



## **Tox Talk: Articles in the Recent Literature**

Keeping up with the latest trends in toxicology can be difficult. New drugs of abuse, drug interactions, and new antidotes will change your practice. The speaker will review the most recent top articles in the toxicology literature. Each article will be analyzed for its clinical relevance to the practice of emergency medicine and whether it should change your practice.

- Review important recent articles in toxicology.
- Identify the newest antidotes for poisonings and overdoses.
- Discuss the applicability of classic articles to current practice.

TH-293  
Thursday, October 30, 2008  
12:00 PM - 12:50 PM  
McCormick Place - Lakeside Building

(+)No significant financial relationships to disclose

(+)Steven E. Aks, DO, FACEP  
Fellowship Director, The Toxikon Consortium/Cook County Hospital; Associate Professor of Emergency Medicine, Rush University; Attending Physician, Department of Emergency Medicine, Cook County Hospital, Chicago, Illinois

# Tox Talk: Articles in the Recent Literature



Steven E. Aks, DO, FACMT, FACEP  
Director, The Toxikon Consortium;  
Division of Toxicology, Department of Emergency Medicine  
Cook County Hospital  
ACEP Scientific Assembly  
Chicago, IL 2008  
saks@ccbh.org

## **Tox Talk: Goal**

We will review of some top recent and some classic articles in medical toxicology. These articles will highlight cutting edge issues, antidotes, controversies, etc. The topic will be approached in a “top ten” clinical question format.

## **Topics**

1. Supportive care (classic article)
2. Cyanide antidote kit
3. Calcium channel blocker overdose and glucose
4. Calcium channel blocker and whole bowel irrigation
5. Duration of n-acetylcysteine treatment
6. Hangover?
7. Beta blockers and cocaine. The controversy continues..
8. IV fat in the ED? Intralipid as an emerging antidotal therapy.
9. Carbon Monoxide, pulse oximetry and screening.
10. A classic of the classic articles

## **Clinical Question #1**

**How good is that fancy critical / supportive care?**

**From the best of the toxicology classics series:**

Clemmesen C, Nilsson: Therapeutic trends in the treatment of barbiturate poisoning. Clin Pharm Therap 1960;2:220-229.

From the Department of Psychiatry at Bispebjergs Hospital in Copenhagen

### Review of the Scandinavian Method

There was a rising incidence of barbiturate poisoning after WWII. A variety of treatments were proposed including the use of analeptics (stimulants) to awaken barbiturate overdose victims. In the 1930's the patients were treated with analeptics and treated with “massive” gastric lavage and suspensions of powdered carbon. The mortality rate at that time was around 10%. Not infrequently at postmortem examination “carbon particles were found in the lungs.”

In 1946 Kirkegaard paved the way to treat circulatory shock. In 1951 hypoxia was recognized as a major cause of morbidity and mortality.

The “Scandinavian Method” was developed as “pharmacotherapeutic nihilism.” No analeptics were employed.

Major advances

Fluid and dextran replacement

Endotracheal intubation

## Artificial ventilation

From 1948 to 1959 mortality dropped from 12% to 1.5%.

### Related Articles:

Frenia ML, Schauben JL, wears RL, et al: Multiple-dose activated charcoal compared to urinary alkalization for the enhancement of phenobarbital elimination. *J Toxicol Clin Toxicol* 1996;34:169-175.

- Multiple dose activated charcoal was superior to urinary alkalization

Mohammed Ebid AH, Abdel-Rahman HM: Pharmacokinetics of Phenobarbital during certain enhanced elimination modalities to evaluate their clinical efficacy in management of drug overdose. *Ther Drug Monit* 2001;23:209-216.

- Multiple dose activated charcoal with supportive care superior to alkalization. Unable to demonstrate a benefit of combined therapy.

Pond SM, Olson KR, Osterloh JD, et al: Randomized study of the treatment of Phenobarbital overdose with repeated doses of activated charcoal. *JAMA* 1984;251:3104-3108.

- Classic paper demonstrating the decrease in half life of elimination with multiple doses of activated charcoal. Does not demonstrate a clinical benefit (e.g. time to extubation)

Thompson T, Aks SE: Case files of the Toxikon medical toxicology fellowship in Chicago: The poisoned Anesthesiologist. *J Med Toxicol* 2007;3:31-36.

- Case discussion and review discussing this issue.

## Clinical Question #2

What's new with the cyanide antidote kit?

Fortin J-L, Waroux s, Giocanti JP, et al: Hydroxocobalamin for poisoning caused by ingestion of potassium cyanide: A case study. *J Emerg Med* doi:10.1016/j.jemermed.2008.04.040

### Background

Traditionally in the US the standard cyanide treatment has included amyl nitrite, sodium nitrite and sodium thiosulfate. Hydroxocobalamin, a precursor of vitamin B12 has a history of use in the pre-hospital setting in France for cyanide poisoning, particularly that associated with smoke inhalation. This case describes the pre-hospital use of hydroxocobalamin for acute cyanide poisoning.

### Case

A 48 year old biochemical engineer was found comatose by his wife in the garden, 10 minutes after ingesting approximately 25 grams of potassium cyanide. He was examined in the field by the Paris Fire Brigade's mobile intensive care unit. Initially, he was comatose (GCS 3) and was gasping for breath. His breath smelled of bitter almonds. BP was 160/80 P 130 beats/minute. An IV line was established and blood samples were obtained. Hydroxocobalamin 5 grams x 2 was infused intravenously, he was intubated. He began to awake, but was sedated.

Initial ECGs showed global myocardial injury, but this normalized approximately 6 hours post-ingestion. The first measured lactate 2 hours after ingestion was 5.0 mmol/L. Initial pH was 7.24 also 2 hours post-ingestion. The pH and lactate normalized over the first 24 hours. The cyanide concentration was 3.64 mg/L (>1 toxic, >3 fatal).

### Conclusion

This new antidote approved in the US was successfully used in the overdose setting (prehospital).

### Related articles:

Borron SW, Baud FJ, Barriot P, et al: Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Ann Emerg Med* 2007;49:794-801.

- Describes the prehospital and ICU use of hydroxocobalamin for smoke inhalation victims with suspected cyanide poisoning.
- Documented cyanide levels.
- Use of antidote appeared safe.
- No control group

Fortin J-L, Giocanti J-P, Ruttimann M, et al: Prehospital administration of hydroxocobalamin for smoke inhalation-associated cyanide poisoning: 8 years of experience in the Paris fire brigade. *Clin Toxicol* 2006;44:37-44.

- Retrospective review of smoke victim population given hydroxocobalamin
- No controls
- No cyanide levels

### **Clinical Question #3**

#### **In a calcium channel blocker overdose, do I care about the accu check?**

Levine M, Boyer EW, Pozner CN, et al: Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med* 2007;35:2071-2075.

##### Background

Overdoses of calcium channel blocker agents result in hyperglycemia, primarily due to the blockade of pancreatic L-type calcium channels and insulin resistance on the cellular level. The clinical significance of the hyperglycemia in this setting has not previously been described.

##### Method

This is a retrospective review of all adult patients with a discharge diagnosis of acute verapamil or diltiazem overdose at five university-affiliated teaching hospitals. The severity of overdose was assessed by determining whether a patient met the endpoints of in-hospital mortality, the necessity for a temporary pacemaker, or the need for vasopressors. The authors compared initial and peak serum glucose concentration with hemodynamic variables between patients who did and did not meet the composite end points.

##### Results

40 patients met the inclusion criteria. 27 patients ingested verapamil and 13 patients ingested diltiazem. For patients who did and did not meet the composite end points, the median initial serum glucose concentrations were 188, and 129 respectively ( $p=.0058$ ). The median peak serum glucose concentrations for the two groups were 364 and 145 respectively ( $p=.0001$ ). The median increase in glucose for those who met the composite endpoints was 71.2%, vs. 0% for those who did not ( $p=.0067$ ).

##### Conclusion

Serum glucose concentrations correlate directly with the severity of the calcium channel blocker intoxication. The percentage increase of the peak glucose concentration is a better predictor of severity of illness than hemodynamic derangements. If validated prospectively, serum glucose concentration alone might be an indicator to begin hyperinsulinemia-euglycemia (HIE) therapy.

##### Related articles

Yuan TH, Kerns WP, Tomaszewski CA, et al: Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *Clin Toxicol* 1999;37:463-474.

- First clinical description of cases of calcium channel blocker OD using HIE.

## Clinical Question #4

### Should I do whole bowel irrigation for sustained release calcium channel blocker overdose?

Cumpston KL, Aks SE, Sigg T, Pallasch E: Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: Primum non nocere. J Emerg Med 2008;Doi:10.1016/j.jemermed.2007.11.100

#### Background

Sustained-release calcium channel blocker overdoses are potentially life-threatening. These patients may not become hemodynamically unstable until many hours after ingestion. ON theoretical grounds, some have suggested that whole bowel irrigation may be of value in the management of these cases.

#### Case 1

58 year old man ingested 7.2 grams of diltiazem extended release. He presented to the ED 3 hours after ingestion. He was lavaged, given activate charcoal, and WBI was begun at 2 liters/hr. One hour later, he became hypotensive to 70/40. The patient continued to be hemodynamically unstable, but WBI was continued for a total of 7 hours until the patient became distended. Attempts to stabilize the patient with multiple agents (calcium, glucagon, hyperinsulinemia-euglycemia) were ineffective. He died 13 hours post-ingestion.

#### Case 2

40 year old man ingested a reported 90 verapamil 240mg extended release. While hemodynamically stable WBI was begun at 2 liters/hour. Subsequently he became hemodynamically unstable, and he developed aspiration pneumonitis secondary to vomiting the large volume of activated charcoal and WBI solution.

#### Conclusion

WBI should be avoided in the setting of the hemodynamically unstable sustained release calcium channel blocker overdose.

#### Related article:

American Academy of Clinical Toxicology, European Association of Poison Centres and Clinical Toxicologists: Position Paper: Whole Bowel Irrigation. J Toxicol Clin Toxicol 2004;42:843-854.

- WBI should not be used routinely, but could have potential value in a limited number of toxic ingestions, based on experimental studies and anecdotal reports.
- WBI should be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs.

- WBI should be considered in the management of patients who have ingested substantial amounts of iron because of the high morbidity and mortality of this poisoning and a lack of other options for gastrointestinal decontamination.
- WBI should be considered for the removal of ingested packets of illicit drugs.

## **Clinical Question #5**

### **If I'm treating with N-acetyl cysteine for acetaminophen poisoning, do I need to treat for the full 17 doses?**

Betten DP, Cantrell FL, Thomas SC, et al: A prospective evaluation of shortened course oral N-acetylcysteine for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 2007;50:272-279.

#### **Background**

Traditionally oral therapy with NAC is administered for a 72 hour course. Effective intravenous regimens have been established to be effective at 48 and 21 hours in duration. This study aims to look at a shortened duration of therapy with oral NAC for acetaminophen overdose.

#### **Method**

Individuals with a potentially toxic acetaminophen ingestion according to serum acetaminophen levels were identified prospectively using a large statewide poison control system database throughout a 12 month period. NAC was administered for a minimum of 6 doses (20 hours), after which laboratory studies were obtained. Discontinuation of NAC was recommended by the poison center when two criteria were met: serum acetaminophen was undetectable (<10 mcg/ml) and liver test results were normal (AST, INR). A follow-up questionnaire was administered to individuals treated with NAC for 48 hours or less to ascertain the presence of symptoms consistent with hepatotoxicity.

#### **Results**

Of 205 acutely poisoned individuals treated with NAC for 48 hours or less, 195 were successfully contacted after discharge, and 187 of 195 (95.9%) reported no symptoms consistent with hepatic failure. Eight individuals (4.1%) reported abdominal pain or vomiting; however, non received further NAC treatment or additional hospitalization.

#### **Conclusion**

A shortened duration of treatment with NAC (20 to 48 hours) may be an effective treatment option in individuals considered to be at no further risk of developing liver toxicity according to the fulfillment of appropriate laboratory criteria before NAC discontinuation.

Related articles:

Dart RC, Rumack BH: Patient-tailored acetyl cysteine administration. *Ann Emerg Med* 2007;50:280-281.

- It's time patient-tailored, goal directed therapy be applied to acetaminophen toxicity
- This represents the current practice of many toxicologists. It is gaining acceptance, and seems to be the clear trend.

Heard KJ: Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 2008;359:285-292.

- Nice review article in *NEJM*.
- Proposes oral NAC for selected (non-suicidal) outpatients in settings where there is excellent follow-up.

## **Clinical Question #6**

### **Should the treatment of a hangover be subjected to randomized controlled trials?**

Pittler MH, Verster JC, Ernst E: Interventions for preventing or treating alcohol hangover: systematic review of randomized controlled trials. *BMJ* 2005;331:1515 (online)

#### Objective

To assess the clinical evidence on the effectiveness of any medical intervention for preventing or treating alcohol hangover.

#### Method

Systematic searches of major medical databases: Medline, Embase, etc. Also hand searches of conference proceedings and bibliographies. All randomized controlled trials of any medical intervention for preventing or treating alcohol hangover were included. Trials were considered if they were placebo controlled or controlled against a comparator intervention.

#### Results

Fifteen potentially relevant trials were identified. Seven were omitted. Eight RCTs were assessing eight different interventions were reviewed. The agents tested were propranolol, tropisetron, tolfenamic acid, fructose or glucose, and the dietary supplement *Borago officinalis*, Artichoke, prickly pear and a yeast based preparations. All trials were double blind. Significant differences for overall symptom scores and symptoms were reported only for tolfenamic acid, linolenic and from *B officianalis* and a yeast based preparation.

#### Conclusion

No compelling evidence exists to suggest that any conventional or complementary intervention is effective for preventing or treating a hangover. The most effective way to avoid the symptoms of alcohol induced hangover is to practice abstinence or moderation.

Related Articles:

Smith GC, Pell JP: Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized controlled trials. *BMJ* 2003;327:1459-61.

## **Clinical Question #7**

### **Beta blockers and cocaine.....**

Dattilo PB, Hailpern SM, Fearon K, et al: Beta-Blockers are associated with reduced risk of myocardial infarction after cocaine use. *Ann Emerg Med* 2008;51:117-125.

#### Objective

Beta blocker use is associated with coronary artery spasm after cocaine administration but also decreases mortality in patients with myocardial infarction or systolic dysfunction. We conduct a retrospective cohort study to analyze the safety of beta-blockers in patients with positive urine toxicology results for cocaine.

#### Methods

363 consecutive telemetry and ICU patients who were admitted to a municipal hospital and had positive urine toxicology results for cocaine during a 5-year period (307 patients). Fifteen patients with uncertain history of beta blocker use before admission were excluded. The primary outcome measure was MI; secondary outcome measure was in hospital mortality.

#### Results

Beta blockers were given in 60 of 348 admissions. The incidence of MI after administration of beta blocker was significantly lower than without treatment (6.1% vs.26%; difference in proportion 20%, CI 10.3 – 30%). One of the 14 deaths occurred in patients who received Beta blockade 1.7% vs. 6.7%. Multivariate analysis showed that the use of beta blockers significantly reduced the risk of MI.

#### Conclusion

In this cohort, administration of beta-blockers was associated with reduction in incidence of MI after cocaine use. The benefit of beta-blockers on MI may offset the risk of coronary spasm.

Related Articles:

Editorials:

**Point:** Hoffman RS: Cocaine and beta-blockers: Should the controversy continue? *Ann Emerg Med* 2008;51:127-129.

- Cites methodological problems with this retrospective study.
- Notes concern over coronary artery vasoconstrictive properties of beta blockers in the face of cocaine use.
- Argues that although generally accepted urine tox screens will be positive for 2-3 days after cocaine use, that chronic users may be positive for up to 2 weeks.
- States the call for a prospective trial of beta adrenergic antagonists is dangerous.

**Counter Point:** Freeman K, Feldman JA: Cocaine, myocardial infarction, beta-blockers: Time to rethink the equation? *Ann Emerg Med* 2008;51:130-133.

- Argues that in the current article death was decreased in the patients with positive urinary drug screening test result for cocaine metabolite (benzoylecgonine)
- The dictum of unopposed alpha stimulation lacks rigorous investigation and relies on predominantly uncontrolled observations.
- Self reporting of cocaine use is unreliable.
- Maybe a controlled trial is warranted.
- Is this interaction “toxicomythology?”

Chen ZM, Pan HC, Chen YP, et al: (COMMIT) Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005;366:1622-1632.

- Big, big, big trial.
- 11 more per thousand developed cardiogenic shock.
- Shock was most often seen during days 0-1.
- Death, reinfarction, arrest and shock was significantly better after the first 24 hours!
- Is the use of beta blockers becoming moot?
- Is it all about hemodynamic instability (hyperdynamic in the setting of cocaine)

- I'd like to see a clinical trial on cocaine induced chest pain in the hemodynamically stable patient that does not exhibit the sympathomimetic toxidrome

## **Clinical Question #8**

### **Should I start stocking intralipid in the ED?**

Sirianni AJ, Osterhoudt KC, Calello DP, et al: Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med* doi:10.1016/j.annemergmed.2007.06.004

#### Background

Animal studies show efficacy of intravenous lipid emulsion in the treatment of severe cardiotoxicity associated with local anesthetics, clomipramine, and verapamil.

#### Case Report

A 17 year old girl developed seizure activity and cardiovascular collapse after initial ingestion of up to 7.95 grams of bupropion and 4 grams of lamotrigine. Standard CPR for 70 minutes was unsuccessful in restoring sustained circulation. A 100 ml bolus of 20% lipid emulsion was then administered, and after one minute an effective sustained pulse was observed. The patient subsequently manifested significant ALI but had rapid improvement in cardiovascular status and recovered, with near normal neurologic function. Serum bupropion levels before and after lipid infusion paralleled triglyceride levels.

#### Conclusion

This patient developed cardiovascular collapse because of intentional, oral overdose of bupropion and lamotrigine that was initially refractory to standard resuscitation measures. An infusion of lipid emulsion was followed rapidly by restoration of effective circulation. The mechanism may be consistent with the lipid sink theory of antidotal efficacy, but the mechanism of action is not established.

#### Going back:

Weinberg GL, VadeBoncouer T, Ramaraju GA, et al: Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesth* 1998;88:1071-1075.

#### Where else may it work?

Harvey M, Cave G: Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. *Ann Emerg Med* 2007;49:178-185.

Tebbutt S, Harvey M, Nicholson T, et al: Intralipid prolongs survival in a rat model of verapamil toxicity. *Acad Emerg Med* 2006;13:134-139.

Bania TC, Chu J, Perez E, et al: Hemodynamic effects of intravenous fat emulsion in an animal model of severe verapamil toxicity resuscitated with atropine, calcium, and saline. Acad Emerg Med 2007;14:105-111.

On the web:

[www.lipidrescue.org](http://www.lipidrescue.org)

Example Instructions:

(this is not FDA approved, and should be considered experimental at the time of this lecture)

**20% Intralipid:**

- **1.5 mL/kg as an initial bolus, followed by**
- **0.25 mL/kg/min for 30-60 minutes**
- **Bolus could be repeated** 1-2 times for persistent asystole
- **Infusion rate could be increased** if the BP declines.

Good Review Article:

Weinberg GL: Lipid Infusion Therapy: Translation to clinical practice. Intl Anesth Resear Soc 2008;106:1340-1342.

## **Clinical Question #9**

### **CO and pulse oximetry? CO and ED screening? When should we do it?**

Suner S, Partridge R, Sucov A, et al: Non-invasive pulse co-oximetry screening in the ED identifies occult carbon monoxide toxicity. J Emerg Med 2008;34:441-450.

Background

CO toxicity may present with non-specific signs and symptoms and without history of exposure. Screening for CO toxicity may identify occult cases. Can non-invasive screening for CO exposure be performed in all patients presenting to a high-volume urban ED and would identify patients with unsuspected CO toxicity.

Method

Adult patients who presented to the ED for any complaint, were prospectively screened for carboxyhemoglobin by a pulse CP-oximeter. ED triage staff recorded SpCO on the patient's chart at triage. When available carboxyhemoglobin concentration obtained by venous blood was also include in the data set.

Results

There were 14,438 patients who presented to the ED and were entered in the study. Data from 10,856 patients receiving screening for spCPO were analyzed. 32% of the patients smoked. The mean SpCo was 5.17% +/- 3.78% among smokers and 2.90% +/- 2.76% among non-smokers. During the study period, 11 patients with presenting signs and symptoms non consistent with CO toxicity were identified through SpCO screening.

#### Conclusion

Screening for CO using a non-invasive pulse CO-oximeter can be conducted even in a busy tertiary center ED and identify patients with occult CO toxicity.

- Only 64 patients had serum carboxyhemoglobin measured. There was an average lag of 67 minutes after SpCO was obtained.
- Examples of + CO
  - Headache and palpitations: CO = 25
  - Weakness and dizziness: 28
  - Headache and body aches: 24
  - Syncope: 26
  - Headache: 36
  - Nausea, vomiting: 17
  - Fall: 17 (smoker)
  - Depression: 12 (smoker)
  - Toothache: 14 (smoker)
- Did not establish sensitivity / specificity

#### Related Articles:

O'Malley G: Non-invasive carbon monoxide measurement is not accurate. *Ann Emerg Med* 2006;48:477-478. (letter)

- Found a high false positive rate

Heckerling PS, Leikin JB, Maturen A: Predictors of occult carbon monoxide poisoning in patients with headache and dizziness. *Ann Intern Med* 1987;107:174-176.

- 89 patients with headache or dizziness studied for CO exposure.
- 4 patients had carboxyhemoglobin > 10%.
- If patients had used stoves for heat, or if there were similarly affected cohabitants, all cases were identified.

## **Clinical Question #10**

**Should I let my Dad suck me into a medical experiment on the beach?  
From the best of the toxicology classics series:**

**Answer.....**

Barnes JH: Cause and effect of Irukandji stings. Med J Aust 1964;24:897-904.