Physostigmine

CAS: 57-47-6
MF: C₁₅H₂₁N₃O₂
MW: 275.3
Solubility: physostigmine is poorly soluble in water (1:90, salicylate); it is soluble in alcohol (1:25, salicylate; 1:1, sulphate).

Major uses
Physostigmine, also called eserine, is an alkaloid (tertiary amine) isolated from “Calabar beans”, which are seeds of the plant Physostigma venenosum from West Africa. Physostigmine is used in ophthalmology, in eye drops (in form of physostigmine sulfate), in combination with pilocarpine, for the lowering of intraocular pressure, in glaucoma.

Physostigmine is also used as an antidote at the poisoning by compounds with anticholinergic effect (e.g. atropine, scopolamine and imipramine) and tricyclic antidepressants, as well as at the poisoning with anti-cholinergic organophosphates [1].

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 [1].

The usual adult dose is 0.5 to 2.0 mg [2]. The minimum lethal dose is 60 mg/70 kg person [3]. 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 [4]. However, neither toxic nor lethal serum concentrations have been reported in the literature.

Kinetic data
Absorption: Between 5.2 and 11.7 percent of an oral dose of physostigmine was absorbed in three volunteers [5]. Physostigmine is readily absorbed from the gastrointestinal tract. Oral bioavailability is between 1 and 8 % [6].

Volume of distribution (Vd) is 15-75 l (46±19.5) [1]. According to other authors, Vd is in the range of 72 - 510 liters [6].

Peak plasma concentration after 2 mg oral dose of physostigmine salicylate was reached at 30 minutes [5]. 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 [6]. Time to maximum serum concentration after oral administration was 0.3 to 0.8 hours in one study [7].

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).

**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 [2].

**Excretion:** very small amount of physostigmine is eliminated unchanged via urine [1].

**Pharmacological mechanisms**
Physostigmine is used as antidote in organophosphate poisoning (e.g. poisoning with parathion, malathion and dichlorvos) because it binds to the enzyme acetylcholinesterase (AChE) reversibly and preserves the enzyme from irreversible phosphorylation by organophosphates. Physostigmine serves as alternate substrate for AChE [8].

**Toxicological 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 [8].

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 [8].

**Target organs:** CNS and PNS.

**References**

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