Eptastigmine: Ten Years of Pharmacology, Toxicology, Pharmacokinetic, and Clinical Studies

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ABSTRACT

Eptastigmine (heptyl-physostigmine tartrate) is a carbamate derivative of physostigmine in which the carbamoylmethyl group in position 5 of the side chain has been substituted with a carbamoylheptyl group. In vitro and ex vivo results suggest that eptastigmine has a long-lasting reversible brain cholinesterase (i.e., acetylcholinesterase and butyrylcholinesterase) inhibitory effect. When administered in vivo to rodents by various routes, eptastigmine inhibits cerebral acetylcholinesterases (AChE) and increases acetylcholine (Ach) brain levels by 2500–3000%, depending on the dose. This effect leads to an improvement in the cerebral blood flow in the ischemic brain, excitatory and inhibitory effects on the gastrointestinal tract and to a protection from acute soman and diisopropylfluorophosphate intoxication.

Eptastigmine, by either acute or chronic administration, has been found to have memory enhancing effects in different species of normal, aged and lesioned animals. It also restored to normal the age-related increase of EEG power without affecting spontaneous motor activity.

Clinical investigations on more than 1500 patients with Alzheimer’s disease demonstrated that eptastigmine significantly improved cognitive performance (as assessed by the cognitive subscale of the Alzheimer’s Disease Assessment Scale) as compared with placebo. This improvement was most evident in patients with more severe cognitive impairment at the baseline. The relationship between patient performance and average steady-state AChE inhibition was described by an inverted U-shaped dose-response curve.

Pharmacokinetic studies have revealed that after oral administration eptastigmine is rapidly distributed to the tissues and readily enters the CNS, where it can be expected to inhibit AChE for a prolonged period.

Eptastigmine is generally well tolerated and the majority of adverse events (cholinergic) were mild to moderate in intensity. However, the adverse hematologic (granulocytopenia) effects reported in two studies have resulted in the suspension of further clinical trials.