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Controversial Antidotes

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.

Physostigmine

Use in Anticholinergic Poisoning - Clearly beneficial (Arens 2018, Boley 2019, Arens 2019, Wang 2020). Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively (Burns 2000). Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. It also decreased resource utilization including intubation and ICU placement (Boley 2019).

Use in TCA Overdose - The safety of physostigmine for TCA toxicity was difficult to predict (Suchard 2003); newer, higher-quality data suggest it is probably ok for anticholinergic delirium related to TCAs (Rasimus 2018). [In-depth review by Dr. Jon Cole]

Adverse Effects - Have atropine available at the bedside.

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 (Holzgrafe 1973); can be repeated after 10 to 15 minutes

My Algorithm - Lorazepam 2 mg IV for agitation (can be repeated) PLUS Physostigmine 1 mg IV over 5 minutes mixed in 50 mL NS (can be repeated)

Stock it in your ED!

Flumazenil

On one hand, flumazenil can reverse CNS depression. On the other hand, resedation, seizure/withdrawal, inconsistent reversal of respiratory depression, and proconvulsant coingestions are problematic, potentially swinging the pendulum more in favor of risk than benefit. (Goldfrank 1997)

- *Procedural Sedation* - Flumazenil seems safe and effective for reversing over-sedation (Girdler 2002)
- *Paradoxical Reactions* - Flumazenil seems safe and effective (Weinbroum 2001)
- *Overdose in Pediatric Patients* - In patients not chronically on benzodiazepines, flumazenil is reasonable to consider, either for diagnostic or therapeutic purposes (Wiley 1998)
- *Overdose in Adult Patients* - In high-risk patients, the seizure/withdrawal risk is real (Gueye 1996, Kamijo 2000). Past attempts to prove safety have flaws (Kreshak 2012, Kreshak 2012, Veiraiah 2012, Nguyen 2015). Low-dose flumazenil (~0.2 mg) may be an option (Schult 2021).

Bottom Line - A systematic review/meta-analysis of RCTs concluded: "Flumazenil should not be used routinely, and the harms and benefits should be considered carefully in every patient (Penninga 2016, Sivilotti 2016)." Consider flumazenil in pediatric patients and reversal of procedural sedation if needed. The 2020 ACLS guidelines recommend against flumazenil in undifferentiated coma (Panchal 2020).