Clinical Pharmacology & Toxicology Pearl of the Week

~ Physostigmine for Antimuscarinic Delirium ~

- ✓ Physostigmine is an acetylcholinesterase inhibitor that, unlike others (ie. neostigmine and pyridostigmine), can 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:
  - Do not use as treatment for seizures or as a general anti-delirium medication for all causes of delirium
  - Hypotension (systolic blood pressure less than 90 mmHg or ventricular dysrhythmia)
  - Bradycardia less than 60 bpm
  - Evidence of sodium channel blockade on ECG (widened QRS greater than 100ms in adults, greater than 80ms in children 12 and under; RBBB pattern in precordial leads, R wave in avR greater than 3mm)
  - Hypoxia requiring intubation, non-invasive positive pressure ventilation, or bag-valve-mask
  - Diaphoresis (inconsistent with clinical features of antimuscarinic poisoning)
  - 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
  - Respiratory rate greater than 24 (may represent co-ingestants, metabolic acidosis, underlying respiratory disease)
  - QTc greater than 500 ms (may increase risk of torsades if physostigmine is given and bradycardia is induced)

Adverse effects:

- Cholinergic toxicity is expected to occur with inappropriate (i.e. non-antimuscarinic toxidrome), excessive dosing, or rapid dosing. Patients are at higher risk of adverse effects with rapid IV bolus and doses larger than 2 mg.
- Symptoms of cholinergic toxicity include the following:
  - 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 minutes following administration to monitor for adverse effects and to determine 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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The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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