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A review on physostigmine: As antidote and treatment of Alzhemier disease

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ABSTRACT

Physostigmine is Anticholinesterase (AChE) agent belongs to the class of serine hydrolases. The active site of AChE comprises teo distinct regions an anionic site that possesses a glutamate residue and an esteratic site in which a histidine imidozole ring and a serine –OH group are particularly important. Physostigmine is tertiary amine derivative. Physotigmine is used in the treatment of myasthenia gravis, atony in the GI tract, and glaucoma. More recently, they have received attention as symptomatic drug treatments in patients suffering from Alzheimer disease. Physostigmine is another name is Eserine and Isopto- Eserine. Physostigmine is available in various salt forms like Physostigmine salicylate and Physostigmine sulfate. Physostigmine action of main site postganlionic parasympathetic junction and duration of action is medium. It is rapidly absorbed on oral or parental administration, crosses the blood brain barrier and exerts central cholinergic action. This paper reviews the pharmacological and pharmaceutical properties of Physostigmine.

KEYWORDS: Physostigmine, Reversible Anticholinesterase, Glaucoma, Alzhemier disease.

INTRODUCTION

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.[1] Since that time. Physostigmine has been used to treat glaucoma, post-operative ileus. And atropine-induced coma.[2] A 1980 report of asystole complicating physostigmine use in two patients with serious tricyclic antidepressant poisoning[4] heralded a retreat fi-om indiscriminate use of the antidote. More recently. opinion has shifted again towards favoring the cautious use of physostiglnine as an antidote in selected cases of anticholinergic toxicity.[5] Physostigmine is also used as an antidote at the poisoning by compounds with anticholinergic effect (e.g. atropine, scopolamine and imipramine) and tricyclic anti-depressants, as well as at the poisoning with anti-cholinergic organophosphates.[6.] Rapid treatment of patients with anticholinergic toxicity in the Ernergency Department (ED) has remained problematic for many years. These patients are often agitated. uncorperative, and unable to provide a clear history. Physostigmine is a specific antidote for anticholinergic toxicity. That 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 and contraindications, dosing and its use in the ED. Most anti-Alzheimer drug design studies directed at enzyme inhibition have sought compounds that inhibit acetylcholinesterase, but have little or no effect on butyrylcholinesterase. However, based on cited littérature suggestions that "inappropriate" butyryl cholinesterase activity increases the risk and/or progression of Alzheimer's disease[16]. 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.[1,3] Physostigmine is an acetyl cholinesterase inhibitor; it works by obstructing the enzyme responsible for Ach destruction in the synaptic cleft. Studies conducted more than 20 years ago suggested that Physostigmine could improve memory in peoples. Investigation of this property has been limited by the very short half-life of physostigmine. Various forms of administering the drug have been tried to overcome this problem, most recently a controlled-release (CR) oral formulation, and a skin patch. An additional limiting factor has been a high incidence of adverse effects, including nausea, vomiting and diarrhoea. Physostigmine appears to have no advantage over some newer anticholinesterase drugs. [10] The prototype carbarnate-derived acetylcholinesterase inhibitor is Physostigmine. Acetylcholinesterase (AChE) inhibitors are an important class of medicinal agents useful for the treatment of Alzheimer's disease, glaucoma, myasthenia gravis and for the recovery of neuromuscular block in surgery.

PHARMACOLOGICAL AND PHARMACOKINETIC ACTION

The Action of AChEs is due to amplification of endogenous Ach. As such they are qualitatively similar to those of directly acting cholinoreceptor stimulants. However, relative intensity of action on muscarinic, ganglionic, skeletal muscle and CNS sites varies among the different agents. Lipid-soluble agents (Physostigmine and organophosphates) have more marked muscarinic and CNS effects; stimulate ganglia but action on skeletal muscle is less prominent. Lipid-insoluble agents (Neostigmine and other quaternary ammonium compounds) produce more marked effect on the skeletal muscle (direct action on muscle endplate cholinoreceptors as well), stimulate ganglia, but muscarinic effects are less prominent[13].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 rnuscarinic 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 anticholincrgic agents include many antihistamines, antiparkinsonian drugs, antipsychotics, antispasmodics, tricyclic antidepressants, belladonna alkaloids and compounds found in several other poisonous plants and fungi[11]. Physostigmine is a carbamate that reversibly inhibits acetylcholinesterase. Physostiglnine acts as a competitive substrate for Ach, allowing acetylcholine to accumulate in the synaptic clefts and overcome the blockage of muscarinic receptors by the anticholinergic agents. Because physostigmine is a tertiary amine, it is uncharged, lipophilic, and easily crosses the blood-brain barrier [12]. This action allows Physostigmine to reverse toxic CNS effects, whereas other carbamated 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 Antiliriurn, since it can reverse the delirium associated with anticholinergic toxicity. Physostigmine is rapidly absorbed from gastrointestinal tract and parentral sites. Applied to the eye, it penetrates cornea freely. It crosses blood-brain barrier and its disposed after hydrolysis by cholinesterase[13].

KINETIC DATA

ABSORPTION

Between 5.2 and 11.7 percent of an oral dose of physostigmine was absorbed in three volunteers [7]. Physostigmine is readily absorbed from the gastrointestinal tract. Oral bioavailability is between 1 and 8 % [8].

VOLUME OF DISTRIBUTION (VD)

Is 15-75 l (46±19.5) [6]. According to other authors, Vd is in the range of 72 - 510 liters [8].

PEAK PLASMA CONCENTRATION

After 2 mg oral dose of physostigmine salicylate was reached at 30 minutes [7]. Following oral administration of 4 mg in a single healthy subject, peak serum levels occurred in 45 minutes falling to undetectable serum levels at 3 hours [8]. Time to maximum serum concentration after oral administration was 0.3 to 0.8 hours in one study [9].

PLASMA ELIMINATION HALF-LIFE

Is about 20 min

PASSAGE OF BLOOD-BRAIN BARRIER

Physostigmine permeates blood-brain barrier and enters the central nervous system (CNS).

TOXILOGICAL MECHANISMS

Acetylcholine (ACh) plays an important role as a neurotransmitter in the CNS and in the parasympathetic nervous system (PNS). At the high concentrations of ACh, neuromuscular transmission may be blocked and the adverse effects can occur [22]. In similarity with other anti-cholinergic agents, physostigmine is an inhibitor of the enzyme AChE, which catalyzes hydrolysis of ACh into choline and acetic acid. The following acute toxic effects can be produced: a) stimulation of muscarinic receptor responses at autonomic organs; muscarinic effects include nausea, vomiting, abdominal pain, diarrhea, increased salivation, perspiration and tearing, blurred vision (miosis), respiratory tract secretions, bradycardia and atrio-ventricular block; b) nicotinic receptor stimulation, followed by muscle twitching, weakness and paralysis; c) stimulation of cholinergic receptor sites in the CNS, following in severe cases by CNS depression, convulsions, coma, and death[22].

HUMAN TOXICITY

Physostigmine is an extremely toxic chemical even at very low oral doses of 1-2 mg. The systemic toxic effects by ingestion can include nausea, dispnea, coma, respiratory distress, blood pressure elevation, muscle weakness etc. Death from overdose is usually due to pulmonary edema and/or respiratory failure. Time to death may occur from 5 minutes to 24 hours in severely poisoned patients, depending on factors such as dose and route of exposure [23]. The usual adult dose is 0.5 to 2.0 mg [24]. The minimum lethal dose is 60 mg/70 kg person [25]. Poisoning can occur as a mistake in dosage or due to hypersensitivity of the patients; however, rare cases of the intentional poisoning have occurred. The therapeutic blood concentration level is in the range of 0.001-0.01 mg/l [26].

DOSING AND PRECAUTIONS

The initial dose of physostigmine is 1-2 mg in adults and 0.02 mglkg in children administered slowly IV over at least 5 minutes. Many physicians are even Inore cautious, and utilize 0.5 mg aliquots. titrated slowly to desired effect. Rapid administration is associated with induction of seizures[2]. 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 recul-rence of life-threatening conditions initially treated with the first dose [14,15]. Continuous physostigmine infusions have been reported but are not recommended. Although effective in reversing anticholinergic toxicity, treatment with physostignlinc can lead to adverse side-effects and complications. Excessive doses of physostigmine may induce cholinergic toxicity. Prior to administering physostigmine, rcaction to potential complications should be anticipated. Urinary outlet obstruction can be prevented by the placement of a Foley catheter and bedside selections 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 physostigrnine 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 [11]. Serious but relatively infrequent complications, such as seizures, symptomatic bradycardia, chospasm, have been associated with Physostigmine treatment [1,2].

INDICATIONS

Physostigmine treatment may be indicated for patients with moderate to severe anticholinergic poisoning with evidence of both peripheral and central toxicity[14].Physostigmine is not generally considered a first-line agent, and should probably be reserved for patient 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 dysrrhythmias). 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 tornogaphy, may be avoided;[5,15] this is particularly true if the patient is then able to identify the substance ingested. One caution must be noted physostigrnine is an "analeptic" agent and may cause non-specific arousal whcn 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.

CONTRAINDICATIONS

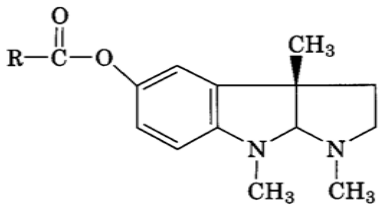
The contraindications to Physostigmine use form one of the most controversial issues regarding the drug. Several conditions listed as contraindications are predictable, as enhancing cholinergic tone may exacerbate them, including asthma, chronic obstructive pulmonary disease, atherosclerotic heart disease, bradycardia, peripheral vascular disease, genitourinary and gastrointestinal obstruction [2,11,14]. Many sources list tricyclic antidepressant (TCA) overdose and prolongation of the QRS complex on the ECG >0.10 sec as absolute contraindications to Physostigmine [14,15]. Use in these circumstances has been associated with severe bradyarrhythrnias and asystole[4]. 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 overdoses [4, 15, 27]. 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 [1,2,3,11,12]. Indeed, physostigmine had been considered the treatment of choice for neurologic and cardiac complications of TCA overdose in the early 1970s [3].

METABOLISM AND EXCRETION

Physostigmine is rapidly metabolized in the body, mainly by hydrolytic cleavage at the ester linkage by plasma esterases. With the exception of eseroline, which is a minor metabolite, the metabolites have not been identified in blood. Metabolism leads to the loss of pharmacological activity [24]. Very small amount of physostigmine is eliminated unchanged via urine [23].

SALT'S

Heptylphysostigmine (1a) is a more lipophilic homolog and is reported [17] to be less toxic than physostigmine, while retaining its in vitro acetylcholinesterase inhibiting potency. Phenserine (1b), a selective inhibitor of acetylcholinesterase with minimal effect on butyrylcholinesterase, was cited as a possible anti-Alzheimer drug [18].



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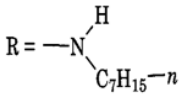

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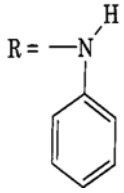

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PHYSOSTIGMINE SALICYLATE [USP]

The salicylate of physostigmine (eserine salicylate) may be prepared by neutralizing an ethereal solution of the alkaloid with an ethereal solution of salicylic acid. Excess salicylic acid is removed from the precipitated product by washing it with ether. The salicylate is less deliquescent than the sulfate. Physostigmine salicylate occurs as a white, shining, odorless crystal or white powder that is soluble in water (1:75), alcohol (1:16), or chloroform (1:6) but much less soluble in ether (1:250)[19,20]. On prolonged exposure to air and light, the crystals turn red. The red may be removed by washing the crystals with alcohol, although this causes loss of the compound as well. Aqueous solutions are neutral or slightly acidic and take on a red coloration after a period. The coloration may be taken as an index of the loss of activity of physostigmine solutions. Solutions of physostigmine salicylate are incompatible with the usual reagents that precipitate alkaloids (alkalies) and with iron salts. Incompatibility also occurs with benzalkonium chloride and related wetting agents because of the salicylate ion.

PHYSOSTIGMINE SULFATE [USP]

Physostigmine sulfate occurs as a white, odorless, microcrystalline powder that is deliquescent in moist air. It is soluble in water (1:4), alcohol (1:0.4), and ether (1:1,200)[21]. It has the advantage over the salicylate salt of being compatible in solution with benzalkonium chloride and related compounds.

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