

**NOVEL PRO-DRUG DERIVATIVES OF
PYRIDINIUM ALDOXIME TYPE
CHOLINESTERASE REACTIVATORS AND
PROCESS FOR PREPARING SAME**

BACKGROUND OF THE INVENTION

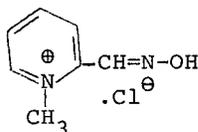
1. FIELD OF THE INVENTION

The present invention is directed to novel pro-drug forms of cholinesterase reactivators, and more specifically, the present invention is directed to pro-drug forms of pyridinium aldoxime type cholinesterase reactivators. A most representative member of this class of cholinesterase reactivators is 1-methyl-pyridinium-2-aldoxime iodide (or chloride or methanesulfonate), hereinafter referred to as "2-PAM."

As employed in this application, the term "pro-drug" refers to a derivatized form of a proven drug, for example, 2 PAM, which when administered to an individual, is enzymatically oxidized in the bloodstream, to the extent that the proven drug (2-PAM) is released at its therapeutic site or sites of activity and especially the brain.

2. DESCRIPTION OF THE PRIOR ART

2-PAM, chemically known as 1-methyl pyridinium-2-aldoxime is a white crystalline, water-soluble powder, usually employed in the chloride form, having the following formula:



Conventionally, the compound is employed in the form of its acid addition salt, such as, the chloride salt, the iodide salt, or the methanesulfonate salt.

Intoxication by anti-cholinesterase compounds may occur following accidental exposure to organophosphorus insecticides and other toxic chemical agents or even after administration of excessive amounts of drugs like neostigmine, normally employed for the management of glaucoma or myasthenia gravis. The pharmacologic effect of anti-cholinesterases is chiefly due to the inhibition of cholinesterase enzymes throughout the body. The search for satisfactory antidotes to counteract the effect of such toxic agents has led to a series of oxime derivatives of which 2-PAM appears to be the compound of choice, namely because of its physiologic compatibility, its excellent water solubility and its high oxime content per mole of compound. The most striking characteristic of the oxime is that it reactivates cholinesterase, which becomes inhibited by the anti-cholinesterase agent.

The pharmacologic effects of anti-cholinesterases, such as nerve agents (GB and VX), organophosphorus insecticides (Parathion), and quaternary ammonium compounds (neostigmine), may be ascribed to the inhibition of cholinesterase enzymes in the tissues, thereby resulting in cholinergic effects caused by the accumulation of acetylcholine in the effector organs. The chief actions of these compounds can be classified as follows:

1. Muscarine-like effect, manifested by nausea, vomiting, abdominal cramps, diarrhea, sweating, increased salivation, bronchial secretion, and bradycardia;

2. Effect on the central nervous system, characterized by anxiety, headache, and sometimes ataxia, coma, and convulsions; and
3. Nicotine-like effects, including as the most important one, muscular paralysis.

Severe poisoning by anti-cholinesterases results in paralysis of respiration by both central and peripheral effects, with consequent death unless prompt therapy is instituted.

While large doses of atropine abolish the muscarine-like effect, and partially alleviate the central nervous system manifestations of intoxication by the anti-cholinesterase compounds, the peripheral neuromuscular blockade (nicotine-like effect) is not appreciably diminished. See, R. V. Brown, et al., *J. Pharmacol. Exp. Therap.*, 120, 276, (1957); D. Grob, *Arch. Internal Med.*, 98, 221, (1956); and H. M. Kunkel, et al., *Proc. Soc. Exp. Biol. Med.*, 92, 529, (1956).

The neuromuscular blockade, attributable to the accumulation of acetylcholine at the motoneurone-plate, persists until partial restoration of cholinesterase activity of the muscle can be brought about. The effectiveness of oximes in treating anti-cholinesterase intoxication is attributable largely to their ability to overcome the neuromuscular blockade. The reversal of the neuromuscular blockade produced by alkyl phosphates is believed to be due to reactivation of muscle cholinesterase. See, D. Grob, and R. J. Johns, *Am. J. Med.*, 24, 497, (1958).

Many workers have demonstrated that cholinesterase inactivated by organophosphorus compounds may be reactivated "in vitro" by oximes. In studies with experimental animals, the actions of anti-cholinesterase agents on smooth, cardiac and skeletal muscles could be reversed by oximes, and in addition, their lethal effects reduced, although the effectiveness of the oximes will vary considerably in different species. See, B. M. Askew, *Brit. J. Pharmacol.*, 11, 417, (1956); R. V. Brown, *J. Pharmacol. Exp. Therap.*, 120, 276, (1957); R. Holmes, and E. L. Robins, *Brit. J. Pharmacol.*, 10, 490, (1955); H. Kewitz, et al., *Arch. Biochem. Biophys.*, 64, 456, (1956); and J. H. Wills, et al., *Science*, 125, 743, (1957).

In man, the intravenous dose of 2-PAM (as the iodide) required to alleviate the toxic effect of a nerve agent, such as G. B. (Sarin) has been reported to be in the range of 14 to 28 mg./Kg. of body weight. See, D. Grob, and R. J. Johns, *Am. J. Med.*, 24, 497, (1958). Consequently, since 1.4 g. of the iodide are equivalent in oxime content to 1 g. of the chloride, the corresponding intravenous dose of 2-PAM chloride is 10 to 20 mg./Kg. of body weight. See, A. A. Kondritzer, et al., *J. Pharm. Sci.*, 50, 109, (1961).

Zvirblis has studied the distribution of 2-PAM in serum and tissues of rabbits. The greatest concentration of 2-PAM found in the kidney. In man, 2-PAM is eliminated primarily via the kidney. See, P. Zvirblis, unpublished data, U.S. Army Chemical Research and Development Laboratories. Following an intravenous dose of 15 mg. of 2-PAM per Kg. of body weight, the half-life in man has been found to be about 0.8 hours. See, B. V. Jager, and G. N. Stagg, *Bull. Johns Hopkins Hosp.*, 102, 203, (1958). Approximately 80% of the compound was excreted during the first 6 hours, and most of the unchanged oxime was found in the urine within the first 30 minutes. 2-PAM was not found to be bound appreciably to human serum protein, nor for that matter, to enter the erythrocytes.