

## Settling Controversies in Emergency Medicine Drug Therapy

### Session overview

Physostigmine and flumazenil get a bad rap, but should they? In addition, several controversies exist related to the management of hyperkalemia, some of which include administration of calcium in the absence of ECG changes, which calcium salt is best, and co-administration of dextrose plus insulin. This session will explore the reasons why we rarely use these two antidotes and evaluate whether a change in practice is needed. We will also address practical issues associated with hyperkalemia pharmacotherapy and associated patient-oriented outcomes.

### Objectives

- In a patient with benzodiazepine or anticholinergic poisoning, determine when it is appropriate to administer flumazenil or physostigmine, respectively.
- Evaluate recommendations for dosing and administration of parenteral calcium in the treatment of hyperkalemia.
- Apply practical methods for co-administration of insulin and dextrose in the management of hyperkalemia.

### **Flumazenil**

I like to think of flumazenil as the naloxone of benzodiazepines. Flumazenil is an antagonist at the benzodiazepine receptor, has a similar onset (1-2 min) and duration (45-60 min) to naloxone, and also has similar dosing 0.5-1 mg.

Flumazenil can reverse CNS depression. On the other hand, re-sedation, seizure/withdrawal, inconsistent reversal of respiratory depression, and proconvulsant co-ingestions are all problematic, potentially swinging the pendulum more in favor of risk than benefit ([Acad Emerg Med 1997](#)).

#### Reversing Procedural Sedation

Flumazenil seems safe and effective for reversing over-sedation when a benzodiazepine is used for PSA ([Br Dent J 2002](#)). Resedation can occur after flumazenil wears off so continued monitoring is needed.

#### Reversing Paradoxical Reactions

Flumazenil seems safe and effective for paradoxical reaction to benzodiazepines, ([Eur J Anaesthesiol 2001](#)). Higher benzodiazepine dosing can also overcome the problem ([Pharmacotherapy 2004](#)).

#### Reversing Overdose in Pediatric Patients

In pediatric overdose patients not chronically on benzodiazepines, flumazenil is reasonable to consider, either for diagnostic or therapeutic purposes ([J Toxicol Clin Toxicol 1998](#)).

### Reversing Overdose in Adult Patients

Overall complication rate with benzodiazepine overdose is low: Of 702 patients who had taken benzodiazepines alone or in combination with ethanol or other drugs, 0.7% died and 9.8% had complications ([Acta Med Scand 1998](#)).

In a retrospective study, overdosed comatose patients were assigned to either a low-risk or non-low-risk group ([Ann Emerg Med 1996](#)). Low-risk patients had CNS depression with normal vital signs, no other neurologic findings, no evidence of ingestion of a tricyclic antidepressant, no seizure history, and absence of an available history of chronic benzodiazepine use. Of 35 consecutive patients, 4 were assigned to the low-risk group. In the low-risk group, 3 patients had complete awakening and the 4th had partial awakening, with no adverse events. In the non-low-risk group, 4 patients had complete awakening and 5 had partial awakenings. Seizures occurred in 5 patients. Therefore, although flumazenil use probably was safe and effective in the low-risk group, few patients could be considered low risk. Risk of seizures appears significant in non-low-risk patients.

14 of 1700 patients developed adverse drug reactions, half were related to abrupt arousal ([Med Toxicol Adverse Drug Exp 1987](#)). Flumazenil was given to 12 patients on midazolam infusions. Serum norepinephrine and epinephrine concentrations rose within 10 minutes and correlated with increased heart rate, blood pressure, and myocardial oxygen consumption ([Crit Care Med 2000](#)). Flumazenil also may cause a large increase in ICP in patients receiving midazolam for head injury.

### Attempts to Prove Safety

Three relatively recent poison center studies have attempted to demonstrate the safety of flumazenil in this setting. In the first study there were 904 adult patients with 13 reported seizures and 1 death ([J Emerg Med 2012](#)). A second study specific to pediatric patients reported 83 patients with no seizures and no deaths ([Pediatr Emerg Care 2012](#)). A third study found 80 patients with 1 seizure and 0 deaths ([Emerg Med J 2012](#)). A fourth small retrospective study 23 ED patients found that 15 woke up (at least partially) and there were no seizures even in the 7 patients with reported proconvulsant coingestants ([Am J Emerg Med 2015](#)).

On the surface, it may appear that flumazenil is safe to give. But, retrospective poison center studies from voluntary reporting cannot be used to prove a drug's safety. The true denominator is unknown. In the pediatric study, we wouldn't expect children to experience withdrawal since they aren't on chronic benzodiazepine therapy. So, it's no surprise there weren't any seizures or deaths.

### Bottom Line

A 2016 systematic review and meta-analysis of randomized trials summed it up perfectly: "Flumazenil should not be used routinely, and the harms and benefits should be considered carefully in every patient ([Basic Clin Pharmacol Toxicol 2016](#))." Cases in which to consider flumazenil are pediatric patients and reversal of procedural sedation if needed.

## Physostigmine

Physostigmine gets a bad rap, in my opinion. I remember back to my PGY-1 pharmacy residency when we had a teenage female present with AMS after being found in the woods ([Clin Toxicol 2006](#)). She was clearly anticholinergic and the suspected medication, by history, was olanzapine. It was like watching pharmacology in action. Physostigmine transformed a delirious patient into one with normal mentation telling us exactly what happened.

### Use in TCA Overdose

Physostigmine used to be part of the 'coma cocktail,' until 2 patients developed asystole in the setting of TCA overdose ([Ann Emerg Med 1980](#)). TCA overdose pathophysiology is complex, with more than just anticholinergic effects are contributing. Unfortunately, we somewhat overreacted and stopped using physostigmine regularly even when true anticholinergic poisoning was staring at us. The safety of physostigmine use for seizures or cardiotoxicity in the setting of TCA toxicity is difficult to predict and thus not recommended ([J Emerg Med 2003](#)).

### Use in Anticholinergic Poisoning

Clearly beneficial: Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively ([Ann Emerg Med 2000](#)). Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium.

Indications - Peripheral or central antimuscarinic effects without significant QRS or QT prolongation

- Peripheral: dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia
- Central: agitation, delirium, hallucinations, seizures, and coma

### Adverse Effects

Have atropine available at the bedside in case you overshoot or an alternative diagnosis is underlying.

### Contraindications (package insert)

Reactive airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, AV block, and in patients receiving of choline esters and succinylcholine.

### Dose

- 1 to 2 mg in adults and 0.02 mg/kg (max, 0.5 mg in children) IV infused over at least 5 minutes
- Onset is within minutes ([Anesth Analg 1973](#)); can be repeated after 10 to 15 minutes

### My Algorithm

1. Lorazepam 2 mg IV for agitation, can be repeated
2. Physostigmine 1 mg IV over 5 minutes (mixed in 50 mL NS), can be repeated

Stock it in your ED.

## Hyperkalemia

### Calcium

- Why we give it
  - An elevated calcium concentration decreases the depolarization effect of an elevated K<sup>+</sup> concentration. IV calcium antagonizes the cardiac membrane excitability thereby protecting the heart against dysrhythmias. ([Am J Physiol 1956](#); [Treatment of Acute Hyperkalemia in Adults - Clinical Practice Guideline. UK Renal Association 2014](#))
- When we give it
  - Life-threatening ECG changes, dysrhythmias, & cardiac arrest - YES
  - Peaked T waves - PROBABLY
  - Normal ECG - PROBABLY NOT
    - ECG can be normal, but in some cases is an insensitive marker for assessing severity ([Tex Heart Inst J 2006](#); [Am J Kidney Dis 1986](#); [Int J Clin Pract 2001](#))
- How to dose it
  - Optimal dose unclear; start with at least 1 gm CaCl<sub>2</sub> or 2 gm calcium gluconate IV
  - Onset ~3 minutes; redose in 5-10 minutes if no effect seen from first dose
  - Effects last 30-60 minutes (may need to redose if further treatment needed while awaiting emergent HD)
- Which salt to give
  - Calcium gluconate does not act slower than CaCl<sub>2</sub> because it needs hepatic activation!
    - Serum ionized calcium levels were measured in 15 hypocalcemic patients during the anhepatic stage of liver transplantation. Half received CaCl<sub>2</sub> 10 mg/kg, the other half received calcium gluconate 30 mg/kg. Serum concentrations of ionized calcium were determined before and up to 10 min after calcium therapy. Equally rapid increases in calcium concentration after administration of CaCl<sub>2</sub> and gluconate were observed, suggesting that calcium gluconate does not require hepatic metabolism for the release of calcium. ([Anesthesiology 1990](#))
    - A weird randomized prospective study in both children and dogs compared ionization of CaCl<sub>2</sub> and calcium gluconate. The authors conclude that equal elemental calcium doses of calcium gluconate (10%) and CaCl<sub>2</sub> (10%) (approximately 3:1) are equivalent in their ability to raise calcium concentration during normocalcemic states in children and dogs ([Anesthesiology 1987](#))
    - In ferrets and in vitro human blood, equimolar quantities of CaCl<sub>2</sub> and calcium gluconate produced similar changes in plasma ionized calcium concentration when injected IV into anaesthetized ferrets or when added to human blood in vitro. In vivo changes were followed with a calcium electrode positioned in the animal's aorta, and this showed that the ionization of calcium gluconate on its first pass through the circulation is as great as that of CaCl<sub>2</sub>. ([Anaesthesia 1984](#))
- Calcium in digoxin overdose
  - There are only 5 case reports suggesting a temporal relationship between calcium administration and death in the setting of digoxin toxicity (primarily from the 1930s and

- 1950s) — symptoms of digoxin toxicity are not described, no digoxin levels were taken and only 2 cases had a strong temporal relationship (which does not imply causation). There are also cases of calcium use in digoxin toxic patients without any ill effects.
- Original animal models flawed — toxic effects only occurred when animals were made severely hypercalcemic prior to digoxin administration. Subsequent animal models mimicking digoxin toxicity failed to demonstrate adverse effects.
  - A retrospective study reviewed 159 dig toxicity cases, 23 of which received calcium ([J Emerg Med 2011](#)). Death rate was same in both groups and no dysrhythmias were noted. The problem is all except 1 were chronic digoxin overdose. Hyperkalemia is more problematic in the acute overdose.
  - Stone heart theory is probably false. Calcium appears safe, but we don't even know if it would work the same as in hyperK from other causes. Little evidence in acute OD where hyperK more problematic. If known digoxin-induced hyperkalemia, give antidote. Otherwise give calcium.

### Insulin and Dextrose

- How insulin works
  - Temporarily shifts potassium intracellularly through a complex process of activating Na<sup>+</sup>-K<sup>+</sup> ATPase and by recruitment of intracellular pump components into the plasma membrane. Insulin binding to specific membrane receptors results in extrusion of Na<sup>+</sup> and cellular uptake of K<sup>+</sup>. ([J Biol Chem 1992](#))
- The right insulin dose
  - 5 unit boluses up to 20 unit/hr infusions have been used ([Am J Med 1988](#)). Most common dose studied is 10 units IV regular insulin bolus (lowers K<sup>+</sup> by about 1 mEq/L).
- Preventing hypoglycemia
  - Incidence of hypoglycemia
    - A 10 unit dose of IV regular insulin has an onset of action of about 5-10 minutes, peaks at 25-30 minutes, and lasts 2-3 hours. Herein lies the problem in that IV dextrose only lasts about an hour (at most).
    - Overall incidence of hypoglycemia appears to be ~10%, but could be higher ([Kidney Int 1990](#); [J Hosp Med 2012](#); [Apel J, et al. Clin Kidney J 2014;0:1-3](#))
    - The overall incidence of hypoglycemia appears to be ~10%, but could be higher.
  - Risk factors for developing hypoglycemia ([Apel 2014](#))
    - No prior diagnosis of diabetes
    - No use of diabetes medication prior to admission
    - Lower pretreatment glucose level (104 ± 12 mg/dL vs 162 ± 11 mg/dL, P = 0.04)
    - Renal dysfunction (some evidence suggests that insulin is metabolized by the kidneys to some extent) ([Nutrition 2011](#))
  - Strategies for avoiding hypoglycemia
    - Here is a [suggested strategy](#) for administering enough dextrose to counter the initial insulin bolus of 10 or 20 units. It is loosely based on the Rush University protocol ([Apel 2014](#)).