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## Toxicology Review

### Physostigmine as an Antidote

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#### Introduction:

Rapid treatment of patients with anticholinergic toxicity in the Emergency Department (ED) has remained problematic for many years. These patients are often agitated, uncooperative, and unable to provide a clear history. Physostigmine is a specific antidote for anticholinergic toxicity, yet its popularity has waned due to controversy surrounding its potential central nervous system and cardiac toxicities. In this brief review, we discuss physostigmine's history, method of action, indications, contraindications, dosing, and its use in the ED.

#### Background:

Physostigmine is a naturally-occurring compound first isolated from the extract of the West African Calabar bean (*Physostigma venosum*) in 1864. In the same year, a crude Calabar bean extract was first used as an antidote for anticholinergic toxicity among three prisoners ingesting belladonna.<sup>1</sup> Since that time, physostigmine has been used to treat glaucoma, post-operative ileus, and atropine-induced coma.<sup>2</sup> Physostigmine's popularity as an antidote grew in the late 1960s and 1970s, particularly for the treatment of altered mental status associated with tricyclic antidepressant poisoning.<sup>1,3</sup> A 1980 report of asystole complicating physostigmine use in two patients with serious tricyclic antidepressant poisoning<sup>4</sup> heralded a retreat from indiscriminate use of the antidote. More recently, opinion has shifted again towards favoring the cautious use of physostigmine as an antidote in selected cases of anticholinergic toxicity.<sup>5</sup>

#### Clinical Pharmacology:

Acetylcholine is a neurotransmitter that acts at muscarinic and nicotinic receptors of the cholinergic nervous system. Under normal conditions, the action of acetylcholine is quickly terminated by the enzyme acetylcholinesterase (AChE) found in the synaptic cleft. Drugs and other compounds that are typically classified as "anticholinergic" are actually antimuscarinic, since they block the effect of acetylcholine at muscarinic receptors within the central nervous system, in peripheral ganglia, and on effector organs of the autonomic nervous system, namely the exocrine glands (bronchial, sweat, lacrimal), and cardiac and smooth muscles. Such anticholinergic agents include many antihistamines, antiparkinsonian drugs, antipsychotics, antispasmodics, tricyclic antidepressants, belladonna alkaloids and compounds found in several other poisonous plants and fungi.<sup>6</sup>

Physostigmine is a carbamate that reversibly inhibits acetylcholinesterase. Physostigmine acts as a competitive substrate for AChE, allowing acetylcholine to accumulate in the synaptic clefts and overcome the blockade of muscarinic receptors by the anticholinergic agents. Because physostigmine is a tertiary amine, it is

uncharged, lipophilic, and easily crosses the blood-brain barrier.<sup>7</sup> This action allows physostigmine to reverse toxic CNS effects, whereas other carbamate drugs that are charged quaternary amines (such as neostigmine and pyridostigmine) will only reverse peripheral signs and symptoms. Physostigmine's ability to reverse central effects led to its trade name of Antilirium®, since it can reverse the delirium associated with anticholinergic toxicity.

#### Indications:

Physostigmine treatment may be indicated for patients with moderate to severe anticholinergic poisoning with evidence of both peripheral and central toxicity.<sup>8</sup> Physostigmine is not generally considered a first-line agent, and should probably be reserved for patients with potentially life-threatening complications of anticholinergic toxicity that are unresponsive to standard treatment regimens. Such complications include severe agitation, seizures, persistent hypertension, and hemodynamic compromise secondary to tachycardia (i.e. unstable narrow complex dysrhythmias).

In addition to a therapeutic role in clear-cut cases of anticholinergic poisoning, physostigmine also has a potential diagnostic role. In patients with altered levels of consciousness, who by relevant history and examination may be suffering from anticholinergic poisoning, a test dose of physostigmine may help to confirm the diagnosis. If the patient's mental status significantly improves, more invasive and time-consuming diagnostic tests, such as lumbar puncture and cranial computed tomography, may be avoided;<sup>5,9</sup> this is particularly true if the patient is then able to identify the substance ingested. One caution must be noted: physostigmine is an "analeptic" agent and may cause non-specific arousal when used in the presence of many drugs causing depressed mental status. Therefore, minor improvements in a patient's level of consciousness do not prove that they were poisoned with an anticholinergic agent.

#### Dosing and Precautions:

The initial dose of physostigmine is 1-2 mg in adults and 0.02 mg/kg in children administered slowly IV over at least 5 minutes. Many physicians are even more cautious, and utilize 0.5 mg aliquots, titrated slowly to desired effect. Rapid administration is associated with induction of seizures.<sup>2</sup> Because of its short half-life and rapid elimination, the clinical effects of physostigmine are short in duration. Repeat dosing every 20-60 minutes may be needed to correct the recurrence of life-threatening conditions initially treated with the first dose.<sup>8,9</sup> Continuous physostigmine infusions have been reported but are not recommended. Although effective in reversing anticholinergic toxicity, treatment with physostigmine can lead to adverse side-effects and complications. Excessive doses of physostigmine may induce cholinergic toxicity. Prior to administering physostigmine, reaction to potential complications should be anticipated. Urinary outlet obstruction can be prevented by the placement of a Foley catheter and bedside suction should be immediately available if needed to clear excess salivation, bronchial secretions, or emesis. The patient should also be placed on continuous electrocardiographic and pulse oximetry monitoring. Close physician supervision during and immediately following physostigmine administration is desirable. Atropine should also be rapidly available to counteract excessive cholinergic tone, and is administered IV at a dose equal to half the initial dose of physostigmine if such complications occur.<sup>6</sup> Serious but relatively infrequent complications, such as seizures, symptomatic bradycardia, and bron-

chospasm, have been associated with physostigmine treatment.<sup>1,2</sup>

#### Contraindications:

The contraindications to physostigmine use form one of the most controversial issues regarding the drug. Several conditions listed as contraindications are predictable, as enhancing cholinergic tone may exacerbate them, including asthma, chronic obstructive pulmonary disease, atherosclerotic heart disease, bradycardia, peripheral vascular disease, genitourinary and gastrointestinal obstruction.<sup>2,6,8</sup> Many sources list tricyclic antidepressant (TCA) overdose and prolongation of the QRS complex on the ECG  $\geq 0.10$  sec as absolute contraindications to physostigmine.<sup>8,9</sup> Use in these circumstances has been associated with severe bradyarrhythmias and asystole.<sup>4</sup>

The contraindication against physostigmine use in TCA overdose patients has reached the status of treatment dogma despite the fact that it is based on only a few case reports. We could find only 4 reported cases of asystole associated with physostigmine use if the setting of TCA overdose.<sup>4,9,10</sup> In contrast, numerous case reports and series have documented successful treatment of TCA overdose with physostigmine without serious cardiac side effects or complications, only a few examples of which are referenced here.<sup>1,2,3,6,7</sup> Indeed, physostigmine had been considered the treatment of choice for neurologic and cardiac complications of TCA overdose in the early 1970s.<sup>3</sup> This disparity most likely stems from several causes: 1) reporting bias, where positive outcomes are more likely to be submitted for publication, 2) the cardiotoxicity of TCAs was not as well understood in decades past, and the reversal of altered mental status appeared to be the primary therapeutic goal; 3) TCA overdose can present with a spectrum of disease, where mildly toxic TCA overdose patients may benefit from reversal of CNS anticholinergic effects, while seriously poisoned patients are more prone to severe bradyarrhythmias and asystole. The associated electrocardiographic contraindications to physostigmine rely on using the QRS complex as a surrogate marker for TCA toxicity,<sup>11</sup> where a prolonged QRS is presumed to represent a patient at risk for complications with physostigmine. Burns *et al.* recently reported 5 patients (from a larger case series) with known amitriptyline overdose who suffered no serious complications from physostigmine given to reverse anticholinergic effects. But even so, all these patients had ECGs documenting a QRS interval less than 0.10 seconds and were given physostigmine at least 12 hours after the initial ingestion.<sup>5</sup> Thus, it appears that TCA overdose alone is not an absolute contraindication to physostigmine use. It may still be prudent, however, to withhold physostigmine when there is any evidence of QRS interval prolongation.

#### Summary - Using Physostigmine in the ED:

Since physostigmine is relatively short-acting, and because many aspects of anticholinergic toxicity can be managed by standard treatment regimens (e.g. benzodiazepines for agitation or seizures), the ideal role of physostigmine in the ED has not been clearly determined. Physostigmine's primary role is probably as a back-up agent in cases where standard treatment fails for neurologic and cardiac complications of anticholinergic toxicity. Furthermore, physostigmine appears to have some benefit over benzodiazepines in the management of anticholinergic-induced agitation.<sup>5</sup> In some cases with features suggestive of anticholinergic toxicity but where the differential diagnosis remains broad, physostigmine may con-

firm the diagnosis and obviate the need for additional invasive or expensive testing. Further review and prospective analysis concerning its use in the setting of TCA overdose or QRS interval prolongation is needed to provide clear-cut contraindications. When used with proper precautions, however, physostigmine can be a valuable tool in the ED armamentarium.

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