INTRODUCTION

Physostigmine is a carbamate that reversibly inhibits cholinesterases in both the peripheral nervous system and the central nervous system (CNS). The tertiary amine structure of physostigmine permits CNS penetration and differentiates it from neostigmine and pyridostigmine, from the quaternary amines that have limited ability to enter the CNS. The inhibition of cholinesterases prevents the metabolism of acetylcholine, allowing acetylcholine to accumulate and antagonize the anticholinergic effects of xenobiotics such as atropine, scopolamine, and diphenhydramine. Although physostigmine previously was used as an antagonist to the anticholinergic effects of the cyclic antidepressants and the phenothiazines, this use is no longer recommended because of a poor risk-to-benefit ratio given the potential for exacerbation of life-threatening cardiotoxicity. A review of 30 years of the literature reassessed and questioned the contraindication to physostigmine use for cyclic antidepressant ingestions. The review concluded that the safety of physostigmine use for seizures or cardiotoxicity was difficult to predict, but the author still did not recommend physostigmine use in the setting of cyclic antidepressant toxicity. Similarly, physostigmine has a poor risk-to-benefit ratio in the management of presumed 3-hydroxybutyrate (GHB) toxicity. A study in rats given GHB revealed that physostigmine did not effect arousal but increased the risk of physostigmine-induced toxicities of fasciculations and seizures.

Atypical antipsychotics have complex pharmacologic effects. Although some atypical antipsychotics such as olanzapine have significant antimuscarinic side effects, the benefit of treating these anticholinergic effects with physostigmine in the often confusing overdose setting must be weighed against the potential risks of exacerbating cardiotoxicity.

HISTORY

The history of physostigmine dates to antiquity and the Efik people of Old Calabar in Nigeria. The chiefs in this area used a poisonous concoction made from the beans of an aquatic leguminous perennial plant found in the area to deliver the esere ordeal. Esere was the word used to represent both the bean and the ritual used to test the innocence or guilt of an accused person. They also believed that the esere had the power to detect and kill those persons practicing witchcraft. Supposedly, innocent persons quickly swallowed the poison, which caused immediate vomiting. Vomiting allowed them to survive without therapy or to be given an antidote of excrement in water. The guilty, however, hesitated swallowing, leading to speculation that sublingual absorption led to severe systemic symptoms without the benefit of vomiting. These persons were noted to develop mouth fasciculations and died foaming at the mouth. Daniell, a British medical officer stationed in Calabar, brought samples of the bean and the plant back to England in 1840. John Balfour, a professor of medicine and botany at the Edinburgh Medical School, is credited with characterizing the plant, which became known as Physostigma venenosum Balfour (family Leguminoseae) in 1857. The active alkaloid was isolated by Jobst and Hesse in 1864 and was named physostigmine. Independently, one year later Vee and Leven...
also isolated the active alkaloid and named it eserine. Christison performed the first toxicologic studies, including self-experimentation with increasing doses of the seed. Fraser, Christison's student and successor, originated the concept of antagonism from his experiments with physostigmine and atropine. Fraser plotted the dose relationships between the effects of atropine versus physostigmine on various organs such as the eye and the heart, demonstrating the antidotal effects of atropine for the lethal effects of physostigmine. Subsequent experiments with physostigmine led to the development of the theory of neurohumoral transmission. By the 1930s physostigmine was already used as a miotic for patients with glaucoma, a treatment for myasthenia gravis, for reversal of the paralytic effects of curare, an antidote to atropine, and an insecticide.

CHEMISTRY AND AFFINITY FOR CHOLINESTERASE

Figure 113–4 shows the general formula for carbamate inhibitors. shows the chemical structures of physostigmine (C₁₅H₂₁O₂N₃), a tertiary amine, and neostigmine, a quaternary amine. Like acetylcholine, physostigmine is a substrate for the cholinesterases (choline ester hydrolases), erythrocyte acetylcholinesterase and plasma cholinesterase. Both acetylcholine and physostigmine bind to cholinesterases to form a complex. Then a part of the substrate known as the leaving group (ie, choline for acetylcholine) is removed, and the remaining acetylated (for acetylcholine) or carbamoylated (for physostigmine) enzyme is hydrolyzed, regenerating the enzyme and freeing the acetate or carbamate groups, respectively (Figs. 113-2 and 113-3). For acetylcholine, the process is extremely quick, with a turnover time of 150 msec. In contrast, the half-life for hydrolysis of the carbamoylated enzyme is 15 to 30 minutes. The IC₅₀ (molar concentration that inhibits 50% of the enzyme) of physostigmine is 2.3 × 10⁻⁷ M for acetylcholinesterase, which is much weaker than for other carbamates at 1 × 10⁻¹⁰ M or many organic phosphorus compounds at 1 × 10⁻¹¹ M. Only the S-isomer inhibits cholinesterases, with plasma cholinesterase just a little more sensitive than acetylcholinesterase. Newer pharmaceuticals used in patients with Alzheimer disease show selectivity for the CNS and for acetylcholinesterase. They include tacrine, donepezil, and galantamine, which are reversible cholinesterase inhibitors, and rivastigmine, a pseudo-irreversible or slowly reversible inhibitor. These pharmaceuticals and neostigmine have undergone limited study for reversal of anticholinergic poisoning.
**PHARMACOKINETICS**

Physostigmine is poorly absorbed orally, with a bioavailability of less than 5% to 12%.\(^1\)\(^,\)\(^3\) Cholinesterases cleave the ester linkage, and very little physostigmine is eliminated unchanged in the urine. Pharmacokinetic parameters following IV administration of 1.5 mg over 60 minutes in nine patients with Alzheimer disease demonstrated the following: Vd 2.4 ± 0.6 L/kg; t\(_{1/2}\) 16.4 ± 3.2 minutes; peak serum concentration 3 ± 0.5 ng/mL; clearance 0.1 L/min/kg (7.7 L/min). There was a threefold inter individual variability in plasma physostigmine concentrations. Plasma cholinesterase concentrations demonstrated inhibition within 2 minutes of initiating the physostigmine infusion. The half-life of plasma cholinesterase inhibition was 83.7 ± 5.2 minutes, with full recovery within 3 hours of termination of physostigmine infusion. The effects on plasma cholinesterase inhibition lasted approximately five times longer than the half-life of physostigmine.\(^2\)\(^,\)\(^5\) All patients experienced varying degrees of diaphoresis, nausea, vomiting, headache, and generalized fatigue despite pretreatment with 2.5 mg methscopolamine.\(^2\)\(^,\)\(^2\)\(^5\)

**CLINICAL USE**

Physostigmine was first used as an antidote in 1864 to counteract severe atropine poisoning.\(^3\)3 Today its role is primarily in the treatment of antimuscarinic poisoning. More than 600 xenobiotics respond to physostigmine.\(^1\)\(^2\) Anticholinergics fall into the categories of antimuscarinic (atropine, scopolamine, propantheline, benztpine, trimethobenzyl), neuromuscular blockers (exemplified by curare), and ganglionic blockers (eg, trimethaphan). Other xenobiotics (eg, antihistamines, antipsychotics, and antidepressants) have anticholinergic properties that are not their primary therapeutic actions and are often considered adverse drug effects. The clinical use of physostigmine has varied over time.\(^4\)\(^1\) Owing to its ability to cause CNS arousal physostigmine was used in the 1970s to reverse the CNS effects of a large number of anticholinergics. It also was used inappropriately to treat toxicity from nonanticholinergics.\(^1\)\(^8\),\(^3\)\(^0\),\(^3\)\(^2\),\(^3\)\(^4\),\(^3\)\(^7\) The success with regard to anticholinergics is directly antidotal by virtue of its inhibition of cholinesterase. Effects of physostigmine on xenobiotics such as the benzodiazepines, opioids,\(^2\)\(^7\),\(^3\)\(^8\),\(^5\)\(^0\) and GHB\(^4\),\(^4\)\(^7\) result from either acetylcholine's direct action on the reticular activating system or interdependence of central neurotransmitters.\(^3\)\(^4\) Few serious adverse effects are reported.\(^4\)\(^9\) However, asystole followed administration of physostigmine in two patients with tricyclic antidepressant overdose.\(^3\)\(^5\) This occurrence led to the realization that toxicity from tricyclic antidepressants is complex and consists of more than just anticholinergic effects.\(^3\)\(^5\) Cyclic-antidepressant-induced sodium channel blockade causes myocardial depression, QRS interval prolongation, and ventricular dysrythmias. Physostigmine probably augments vagal effects, thus contributing to decreased cardiac output and cardiac conduction defects. A reevaluation must conclude that the risks of physostigmine use for xenobiotics that are not primarily antimuscarinic often outweigh any benefit. This analysis appears to hold true for reversing the effects of GHB (Chap. 80) as well.\(^4\)\(^7\) GHB is rarely used alone, and its effects are highly variable.\(^5\)\(^4\) Recovery from GHB typically occurs spontaneously in approximately 2 hours (16 min-6 h).\(^7\),\(^8\),\(^1\)\(^4\),\(^2\)\(^8\),\(^4\)\(^7\),\(^4\)\(^8\) Three patients in whom a presumptive diagnosis of GHB toxicity was made were treated with physostigmine.\(^7\) The three patients had an improved mental status within 5 to 15 minutes. One of these patients relapsed and then fully awakened 40 minutes later. This patient was incontinent of feces,
adverse effect likely caused by the physostigmine. A closer look at the patient descriptions reveals that all three improved with stimulation prior to physostigmine. Furthermore, justification for use based upon a study performed in the 1970s in the operating room at a time when GHB was first being evaluated as an anesthetic appears illogical when caring for those who illicitly use GHB. However, in cases of anticholinergic overdose, physostigmine use clearly is beneficial. A study of 52 patients showed that physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively, whereas benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. A shorter time to recovery following agitation was observed in those treated with physostigmine. No significant differences between these groups with regard to side effects and length of stay were noted.

INDICATIONS

Indications for physostigmine use include the presence of peripheral or central anticholinergic manifestations without evidence of significant QRS or QT prolongation. Peripheral manifestations include dry mucosa, dry skin, flushed face, mydriasis, hyperthermia, decreased bowel sounds, urinary retention, and tachycardia. Central manifestations include agitation, delirium, hallucinations, seizures, and coma. The peripheral and central findings usually occur simultaneously. In the early phases of overdose, finding only central manifestations is uncommon, although they often are more remarkable. The central findings may persist longer than the peripheral findings, particularly when a patient is recovering from an overdose of an antimuscarinic xenobiotic.

ADVERSE EFFECTS

An excess of physostigmine results in accumulation of acetylcholine at peripheral muscarinic receptors, nicotinic receptors (skeletal muscle, autonomic ganglia, adrenal glands), and CNS sites. Muscarinic effects produce stimulation of smooth muscle and glandular secretions in the respiratory, gastrointestinal, and genitourinary tracts and inhibition of contraction of most vascular smooth musculature. Nicotinic effects are stimulatory at low doses and depressant at high doses. For example, acetylcholine excess at the neuromuscular junction produces fasciculations followed by weakness and paralysis. Its effect on the CNS results in anxiety, dizziness, tremors, confusion, ataxia, coma, and seizures. Electroencephalograms (EEGs) demonstrate desynchronous discharges followed by higher-voltage discharges and a pattern similar to tonic clonic seizures. The cardiovascular effects are dose dependent and directly related to the presence of the diverse muscarinic and nicotinic effects. In addition to its inhibition of cholinesterase, physostigmine has a direct action on the nicotinic acetylcholine receptor ionic channel. Physostigmine toxicity results when physostigmine is used in the absence of antimuscarinic toxicity or when excess is administered with regard to the antimuscarinic xenobiotic. Patients overdosed with physostigmine should be managed with intensive supportive care, including mechanical ventilation if needed, intravenous atropine titrated to reverse bronchial secretions, and, rarely, pralidoxime to reverse skeletal muscle effects. Relative contraindications to physostigmine use include reversible airway disease, peripheral vascular disease, intestinal or bladder obstruction, intraventricular conduction defects, and atrioventricular block. Little information is
available regarding the effects of phystostigmine in pregnancy. Transient muscular weakness occurred in 10% to 20% of neonates whose mothers received anticholinesterase treatment for myasthenia gravis.\textsuperscript{31}

Drug interactions with cholinergic agonists (eg, ophthalmic pilocarpine), depolarizing neuromuscular blockers, or other anticholinesterases such as carbamates, organic phosphorous compounds, and pyridostigmine are expected to be at least additive when taken concomitantly with phystostigmine. The actions of xenobiotics metabolized by plasma cholinesterases such as cocaine, succinylcholine, or mivacurium are expected to be prolonged.

**DOSING**

The dose of phystostigmine is 1 to 2 mg in adults and 0.02 mg/kg (maximum 0.5 mg) in children intravenously infused over at least 5 minutes. The onset of action usually is within minutes.\textsuperscript{21} The dose can be repeated after 10 to 15 minutes if an adequate response is not achieved and muscarinic effects are not noted. Rapid administration may cause bradycardia, hypersalivation leading to respiratory difficulty, and seizures. Although the half-life of phystostigmine is approximately 16 minutes, its duration of action usually is much longer (often >1 hour) and is directly related to the duration of cholinesterase inhibition.\textsuperscript{3} After reversal of anticholinergic symptoms is achieved, additional doses may be required if clinical relapse occurs. The effective dose depends upon the ingested dose and duration of action of the antimuscarinic xenobiotic. Although a total of 4 mg in divided doses usually is sufficient in most clinical situations,\textsuperscript{16} significant inter individual variability exists. Atropine should be available at the bedside and titrated to effect should excessive cholinergic toxicity develop. A dose of atropine administered at half the phystostigmine dose is often recommended.

Phystostigmine is available as an ophthalmic ointment that can be applied topically to the conjunctival sac to produce miosis as treatment of acute angle-closure glaucoma. Miosis occurs within 10 to 30 minutes and persists for 12 to 48 hours.\textsuperscript{31}

**AVAILABILITY**

Phystostigmine is available in 2-mL ampules, with 1 mL containing 1 mg phystostigmine salicylate. The vehicle contains sodium metabisulfite and benzyl alcohol.\textsuperscript{36}

**SUMMARY**

Phystostigmine has been used extensively in the fields of anesthesiology, emergency medicine, and medical toxicology. The only evidence-based use of phystostigmine is for the management of patients with an anticholinergic syndrome, particularly those without cardiovascular compromise who have an agitated delirium and a normal QRS duration. In this population, phystostigmine has an excellent risk-to-benefit profile.

**REFERENCES**


