METHOD OF TREATING ORGANOPHOSPHOROUS POISONING

This patent application is a U.S. national phase application of International Patent Application No. PCT/US2005/033789, filed Sep. 23, 2005, which claims the benefit of U.S. Provisional Patent Application No. 60/613,121, filed Sep. 24, 2004, the contents of which are incorporated herein by reference in their entireties.

STATEMENT OF GOVERNMENT SUPPORT

The invention described herein was made, at least in part, with funding from the U.S. Army under Grant No. DAAD19-02-D-0001, with funding from the U.S. Army Medical Research and Development Command under Contract No. DAMD17-95-C-5063, with funding from the National Institutes of Health under U.S. Public Health Service Grant No. NS25296, and with funding from the National Institute of Environmental Health Sciences under Training Grant No T32 ES07263. Therefore, the United States of America has certain rights in the invention.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a method of treating organophosphorous poisoning in an animal, in particular a mammal, specifically a human.

BACKGROUND OF THE INVENTION

Organophosphorous compounds (OPs), due to their physical state and high lipophilicity, rapidly penetrate and accumulate in the central nervous system (CNS). OP poisoning of military personnel on the battlefield and of common citizens in the event of a terrorist attack with nerve gas, for example, has caused an increase in concern for public and governmental authorities around the world in recent years. In addition, increased demands for food and ornamental crops have resulted in an increase in the use of toxic anti-cholinesterase (anti-ChE)-based pesticides, including OPs such as parathion and malathion, in developed and developing countries. This has resulted in an increase in the accidental poisoning of farmers and gardeners.

It has long been known that the main toxic effects of OPs and other anti-ChE agents result from the inhibition of the enzyme ChE, which is responsible for the inactivation of the neurotransmitter acetylcholine (ACh) in the CNS and peripheral nervous system (PNS), thereby abnormally increasing and prolonging muscarinic and nicotinic cholinergic responses. Unfortunately, current methods to treat or prevent the toxic effects of OPs are still far from acceptable, particularly in the event of acute exposure to nerve agents that are highly absorbable and readily accessible to the brain.

Reversible ChE inhibitors, such as pyridostigmine bromine (PB), physostigmine, and huperzine, have been tested as antidotal therapy against OP poisoning. PB has been used as a preventive treatment by soldiers in the field. While it is a powerful anti-ChE agent, its action is mostly limited to the PNS, due to the fact that it is a charged molecule that hardly penetrates the CNS. Therefore, PB does not effectively confer protection of brain ChE against nerve gases. Physostigmine is more effective than PB, but less safe. Therefore, there currently is no method of protecting the brain from irreversible ChE inhibition by OPs. Rather, those individuals, who have been exposed to OP, have been treated post-exposure with antimuscarinic agents, such as atropine, ChE reactivators, such as oximes, e.g., pyridine-2-aldoxime (2-PAM), and anticonvulsants, e.g., Diazepam.

In view of the above, it is an object of the present invention to provide a method of treating OP poisoning. This and other objects and advantages, as well as additional inventive features, will become apparent from the detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a method of treating OP poisoning. The method comprises administering to a mammal at risk for OP poisoning an OP poisoning-inhibiting amount of galantamine, whereupon the mammal is protected from OP poisoning upon exposure to an OP.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated, at least in part, on the surprising and unexpected discovery, that a tertiary alkaloid, such as galantamine, can be administered to an animal, in particular a mammal, specifically a human, at risk of OP poisoning to protect the animal from OP poisoning. While galantamine is a weaker ChE inhibitor as compared to PB and physostigmine, it is a non-charged molecule and, therefore, has the ability to pass through the blood-brain barrier. Galantamine also functions as an allosteric potentiating ligand (APL) of nicotinic receptors (nAChRs), and is able to "rescue" some nicotinic receptors from desensitization. This property is important in the context of OP poisoning when excess ACh induces massive desensitization of nAChRs.

In view of the above, the present invention provides a method for antidotal therapy of OP poisoning. The method comprises administering to a mammal at risk for OP poisoning an OP poisoning-inhibiting amount of galantamine, whereupon the mammal is protected from OP poisoning upon subsequent exposure to an OP. The galantamine can be administered to the mammal before or after exposure to an OP. If galantamine is administered before exposure, the method further comprises subsequently administering to the mammal an effective amount of an antimuscarinic agent, such as atropine. If galantamine is administered after exposure, the method further comprises administering an effective amount of an antimuscarinic agent, such as atropine, after exposure to an OP and prior to or simultaneously with an OP-poisoning inhibiting effective amount of galantamine. Preferably, the antimuscarinic agent and galantamine are administered as soon as possible after exposure to an OP in order to maximize the effectiveness of the post-treatment. Depending on the timing of subsequent administration of the antimuscarinic agent and galantamine in relation to the time of exposure to an OP, this embodiment can have therapeutic effects as well.

A mammal is at risk for OP poisoning if it is currently exposed to or is at risk of being exposed to a level of OP that is sufficiently high to poison the mammal. Such risk exists for military personnel on the battlefield, common citizens in the event of a terrorist attack with nerve gas, and farmers and gardeners who work with food and ornamental crops treated with anti-ChE-based pesticides.

An amount of galantamine is an "OP poisoning-inhibiting amount" or an "effective amount" when it is sufficient to diminish significantly, preferably completely, the detrimental effects of exposure to OPs as evidenced by signs of ill health, including but not limited to, any peripheral and central hypercholinergic signs of OP intoxication, such as hypersecretion, muscle contraction, respiratory difficulties, convulsion, or