**Cholinesterase Inhibitors**

Anticholinesterase drugs provide the most commonly used means of producing sustained systemic cholinergic agonism. These drugs are used to reverse neuromuscular blockade, to treat myasthenia gravis, and to treat certain tachyarrhythmias.

The first anticholinesterase agent available was physostigmine (see earlier). There are currently three chemical classes of compounds used as cholinesterase inhibitors: carbamates, organophosphates, and quaternary ammonium alcohols. Neostigmine was first used as a gastrointestinal tract stimulant and later as a treatment for myasthenia gravis.

Physostigmine, neostigmine, and pyridostigmine are carbamates, whereas edrophonium is a quaternary ammonium alcohol. The cholinesterase enzyme is inhibited so long as the esteratic site is bound to an acetate, carbamate, or phosphate. Carbamate and phosphate bonds are much more resistant to attack by hydroxyl groups than are acetate bonds. The acetylated form lasts for only microseconds, whereas the carbamylated form lasts for 15 to 20 minutes. Organophosphates include diisopropylfluorophosphate, parathion, malathion, soman, sarin, VX, and a variety of other compounds used as insecticides. Although the toxicity of the organophosphate insecticides is primarily related to their anticholinesterase activity, the mechanism of this effect is different from the clinically used anticholinesterase drugs. The organophosphates produce an irreversible enzyme inhibition and have CNS effects as well. [**411**](javascript:parent.ShowReference('020509r00.htm#02014-411'))  Consequently, treatment of organophosphate insecticide poisoning relies on chemical compounds capable of displacing the insecticides from the enzyme and therefore of reactivating the cholinesterase activity. The best-documented of these chemicals is pralidoxime (2-PAM). Physostigmine and most of the organophosphates are not quaternary ammonium compounds and have major effects on cholinergic functions in the CNS.

Edrophonium is unique in that it lacks an acetate, carbamate, or a phosphate group. It acts because the positive charge of the nitrogen is attracted strongly by the anionic site and physically blocks the esteratic site. Thus, the edrophonium molecule is postulated to be held in place only by an ionic bond. The duration of inhibition provided by each molecule is short (e.g. milliseconds), but because they are not changed in the reaction, the molecules can hop onto and off the enzyme repeatedly and consequently render the enzyme unavailable to ACh.

Aside from reversal of neuromuscular blockade, there are few other therapeutic uses of these compounds. Because these compounds can increase the effect and duration of neurally released ACh, they are useful in situations in which such release is deficient, such as myasthenia gravis. Further, anticholinesterase drugs are occasionally used to stimulate intestinal function and topically in the eye as a miotic. An irreversible organophosphate anticholinesterase that is used clinically is echothiophate iodide (Phospholine), which is available as topical drops for the treatment of glaucoma. Its major advantage over other topical agents is its prolonged duration of action. Because this chemical also inactivates plasma cholinesterase, it may prolong the action of succinylcholine. Although prudence dictates discontinuation of echothiophate for 1 week prior to surgery, there are numerous case reports of successful anesthesia performed under emergency conditions.