

Session Title: Rational Use of Physostigmine and Flumazenil in the ED

Session overview

Physostigmine and flumazenil get a bad rap, but should they? This session will explore the reasons why we rarely use these two antidotes and evaluate whether a change in practice is needed.

Objectives

- In a patient with benzodiazepine poisoning, determine when it is appropriate to administer flumazenil.
- In a patient with anticholinergic poisoning, determine when it is appropriate to administer physostigmine.

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.

Just a year after flumazenil came to market, Dr. Lewis Goldfrank penned an editorial questioning the need for it ([Acad Emerg Med 1997](#)). On one hand, flumazenil can reverse CNS depression. On the other hand, re-sedation, seizure/withdrawal, inconsistent reversal of respiratory depression, and proconvulsant coingestions are all problematic, potentially swinging the pendulum more in favor of risk than benefit.

Reversing Procedural Sedation

When a benzodiazepine is used for procedural sedation, flumazenil seems safe and effective for reversing over-sedation ([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 intracranial pressure 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](#)).¹ 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 two patients developed asystole in the setting of TCA overdose ([Ann Emerg Med 1980](#)). We understand that TCA overdose pathophysiology is complex, certainly much 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

Presence of 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, and AV block and in patients receiving therapeutic doses of choline esters and succinylcholine.

Dose

- 1 to 2 mg in adults and 0.02 mg/kg (maximum, 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.