

NERVE GAS ANTIDOTE

The present invention relates to an oral prophylactic useful for minimizing injury from nerve gas poisons and related compounds such as organophosphorus pesticides.

BACKGROUND OF THE INVENTION

Nerve gas poisons are organic esters of substituted phosphoric acids. They inhibit cholinesterase enzymes and therefore are classified as anticholinesterase agents. Three active agents include Tabun (ethyl phosphorodimethylamidocyanidate— $((\text{CH}_3)_2\text{N})\text{P}(\text{O})(\text{C}-\text{N})\text{OC}_2\text{H}_5$ —GA), Sarin (isopropyl methylphosphonofluoridate— $\text{CH}_3\text{P}(\text{O})(\text{F})\text{OCH}(\text{CH}_3)_2$ —GB) and Soman (pinacolyl methylphosphonofluoridate— $\text{CH}_3\text{P}(\text{O})(\text{F})\text{OCH}(\text{CH}_3)\text{C}(\text{CH}_3)_3$ —GD). These compounds are highly volatile and easily disseminated in vapor form. They are readily absorbed through the lungs and eyes, and also the skin and intestinal tract without producing any irritation or other sensation. They are sufficiently potent that even brief exposure may be fatal. Depending on the concentration of the poison, death may occur in as little as one minute, or it may be delayed for 1–2 hours.

Another category of such agents is the V agents, which are more potent, including VX.

Chemically related insecticides include parathion, methyl parathion and malathion, and these exhibit similar toxicity, although they are generally less potent.

Known treatments for these agents include medications which are administered after exposure to the poisons, such as atropine. Prophylactic agents have been investigated, but, in spite of intensive research, only a small number of agents have been identified which offer effective and safe protection against these agents.

Published German Patent Application DE 28 21 778 discloses a prophylactic antidote for organophosphorus pesticides which protects agricultural workers against lethal pesticides during the course of one workday. The agent administered includes hyoscine butyl bromate, a propanol chlorhydrate, dimethyl-carbamoxy-phenyl-trimethyl ammonium bromate and ephedrine. Leadbeater et al, *Fundamental and Applied Toxicology* Vol. 5, pages S225–S231 (1985) disclose a prophylactic pretreatment comprising an injection with a carbamate and anti-cholinergic drugs such as Aprophene (2-diethyl-aminoethyl- α - α -diphenylpropionate), Hyoscine, Adiphenine, Caramiphen, Dicyclomine and G 3063 (N-methyl-4-piperidiny phenylcyclopentanecarboxylate). Carbamates which are mentioned included pyridostigmine and physostigmine. The authors also demonstrated the combined effect of pretreatment with pyridostigmine or physostigmine, with and without Atropine and post-treatment with a variety of other medications (atropine, P2S and diazepam).

There is a need for more effective prophylactic pretreatments for the foregoing toxic agents. It is desirable to protect against twice the toxic dose, since this is thought to be the maximum possible field concentration. It is desirable that the treatment be administered orally, rather than by injection, that it provide protection for a long time, 10–12 hours, and that treatment can be repeated during an extended period of time, for example 5 days (10 doses) without severely diminishing the patients ability to function or fight in a combat environment.

SUMMARY OF THE INVENTION

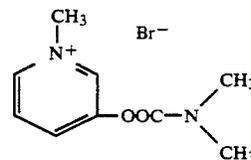
The present invention provides a prophylactic pretreatment which can be administered orally and which comprises the following agents, in combination:

- a. Pyridostigmine (pyridostigmine bromide) or physostigmine
- b. Diazepam or clonazepam
- c. G 3063, Arpenal, Sycotrol (pipetabonate hydrochloride), caramiphen (caramiphen hydrochloride) or benactyzine (benactyzine hydrochloride).

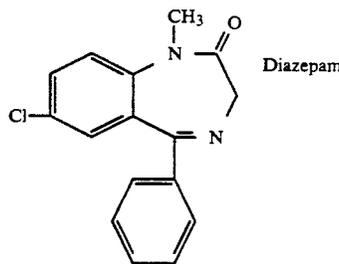
These agents are administered in the form of a capsule which contains, for example, tablets, one a normal release dosage form and one or two in a slow release dosage form. Based on the biological half life of the substances in humans and the desired duration of protection, the components are distributed between the normal release component and the slow release component in the following total amounts:

- a. 30–60 mg pyridostigmine or 0.5–2.0 mg physostigmine
- b. 3–5 mg diazepam or 0.5–2.0 mg clonazepam
- c. 3–8 mg G3063, 5.0–15 mg arpenal, 2–10 mg sycotrol, 5.0–15 mg caramiphen or 3–20 mg benactyzine.

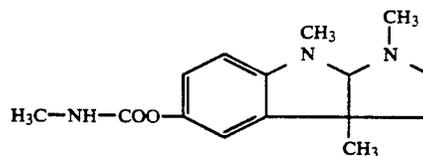
The formulas of these compounds are shown below:



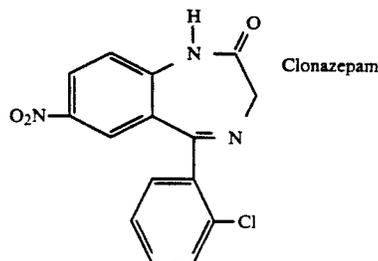
pyridostigmine



Diazepam



Physostigmine



Clonazepam