Clinical Pharmacology & Toxicology Pearl of the Week

~Physostigmine for Anticholinergic Delirium~

- ✓ Physostigmine is an acetylcholinesterase inhibitor that, unlike others (ie. neostigmine and pyridostigmine), is able to cross the blood-brain barrier and reverse central antimuscarinic toxicity.
- ✓ Muscarinic acetylcholine receptors are responsible centrally for alertness via the reticular activating system, and peripherally for sweat glands, slowing the intrinsic cardiac pacemaker, GI motility, pupillary size, and bladder contraction.
- ✓ Competitive inhibition of muscarinic acetylcholine receptors results in the toxidrome of delirium (typically carphologia or "lint-picking"), depressed level of consciousness, mydriasis, anhidrosis, tachycardia and urinary retention.

Many drugs are known to cause antimuscarinic delirium:

- antihistamines (diphenhydramine, hydroxyzine)
- some antiemetics (promethazine, dimenhydrinate)
- some antipsychotics (quetiapine, clozapine, olanzapine)
- muscle relaxants (cyclobenzaprine)
- cyclic antidepressants (amitriptyline, imipramine, nortriptyline, doxepin)
- anticholinergics (atropine, scopolamine)
- plants (Jimsonweed, Angel's Trumpet)

- ✓ Physostigmine can reduce the need for aggressive interventions, physical restraints, and invasive testing in those with antimuscarinic delirium.

Indications: Physostigmine is indicated for the reversal of the antimuscarinic delirium **in** hemodynamically stable patients presenting with clinical features of antimuscarinic toxidrome.

Contraindications:

Absolute:

- Physostigmine should not be used to treat seizures or non-anticholinergic related causes of delirium
- Hypotension SBP < 90 mmHg or ventricular dysrhythmia
- Bradycardia < 60 bpm
- Evidence of sodium channel blockade on ECG (widened QRS > 100ms in adults, > 80ms in children 12 and under; RBBB pattern in precordial leads, R wave in avR > 3mm)
- Hypoxemia requiring intubation, non-invasive positive pressure ventilation, or BMV
- Tachypnea RR > 24
- Diaphoresis
- Concomitant use of depolarizing paralytic agents (e.g. succinylcholine)
- Sensitivity to physostigmine, salicylates, or preservative agent (benzyl alcohol, sodium bisulfate)

Relative:

- History of reactive airway disease requiring ongoing chronic therapy
- Active peripheral vascular disease
- Active intestinal obstruction
- Active urinary obstruction
- Intraventricular conduction delays or AV blockade on current ECG

Adverse effects: Cholinergic toxicity is expected to occur with inappropriate (i.e. non-antimuscarinic toxidrome), excessive or rapid dosing. Patients are at higher risk of adverse effects with rapid IV bolus and doses larger than 2 mg.

- Bradycardia, heart block, asystole
- Seizures

- Nausea, vomiting, diarrhea
- Hypersalivation, diaphoresis
- Bronchorrhea and bronchospasm
- Fasciculations and weakness

Precautions during use:

- Cardiac monitoring with pulse oximetry
- Pre-administration blood pressure and q5mins x 2 following administration
- RN and MD at bedside for 10 mins after administration to watch for adverse effects & assess need for repeat dosing
- Ativan 2 - 4 mg IV (Pediatric: 0.05 - 0.1 mg/kg, maximum 4 mg) at bedside in case of seizures
- Atropine 0.5 mg IV (Pediatric: 0.02 mg/kg, minimum 0.1mg, maximum 0.5mg) at bedside in case of cholinergic toxicity (bronchorrhea, bradycardia)

References:

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3. Olson KR. Poisoning & Drug Overdose 7th Edition. 7th ed. Mcgraw-Hill Education; 2018.
4. Nelson LS, Howland MA, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. Goldfrank's Toxicologic Emergencies 11th Edition. 11th ed. Edmonson KG, Pancotti R, editors. Mcgraw-Hill Education; 2019.
5. Arens AM, Kearney T. Adverse Effects of Physostigmine. Journal of Medical Toxicology. 2019.
6. Rasimas JJ, Sachdeva KK, Donovan JW. Revival of an antidote: bedside experience with physostigmine. Toxicol Commun. 2018.
7. Arens AM, Shah K, Al-Abri S, Olson KR, Kearney T. Safety and effectiveness of physostigmine: a 10-year retrospective review. Clin Toxicol. 2018.
8. Suchard JR. Assessing physostigmine's contraindication in cyclic antidepressant ingestions. J Emerg Med. 2003.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.