Articles You May Have Missed

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Keywords Levamisole · Agranulocytosis · Epinephrine autoinjector · Digital ischemia · Levosimendan · Beta-blocker toxicity · Naloxone · Cardiac arrest

Brackney M, Baumbach J, Ewers C, et al. (2009)
Agranulocytosis associated with cocaine use—four states, March 2008–November 2009. MMWR 58:1381–5

Background: Levamisole is a veterinary antihelminthic drug and a known cause of agranulocytosis. The Drug Enforcement Administration recently reported that 69% of cocaine coming into the United States contained levamisole as an added agent. A report from Canada associated human agranulocytosis with levamisole-contaminated cocaine.

Research Question: Are unexplained cases of agranulocytosis in New Mexico and Washington State associated with cocaine contaminated with levamisole?

Results: Twenty-one cases of unexplained agranulocytosis were reported in four states: New Mexico (eight), Arizona (one), Colorado (two), and Washington (ten). Nineteen patients admitted to crack and/or powder cocaine use. Five of these 19 patients had blood or urine testing for levamisole and four were found to be positive. Outcome was available for 19 patients: one died and 18 made a full recovery. In seven cases, there was at least one recurrence of agranulocytosis with repeated cocaine use.

Critique: As a small, uncontrolled case series, a causal relationship between levamisole-contaminated cocaine and

agranulocytosis has not been proved. The relatively short elimination half-life of levamisole may have limited the ability to confirm exposure, but the association between cocaine use and this rare condition is remarkable, especially in light of the DEA information.

Implication for Toxicologists: Levamisole has joined a long list of cocaine adulterants that may act as secondary toxins. Toxicologists need to be aware of the possible reaction to levamisole and serve an active role in their community regarding continued surveillance, detection, management, and patient counseling.

Leppikangas H, Ruokonen E, Rutanen J, et al. (2009)
Levosimendan as a rescue drug in experimental propranolol-induced myocardial depression: a randomized study. Ann Emerg Med 54:811–17

Background: Levosimendan can increase cardiac contractility by increasing contractile protein sensitivity to calcium.

Research Question: Can levosimendan reverse negative inotropy in a porcine model of β -blocker intoxication?

Methods: Twenty-four anesthetized pigs were intoxicated with propranolol to achieve 60% reduction in cardiac output. They were then divided into three groups and randomized in a double-blind fashion to receive either levosimendan and saline infusion, saline bolus and MAP-targeted dobutamine, or saline placebo. Outcome measures included survival, cardiac output, and other hemodynamic parameters.

Results: Levosimendan-treated pigs showed greater improvement in hemodynamic function and, most importantly, survival: 100% levosimendan group versus 33% and 22% with dobutamine and placebo. Of note, there was no difference in systemic vascular resistance between

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groups and MAP was increased with levosimendan administration.

Conclusion: Levosimendan shows promise as an adjunctive therapy for β -blocker intoxication.

Critique: In this model of β -blocker intoxication, the authors notably chose to administer propranolol to a physiologic endpoint of 60% reduction in cardiac output and continue drug infusion to reflect ongoing drug absorption similar to that expected with human oral intoxication. While this porcine model shows apparent effectiveness of levosimendan treatment, it was only compared to dobutamine infusion and placebo, not to standard treatment such as glucagon, insulin, and vasopressors. In this regard, the design would seem to favor levosimendan. As noted in the article, prior studies comparing dobutamine and levosimendan in the setting of therapeutic β -blockade in heart failure showed that dobutamine may not be the ideal agent for the reversal of propranolol-induced negative inotropy. Further, the hemodynamic effects of multiple sedating and anesthetic agents used in the model must be taken into consideration.

Implication for Toxicologists: While difficult to extrapolate to treatment of human β -blocker intoxication, the apparent success of levosimendan in this porcine model should be viewed in the context of existing literature regarding its use in the treatment of heart failure and calcium channel blocker toxicity. Further animal trials comparing levosimendan to more relevant antidotes in the setting of β -blocker intoxication should be sought before considering levosimendan in human intoxication.

Muck AE, Bebarta VS, Borys DJ, Morgan DL. Six years of epinephrine digital injections: absence of significant local or systemic effects. Ann Emerg Med DOI:10.1016/j.annemergmed.2010.02.019

Background: Epinephrine autoinjectors are commonly prescribed and accidental digital injection is frequent. Many references note that digital ischemia is a concern and recommend empiric treatments such as topical nitroglycerin or local injection of vasodilators, but these are based largely on anecdotes.

Research Question: This study sought to determine the frequency of digital ischemia after inadvertent epinephrine autoinjection and to consider the value of vasodilator treatment.

Methods: Six years of calls to the Texas Poison Center Network regarding inadvertent digital autoinjection of epinephrine underwent a structured review by trained data abstractors. Data collected included demographics, predefined signs of digital ischemia, treatment, duration of symptoms, disposition, and national poison center database-defined clinical outcomes.

Results: A total of 213 cases of accidental digital epinephrine injection were found and 123 that had follow-up were included. Only 3% of patients had ischemia. Other signs and symptoms included pain (68%), blanching (42%), discoloration (17%), ecchymosis (3%), and decreased capillary refill (2%). Six patients had transient tachycardia, and one had palpitations; none had hypertension. No severe cardiovascular or systemic effects were reported. The majority of patients (77%) received no drug therapy, while 15% received topical nitroglycerin paste, 6% phentolamine injection, one patient terbutaline injection, and two patients both nitroglycerin paste and phentolamine. Forty patients (32%) received only warm compresses. Of the 98 patients treated observantly, eight had “moderate” effects as recorded by the poison center and the rest had “minor” or absent effects. All patients had complete resolution of symptoms, none required hospitalization or surgical consultation or intervention, and all patients referred to the ED were discharged for home.

Conclusion: Ischemia after digital epinephrine autoinjection is rare. Most symptoms resolve within 2 h. Drug therapy may not be necessary.

Critique: Since this is a retrospective non-controlled review of poison center data, referral bias and incomplete clinical data are major weaknesses. It is impossible to know whether the patients who received drug therapy would have recovered without it. Within these confines, this is a large and well-conducted study. It demonstrated that most patients did not require drug therapy and all rapidly recovered without complications.

Implication for Toxicologists: Expectant observation at home with poison center follow-up is a viable option for most accidental epinephrine autoinjection cases.

Saybolt MD, Alter SM, Dos Santos F, et al. (2010) Naloxone in cardiac arrest with suspected opioid overdoses. Resuscitation 81:42–6

Background: Opioid toxicity can result in respiratory arrest and subsequent cardiac arrest. In case reports and animal studies, naloxone, an opioid antagonist, has been associated with antiarrhythmic effects.

Research Question: The authors investigated whether administration of naloxone to patients with presumed opioid-induced cardiac arrest was associated with changes in cardiac rhythm and improved survival.

Methods: The authors conducted a structured, retrospective review of advanced life support (ALS) dispatches over a 5-year span involving cases of presumed opioid-induced cardiac arrest that received naloxone as part of resuscitation. Predefined outcomes included positive response to naloxone: either an immediate or delayed (< 10 min)

change in cardiac electrical rhythm following naloxone administration. Other data included baseline rhythm, naloxone dose, other pharmacological therapy, and survival.

Results: Of 32,544 ALS calls with medical cardiac arrest, 42 (0.13%) patients received naloxone and 36 of these patients with complete records were included in the final analysis. Fifteen of the 36 patients (42%; 95% CI 26–58) had a change in their cardiac rhythm following the administration of naloxone and were considered responders.

Among the 15 responders, seven (47%) had an immediate change in their cardiac rhythm, while eight (53%) were defined as having a delayed change. Four responders survived to hospital admission and one survived to hospital discharge. None of the non-responders survived.

Conclusion: The authors cannot firmly recommend the routine use of naloxone during cardiac arrest believed due to opioid toxicity but, given the overall poor outcomes in such cases, suggest that its use presents some potential benefit by improving cardiac rhythm.

Critique: While hypothesis generating, this paper does not have sufficient data to support that naloxone was the

causative factor in any observed changes in cardiac activity. While an immediate response to naloxone is potentially conceivable, it is difficult to attribute a delayed effect solely to naloxone. The doses and timing of naloxone administration were not uniform, further limiting any conclusions. There is the potential for unexpected harm from a novel treatment and this was not addressed in the paper. For example, while we know that 42 patients received naloxone, with one surviving to hospital discharge, we do not know how many patients who did not receive naloxone survived to hospital discharge. It is possible that naloxone may have decreased survival. Because naloxone was not a standard medication to be given for cardiac arrest, the treating paramedics required on-line medical direction prior to its administration. The authors do not discuss if any other non-standard treatments were also given.

Implication for Toxicologists: This paper is interesting but, unfortunately, has many shortcomings that prohibit adopting the routine use of naloxone for opioid-induced cardiac arrests. Further understanding of the direct cardiac effects of naloxone and better, prospective studies would be helpful.