

## Physostigmine

Many prescription and over-the-counter medications and numerous plants have anticholinergic effects. For some medications the anticholinergic properties are responsible for their therapeutic effects while for others the anticholinergic effects are considered adverse effects. These anticholinergic agents are competitive reversible antagonists of muscarinic acetylcholine receptors. Excessive doses and overdoses produce the anticholinergic toxidrome which includes dry skin, flushing, hyperthermia, thirst, dry mouth, mydriasis, tachycardia, hypertension, urinary retention, decreased bowel sounds, and delirium/hallucinations.

**Mechanism/Indications:** Physostigmine is used as an antidote for anticholinergic toxicity. It reversibly inhibits acetylcholinesterase by competitively binding to the enzyme in order to prevent it from degrading acetylcholine. This reversible inhibition of acetylcholinesterase boosts acetylcholine levels to overcome the anticholinergic toxicity. Structurally, physostigmine is a tertiary amine and crosses the blood-brain barrier to reverse both central and peripheral acetylcholine antagonism. Neostigmine, pyridostigmine, and similar drugs are not indicated for anticholinergic toxicity due to poor CNS penetration. Although physostigmine is not a first-line agent for anticholinergic toxicity, it is indicated to reverse agitation/delirium, combativeness and/or hallucinations refractory to benzodiazepines.

**Adverse Effects/Contraindications:** Contraindications include GI/GU obstruction, severe asthma or COPD, cardiovascular arrhythmias, ECG finding of sodium channel blockade (QRS prolongation and terminal R wave in AVR), overdose of any agent known to cause QRS prolongation (e.g. tricyclic antidepressants, procainamide, disopyramide, quinine) and overdose of other cholinesterase inhibitors (e.g. neostigmine, pyridostigmine, edrophonium, carbamate and organophosphate pesticides, nerve agents). Fatalities have been reported in patients with severe cardiac sodium channel toxicity given physostigmine. The patient should be evaluated with an ECG and should have a normal QRS interval in order to minimize adverse effects. Excessive or inappropriate dosing of physostigmine will produce cholinergic toxicity. This includes diaphoresis, diarrhea, excessive salivation, bradycardia, vomiting, miosis, cardiac arrhythmias, and bronchospasm. Atropine at half the physostigmine dose should be at the bedside to reverse cholinergic symptoms should they occur. Seizures may occur if physostigmine is infused too quickly.

**Dosing:** In adults (>12 y.o.), the recommended dose of physostigmine is 0.5-2.0 mg IV. In children ( $\leq$  12 y.o.) the recommendation is 0.02 mg/kg/dose IV (max single dose 0.5 mg). The drug should be given slowly over 3-5 minutes to prevent seizures. The dose can be repeated every 5-15 minutes until normal mental status is achieved or a maximum of 4 mg in adults and 2 mg in children are administered.

*(cont. on pg. 2)*

## Physostigmine (continued)

*For more on physostigmine:*

- Arens AM, Shah K, Al-Abri S et al. Safety and effectiveness of physostigmine: a 10-year retrospective review. *Clin Toxicol* 2018;45(2):101-107.
- Boley, SP, Olives TD, Bangh SA, et al. Physostigmine is superior to non-antidote therapy in the management of antimuscarinic delirium: a prospective study from a regional poison center. *Clin Toxicol* 2018 Jun 29;1-6.
- Howland MA. Antidotes in Depth: Physostigmine salicylate. In: Hoffman RS, Howland MA, Lewin NA Nelson LS, Goldfrank LR, editors: *Goldfrank's Toxicologic Emergencies*. 10<sup>th</sup> ed. New York NY, 2015;677-680.
- Dawson AH, Buckley NA. Pharmacological management of anticholinergic delirium-theory, evidence and practice. *Br J Clin Pharmacol* 2016;81(3):516-24.

March 2011 (revised February 2013, November 2018)