

1

3,629,425

STABILIZED 2-PAM SOLUTIONS

Anwar A. Hussain, Plattsburg, N.Y., assignor to American Home Products Corporation, New York, N.Y.

No Drawing. Filed Nov. 14, 1968, Ser. No. 775,911

Int. Cl. A61k 27/00

U.S. Cl. 424-263

11 Claims

ABSTRACT OF THE DISCLOSURE

There are disclosed herein concentrated aqueous solutions of 2-PAM salts with mineral acids optionally also containing up to 0.5 percent of atropine, stabilized by addition of mineral acid to a final pH of 1.0 to 3.0. Solutions of 2-PAM salts with or without atropine stabilized in this manner are many times more stable than solutions prepared in the conventional way.

This invention relates to the preparation of concentrated 2-formyl-1-methylpyridinium oxime (2-PAM) salt solutions intended for parenteral administration and possessing adequate stability for this purpose. More particularly, this invention relates to the stabilization of 2-PAM salt solution containing at least 10% w./v. of the 2-PAM salt, and from 0 to 0.5% w./v. of atropine sulfate. These solutions are intended for human use as antidotes in cases of acute poisoning arising from accidental or intentional exposure to various cholinesterase inhibitors.

A number of organophosphate compounds are being used presently in agriculture as potent insecticides. Moreover, several of the most potent chemical warfare agents, known as nerve gases, are organophosphates. The organophosphates generally enter the body by absorption through the lungs, gastrointestinal tract or skin; as a result of inhalation of dusts or aerosols, ingestion of liquid sprays or concentrates, or skin contact. Once in the body the organophosphates react with cholinesterase to yield a phosphorylated cholinesterase which is no longer capable of hydrolyzing acetylcholine. The resulting abnormal accumulation of acetylcholine in the body gives rise to both muscarinic and nicotinic effects, leading to eventual paralysis of the respiratory system and death.

Two medicinal agents have been found useful in counteracting the effects induced by cholinesterase inhibitors. Atropine sulfate, used at a dose of 2 to 4 mg., has been shown to be effective in overcoming the muscarinic effect at the ends of the postganglionic nerves, but does not affect the neuromuscular block leading to respiratory failure. On the other hand, 2-PAM salts, used in doses ranging from 0.2 gm. to 8 gm. depending upon degree of exposure to the cholinesterase inhibitor, have been shown to augment atropine therapy by effectively regenerating inactivated cholinesterase. Regeneration of inactivated cholinesterase by 2-PAM has been demonstrated both in vitro and in vivo, and arises from preferential attack by the 2-PAM moiety on the bond between cholinesterase and the phosphate grouping, resulting in hydrolysis of the inactive specie to yield the parent active cholinesterase and non-toxic phosphates. Thus, in cases of severe organophosphate poisoning the treatment of choice is a combination of atropine sulfate and 2-PAM salt, used at an appropriate dose level.

Once body cholinesterase is inactivated through exposure to and reaction with organophosphates, the phosphorylated enzyme undergoes further reaction with time, known as "aging." This aging phenomenon is believed to be due to dealkylation of the phosphate ester, the resulting compound being much more resistant to hydrolysis by 2-PAM salts. Thus it is imperative that severe cases of organophosphate poisoning be treated as quickly as

2

possible in order to minimize the "aging" effect and thus obtain maximum regeneration of cholinesterase. Because of the relatively rapid onset and severity of symptoms arising from overexposure to organophosphates, and the irreversible aging of the phosphorylated enzyme, therapeutic blood levels of the antidote must be obtained as soon after exposure as possible. The results of blood level studies in man indicate that incomplete absorption of 2-PAM occurs from the gastrointestinal tract and that oral administration to obtain a therapeutic blood concentration requires a considerably larger dose than that needed with parenteral routes. Furthermore, it has been demonstrated that peak blood levels are obtained immediately with intravenous administration, within fifteen minutes following intramuscular administration, but only after two to four hours following oral dosing. Thus, the administration route of choice for both atropine and 2-PAM is by intravenous or intramuscular injection, and parenteral dosage forms of these important antidotes are required for this purpose.

Suitable parenteral forms must possess pharmaceutical elegance, must be well tolerated by the patient, and should possess adequate chemical stability. The latter criterion depends on a number of factors including storage temperature and shelf-life desired. Since 2-PAM dosage forms are intended for emergency use only, and hopefully only rarely at that, turnover of stocks will be slow. Because of rarity of use, there is a tendency to overlook expiry date. On the other hand, these dosage forms must be entirely capable of eliciting the desired effects at the critical moment of need. Thus, for maximum safety to the patient, these forms must possess extremely good chemical stability, even at the elevated temperatures to which they might conceivably be exposed during storage.

R. I. Ellin et al. (*J. Pharm. Sci.*, 51, 141 (1962)) and Fan et al. (*J. Pharm. Pharmacol.*, 16, 493 (1964)) have studied the Kinetics of 2-PAM degradation in dilute (0.002% to 0.2% w./v.) solution. R. I. Ellin et al. have shown that at pH 4.3 these solutions possess maximum stability with a chemical half-life of 60 years at 25° C. These authors have also shown that as pH deviates from this optimum value in either direction stability is significantly reduced, the degree of reduction being directly related to the magnitude of deviation. While the stability of these dilute 2-PAM solutions at pH 4.3 would be considered quite acceptable for a 2-PAM dosage form, the concentration tested would require injection of large volumes of solution in order to obtain the dosage required for therapeutic effect. Attempts to prepare more concentrated solutions have resulted in a realization that stability decreases as concentration is increased.

De Luca, P. and Lachman, L. in Belgian Pat. No. 677,444 have described the incorporation of antioxidant agents into concentrated 2-PAM solutions for the expressed purpose of stabilizing the solutions. While antioxidants do minimize the darkening of 2-PAM solutions arising from oxidation of the hydrolytic degradation products, they are not effective in decreasing the rate at which these hydrolytic reactions occur. The hydrolysis reaction becomes so pronounced in the concentration range required for practical dosage that a permanent solution dosage form has been considered not possible due to lack of adequate chemical stability. As a consequence of these findings, the presently available parenteral dosage forms of 2-PAM are supplied as a stable dry powder which must be reconstituted with a suitable diluent at the time of use.

The discovery that certain gaseous organophosphates are extremely potent cholinesterase inhibitors and thus toxic to humans resulted in their development as potential warfare agents. This development then stimulated search for antidotes which could be used by military per-