?

Methods: A retrospective chart review was done of all paracetamol overdoses admitted to a toxicology treatment unit from June 2005 until October 2007. Inclusion criteria included all paracetamol overdoses with a documented serum creatinine greater than 150 $\mu\text{mol/L}$ (1.7 mg/dL) or serum creatinine greater than 50% of baseline. Patients who coingested nephrotoxic drugs or had chronic renal impairment without an increase in creatinine were excluded.

Results: Two thousand sixty-eight patients experienced a paracetamol overdose, and 13 (0.6%) met criteria for renal failure. Five were excluded, leaving eight for analysis.

Of these eight patients with nephrotoxicity, all had coexisting hepatotoxicity, and all recovered without dialysis. Abnormal serum creatinine was noted at approximately 21/2 days postingestion (range 2–3 days). Mean peak serum creatinine levels occurred at 5.5 days, slightly later serum ALT that peaked at 2.5 days.

Conclusion: Current clinical practice may not allow for detection of paracetamol-induced acute renal failure. Acute renal failure can easily be missed in patients discharged within 48 h of their paracetamol overdose. Further studies examining the prevalence of paracetamol-induced nephrotoxicity must take into account the interval between ingestion and discharge.

Critique: This retrospective review examines the occurrence of renal injury associated with paracetamol (acetaminophen) toxicity. Unfortunately, the report has several limitations. The initial pool of 2,068 subjects produced only 8 (0.6%) patients with nephrotoxicity. All recovered renal function, and none required dialysis. There were no deaths. The low incidence of renal dysfunction and lack of mortality suggest that the this particular study population was not as ill as previous papers that report 25–50% renal injury (*Hepatology* 2005;42:1364–1372 and *Drugs* 1983;25:290–314). This paper does confirm that nephrotoxicity develops and recovers later than hepatotoxicity. However, the author's assertion that delayed renal injury may be missed seems unfounded. All patients with criterion renal failure also had hepatotoxicity, and the standard clinical practice for hepatotoxic patients includes monitoring of renal function as one tool for determining need for liver transplantation.

Implications for Toxicologists: This paper may underplay the significance of renal failure following acetaminophen overdose and overstate potential concerns with missed diagnosis of renal injury.