

## **Session Title: Toxicology Articles You Probably Missed**

### Session overview

There is so much literature to sift through each year, it becomes nearly impossible to stay abreast of it. Through a case-based approach, this session will highlight the most important toxicology articles of 2016 with a focus on those that may change your practice. Topics covered will include acetaminophen, digoxin, naloxone, ECMO, lipid emulsion, ketamine, and new calcium channel blocker overdose guidelines.

### Objectives

- Determine the role for ketamine to manage severe agitation in the prehospital and ED environments.
- Develop a treatment plan for treating severe calcium channel blocker poisoning based on the new guidelines and lipid emulsion recommendations.
- Interpret post-overdose acetaminophen concentrations to determine if/when a second concentration is needed.

#### **1. Ketamine for Prehospital Agitation**

Ketamine is gaining traction as a prehospital option for managing severe agitation or excited delirium syndrome. Previous reports have mostly been case series, but a new prospective study adds some important information that may help delineate ketamine's role in this setting. An accompanying commentary was published in the same issue.

#### **What They Did**

Open-label before-and-after prospective comparison of haloperidol (10 mg IM) versus ketamine (5 mg/kg IM) for the treatment of acute undifferentiated agitation.

#### **What They Found**

- Ketamine demonstrated a statistically and clinically significant difference in median time to sedation compared to haloperidol, 5 min vs. 17 min ( $p < 0.0001$ , 95% CI: 9 15)
- Complications: ketamine, 49%; haloperidol, 5%
  - Ketamine complications: hypersalivation (38%), emergence reaction (10%), vomiting (9%), and laryngospasm (5%)
- Intubation rate: ketamine, 39%; haloperidol, 4%

#### **Application to Clinical Practice**

- Ketamine works for prehospital agitation (and more rapidly)
- Ketamine has a higher complication and intubation rate
- Though this study did not find a dose relationship between ketamine and intubations, future studies should evaluate further and potentially use lower ketamine doses

- At Maryland, we start with 2-3 mg/kg IM and repeat if necessary after 5 min. Most patients have not required a second dose and none have been intubated. This allows time to place an IV line and initiate additional treatment.

## References

Cole JB, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol* 2016;54(7):556-62. [[PMID 27102743](#)]

Hayes BD. Ketamine for agitation: a key cog in the prehospital treatment armamentarium wheelhouse. *Clin Toxicol* 2016;54(7):545-6. [[PMID 27163703](#)]

## 2. Does Digoxin Immune Fab Work in Chronic Digoxin Poisoning?

Patients with chronic digoxin toxicity generally have multiple co-morbidities such as renal failure, dehydration, and cardiac failure. Sick patients with chronically high digoxin levels may have more than just digoxin toxicity as the cause of illness.

### A New Study

Prospective observational study with the primary objective to investigate changes in free digoxin concentrations and clinical effects on heart rate and potassium concentrations in chronic digoxin poisoning when digoxin immune Fab are given.

### What They Found

One to two vials of digoxin immune Fab initially bound all free digoxin confirming Fab efficacy. However, this was associated with only a moderate improvement in HR (49 to 57 bpm) and potassium (5.3 to 5.0 mmol/L).

### Application to Clinical Practice

- Elevated digoxin concentrations alone may not be solely responsible for bradycardia and hyperkalemia in the chronic setting.
- Digoxin immune Fab is not a magic bullet in chronic digoxin poisoning.

### Reference

Chan BS, et al. Efficacy and effectiveness of anti-digoxin antibodies in chronic digoxin poisonings from the DORA study (ATOM-1). *Clin Toxicol* 2016;54(6):488-64. [[PMID 27118413](#)]

## 3. ECMO for severely poisoned patients

The American College of Medical Toxicology's ToxIC Registry is a self-reporting database completed by medical toxicologists across 69 institutions in the US.

- Over a 3 year period, just 10 cases in the database received ECMO: 4 pediatric, 2 adolescent, and 4 adults (individual cases presented in the table below)
- Time of initiation of ECMO ranged from 4 h to 4 days, with duration from 15 h to 12 days
- Exposures included carbon monoxide/smoke inhalation (2), bitter almonds, methanol, and several medications including antihistamines (2), antipsychotic/antidepressant (2), cardiovascular drugs (2), analgesics (2), sedative/hypnotics (2), and antidiabetics (2)
- Overall survival rate was 80%

### Application to Clinical Practice

In settings where ECMO is available, it may be a potential treatment option in severely poisoned patients. From the limited data, ECMO was generally administered prior to cardiovascular failure and might be of benefit particularly during the time the drug is being metabolized.

### Reference

Wang GS, et al. Extracorporeal Membrane Oxygenation (ECMO) for Severe Toxicological Exposures: Review of the Toxicology Investigators Consortium (ToxIC). *J Med Toxicol* 2016;12(1):95-9. [[PMID 26013746](#)]

#### 4. Utility of Pre-4-Hour Acetaminophen Levels in Acute Overdose

A full review of this topic was covered in [a previous ALiEM post](#).

### What They Did

- The authors examined serum APAP concentrations obtained less than 4 hours post-ingestion, and again 4 or more hours post-ingestion.
- They specified a cutpoint of 100 mcg/mL (662 micromol/L) obtained between 2 and 4 hours and a subsequent 4 to 20 hour APAP concentration above the nomogram treatment line of 150 mcg/mL (993 micromol/L).

### What They Found

- Almost 2,500 patients were evaluated.
- Concentrations drawn between 2-4 hours post-ingestion demonstrated a sensitivity of 0.96 [95% CI; 0.94, 0.97] and a negative likelihood ratio of 0.070 [0.048, 0.10]. Coingested opioids reduced this sensitivity to 0.91 [0.83, 0.95], and antimuscarinics to 0.86 [0.72, 0.94].
- Only very low to undetectable APAP concentrations prior to 4 hours reliably excluded a subsequent concentration over the treatment line.
- They concluded that applying an APAP concentration cutpoint of 100 mcg/mL (662 micromol/L) at 2-4 hours after an acute ingestion as a threshold for repeat testing and/or treatment would occasionally miss potentially toxic exposures.
- Importantly, their data validated the practice of not retesting when the first post-ingestion APAP concentration is below the lower limit of detection.

### Application to Clinical Practice

1. The Rumack-Matthew nomogram is to be utilized starting at 4 hours after an acute APAP ingestion.
2. Pre-4 hour APAP levels, if not repeated, can lead to unnecessary treatment, admissions, and adverse effects.
3. If an APAP level is drawn **before 1 hour**, a second APAP level must be drawn again at the 4-hour mark.
4. If an APAP level is drawn **between 1-4 hours**, and the level is:
  - **Undetectable** → you can stop additional APAP testing
  - **Detectable** → you should redraw a second APAP level at the 4-hour mark
5. The current data supports waiting until 4 hours after ingestion to draw a level, but optimally less than 7 hours (to allow an hour to start acetylcysteine if needed).

### Reference

Yarema M, et al. Can a serum acetaminophen concentration obtained less than 4 hours post-ingestion determine which patients do not require treatment with acetylcysteine? *Clin Toxicol (Phila)*. October 2016:1-7. [[PubMed](#)]

### 5. Calcium Channel Blocker Overdose Poisoning Guidelines

US, Canadian, and European critical care and toxicology societies published consensus recommendations in the management of CCB poisoning ([St-Onge M, et al. Crit Care Med 2016](#)).

1. for asymptomatic patients, observation and consideration of decontamination following a potentially toxic calcium channel blocker ingestion (1D)
2. as first-line therapies (prioritized based on desired effect), IV calcium (1D), high-dose insulin therapy (1D-2D), and norepinephrine and/or epinephrine (1D). We also suggest dobutamine or epinephrine in the presence of cardiogenic shock (2D) and atropine in the presence of symptomatic bradycardia or conduction disturbance (2D)
3. in patients refractory to the first-line treatments, we suggest incremental doses of high-dose insulin therapy if myocardial dysfunction is present (2D), IV lipid-emulsion therapy (2D), and using a pacemaker in the presence of unstable bradycardia or high-grade arteriovenous block without significant alteration in cardiac inotropism (2D)
4. in patients with refractory shock or who are peri-arrest, we recommend incremental doses of high-dose insulin (1D) and IV lipid-emulsion therapy (1D) if not already tried. We suggest venoarterial ECMO, if available, when refractory shock has a significant cardiogenic component (2D), and using pacemaker in the presence of unstable bradycardia or high-grade arteriovenous block in the absence of myocardial dysfunction (2D) if not already tried

5. in patients with cardiac arrest, we recommend IV calcium in addition to the standard advanced cardiac life-support (1D), lipid-emulsion therapy (1D), and we suggest venoarterial ECMO if available (2D).

## 6. Treat and Release after Naloxone

A full review of this topic was covered in [a previous ALiEM post](#).

A new prehospital study, published in *Prehospital Emergency Care*, assessed the risk of administration of naloxone with subsequent refusal of care. The authors conducted a retrospective review of all patient encounters by the Los Angeles Fire Department during July 1, 2011-December 31, 2013. The Coroner's records were reviewed to determine if a patient with the same or similar name had died within 24 hours, 30 days, or 6 months of the initial EMS encounter. Of the 205 subjects identified, one (0.49%) died within 24 hours of the initial EMS encounter. The cause of death was coronary artery disease and heroin use. Two additional subjects died within 30 days, but the cause of death was either unknown or unrelated in both cases.

### Application to ED Clinical Practice

1. If a patient presents to the ED after receiving prehospital naloxone for opioid toxicity, it is worth observing them for at least an hour (longer dependent on the situation). Be sure that after the naloxone has worn off, s/he doesn't have recurrent opioid toxicity. Only one of the studies evaluated ED patients and found a higher rate of recurrent toxicity compared to the prehospital studies. The primary outcome in the prehospital studies was death. We can monitor more closely in the ED and can provide resources including substance abuse referrals and take-home naloxone.
2. The most common opioid in the earlier studies was heroin. A one-time naloxone dose is generally sufficient to reverse heroin with a limited threat of recurrent toxicity. However, the opioid epidemic has changed, such that [heroin is only part of the current problem](#). Prescription medications, fentanyl, and other opioids can be longer acting than naloxone's 45-60 minute duration of effect. Adulterants also play a role, as highlighted by the [recent CDC report](#) on increased deaths related to fentanyl. The Levine study aimed to reevaluate the earlier data in light of the current times, but only captured patients up through the end of 2013. Although they found a low rate of death in 205 patients, recurrent toxicity may have been missed by their inclusion criteria.

### Bottom Line

- We should not overturn the practice of ED observation for 4-6 hours. The data simply suggests that if a patient refuses transport at the scene or wants to sign out against medical advice after receiving naloxone, s/he has a low risk of death.

- Keep in mind that the available data predate 2014, when fentanyl, carfentanil, etc. were not yet a big part of the scene. Therefore, all of the studies most likely included predominately heroin and oral opioids and do not account for the new, more dangerous adulterants.

## Reference

Levine M, Sanko S, Eckstein M. Assessing the Risk of Prehospital Administration of Naloxone with Subsequent Refusal of Care. *Prehosp Emerg Care*. March 2016;1-4. [[PubMed](#)]

## 7. Evidence-Based Recommendations on Use of Lipid In Poisoning

An international committee published evidence-based recommendations for the use of IV lipid emulsion in poisoning ([Gosselin S, et al. Clin Toxicol 2016;54:899-923](#)).

1. For the management of cardiac arrest, we recommend using ILE with bupivacaine toxicity, while our recommendations are neutral regarding its use for all other toxins.
2. For the management of life-threatening toxicity, (1) as first line therapy, we suggest not to use ILE with toxicity from amitriptyline, non-lipid soluble beta receptor antagonists, bupropion, calcium channel blockers, cocaine, diphenhydramine, lamotrigine, malathion but are neutral for other toxins, (2) as part of treatment modalities, we suggest using ILE in bupivacaine toxicity if other therapies fail, but are neutral for other toxins, (3) if other therapies fail, we recommend ILE for bupivacaine toxicity and we suggest using ILE for toxicity due to other LAs, amitriptyline, and bupropion, but our recommendations are neutral for all other toxins.
3. In the treatment of non-life-threatening toxicity, recommendations are variable according to the balance of expected risks and benefits for each toxin.