Review Article

Recent Advances In Treatment of Acute Organophosphorous Nerve Agents Poisoning

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Abstract

Organophosphorous (OP) chemical warfare nerve agents mainly sarin and tabun were used during the Iran-Iraq war with high mortalities. In addition to atropine and oximes, the followings have recently been used successfully for the treatment of OP poisoning.

1. Sodium Bicarbonate: Infusion of high doses of sodium bicarbonate (5 mEq/kg in 60 min. followed by 5-6 mEq/kg/day to obtain arterial blood pH of 7.45 to 7.55) revealed positive effects in patients with acute OP poisoning in Mashhad.

2. Magnesium Sulfate: Intravenous magnesium sulfate in a dose of 4 g only on the first day after admission was also effective in acute human OP poisoning.

3. Antioxidants: The toxicity of OP compounds is mediated by generation of nitric oxide and other free radicals. These toxic molecules can be counteracted by antioxidants such as vitamins C and E, spin traps, melatonin and low molecule weight thiols. The latter compounds can also increase the synthesis of glutathione, which can both ameliorate the OP-induced oxidative stress and enhance OP detoxification.

It is concluded Sodium bicarbonate, Magnesium sulfate and the antioxidants should be added to the standard treatment of OP poisonings.

Keywords: Organophosphorous; acute poisoning; chemical warfare nerve agents; Sodium bicarbonate; Magnesium sulfate; Antioxidants.

Introduction

Nerve agents are organophosphate compounds, similar to organophosphate pesticides, but a group (lethal agents) of chemical warfare agents. They are extremely potent inhibitors of the enzyme acetylcholinesterase, a key regulator of cholinergic neurotransmission.

Nerve agents are divided into two groups of G and V agents. The G agents are fluorine

compounds of organophosphate except for tabun (GA), which is a cyanide compound of organophosphate. The V agents are sulfur containing organophosphate compounds. The principal G agents; GA, GB and GD have common names of tabun, sarin and soman, respectively.

Although G agents and V agents are commonly called nerve gas, they actually exist under temperate conditions as clear colorless, viscous liquids with high boiling points. They become aerosolized when dispersed by spraying or by explosive blast from a shell or bomb. The G agents are moderately

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volatile (vapor pressure of less than 2 mm Hg at 20 °C), but due to their great toxicity, the vapor poses a significant inhalation hazard. Vapor pressure of the G agents is sufficiently high for the vapor to be lethal rapidly. GB is mainly a vapor hazard, but VX is less volatile and is normally a liquid contact hazard. Delivery systems of nerve agents are bombs, missiles, cluster spray and spray tanks. G agents spread rapidly on surfaces such as skin. They disperse within several hours and are described as non-persistent agents, whereas VX spreads slowly and remains in the place for weeks or longer after exposure and thus called a persistent nerve agent. Clothing releases G agents for about 30 minutes after contact with vapor (1).

Nerve agents are four to six times denser than air. As a result, they tend to remain close to the ground and pose a risk particularly to the people in low areas and below ground shelters. They are soluble in water as well as organic solvents and fat. After contact with water, they are hydrolyzed to products that are less toxic than the parent compounds (2).

Objectives

Chemical warfare nerve agents have similar chemical structures and the same mechanisms of toxicity as organophosphorous pesticide poisoning (OP). Since OP pesticide poisoning are so common in developing countries, particularly in I.R. Iran, there have been advancements in treatments of this poisoning that could be applicable to OP nerve agent poisoning.

Toxicity

The vapor pressure of the three G-agents (GA, GB and GD) makes them significant inhalation hazards, especially at warmer temperatures or when droplets are created by explosion or spray. Based on information from animal studies, the lethal inhaled dose of G-agents in humans may be about 1mg. The G-agents also represent a skin contact hazard, particularly when evaporation is minimized and contact is prolonged by contamination of clothing. However, the percutaneous absorption of G-agents is much less rapid and complete than the inhalation form (1).

VX does not pose a major inhalation hazard under usual circumstances, but it is well absorbed through the skin (1). The relative lethality as determined in animal studies is VX>Soman>Sarin>Tabun (3).

The acute toxicity of nerve agents is due primarily to irreversible inactivation of AChE leading to an accumulation of toxic levels of acetylcholine. Like other OP compounds, these agents act by binding to a serine residue at the active site of a cholinesterase molecule, thus forming a phosphorylating protein that is inactive and incapable of breaking down acetylcholine. The resulting accumulation of toxic levels of acetylcholine at the synapse, initially stimulates and then paralyses cholinergic synaptic transmission. Cholinergic synapses are found in the central nervous system, at the termination of somatic nerves, in the ganglionic synapses of autonomic nerves, at the parasynaptic nerve endings such as those in the sweat glands (4).

The rate of aging varies greatly among the nerve agents. The half-time of aging is within minutes after soman exposure, about five hours after sarin exposure and >40 hours after exposure to tabun and VX (3).

Acute exposure to tabun, sarin and/or soman alters brain levels of cyclic AMP and cyclicGMP as a result effects of adenylcyclase and phosphodiesterase systems (5,6). VX at 10 micro M produced significant reduction in cell metabolism within two minutes as measured by changes in the acidification rate of medium after four hours of exposure. Two alkali degradation products of VX produced no cytotoxicity (7).

The nerve agents cause pathological effects mainly by interfering with cholinergic synaptic function. This effect occurs at cholinergic neuroeffector functions (muscarinic effects), at the skeletal myoneural junctions and autonomic ganglia (nicotinic effects) and in the central nervous system.

Clinical manifestations

The signs and symptoms of nerve agent poisoning are classified below according to whether they are due to overstimulation of muscarinic, nicotinic or central nervous system receptors.

Muscarinic effects of acetyl choline stimulation include: miosis, blurred vision, eye pain, hypersecretion by salivary, sweat, lachrymal and bronchial glands, bronchoconstriction,

cough, cyanosis, pulmonary edema, nausea, vomiting, diarrhea, crampy abdominal pains, tenesmus, urinary and fecal incontinence, hypotension and bradycardia.

Nicotinic effects include easy fatigue, weakness, muscle cramp, fasiculations, skeletal muscle twitching, convulsions and flaccid paralysis. Nicotinic stimulation also can obscure muscarinic parasympathetic effects and produce mydriasis, tachycardia and hypertension by stimulation of the adrenal medulla.

Central nervous system effects include: irritability, nervousness, giddiness, ataxia, fatigue, generalized weakness, depression of respiratory and circulatory centers with dyspnea, cyanosis, hypoventilation and hypotension, lethargy, impairment of memory, confusion, convulsions, coma and respiratory depression (4, 5, 8-10).

Diagnostic considerations

Initial diagnosis of nerve agent poisoning can be made based on the history exposure (accidentally, terrorism, chemical warfare attack) and clinical manifestations. In low-level exposure, the route of absorption may affect the clinical features, but in high-level exposure, severe intoxication occurs, although the occurrence time is faster through inhalation than by skin absorption by both routes may occur. Estimation of acetylcholinestrase in erythrocytes is required to confirm the anticholinesterase diagnosis and to estimate severity of intoxication. Butyrylcholinestrase estimation may also help, although it is not specific and may be low due to genetic variations (11).

Diagnosis of a certain nerve agent requires toxicological analyses of the environmental and/or blood samples for the nerve agents. A biosensor which is a potentiometer enzyme electrode for direct determination of organophosphate nerve agent was developed (12).

A fiber-optic enzyme biosensor for the direct measurement of organophosphate nerve agents was also developed. Concentrations as low as 2 μM can be measured in less than 2 minutes using the kinetic response. When stored in buffer at 4°C, the biosensor shows long-term stability (13). A new method for retrospective detection of exposure to organophosphate nerve agents was applied to estimate serum sarin concentrations of the Matsumoto incident. The concentrations ranged 0.2-4.1 ng/ml serum (14). Definitive evidence for the acute sarin poisoning of the Tokyo subway was made by detecting sarin-hydrolyzed products from erythrocytes of four victims in postmortem examinations (15).

Although diagnosis of an anticholinesterase may be sufficient for the management and administration of atropine, oxime therapy requires the recognition of the agent (16). Cholinesterase activity in post mortem blood as a screening test for organophosphate nerve agent exposure was performed in 53 nonpreserved post mortem whole blood specimens. There was a negligible loss of cholinesterase activity by the seventh day of the study. It could therefore be applied as the screening test for anticholinesterase nerve agents (17).

Diagnosis of the delayed neurotoxic effects can be made by estimation of neuropathy target esterase (NTE), although it is unlikely to occur following the nerve agents poisoning. Marked reduction of the neurotrophic factor (ornithine decarboxylase) during the early stages of the neurotoxicity may also be helpful where it will be possible to perform (18).

Treatment

Priorities: The first rule for managing chemical casualties is that the emergency responders must protect themselves from contamination resulting from contact with casualties and the environment. This can be done by approximate personal protective equipment or by thoroughly decontaminating the patient. At minimum, rescuers should wear a protective mask (or mask containing a charcoal filter for a SCBA device, not a surgical or similar mask) and heavy rubber gloves (surgical gloves offer negligible protection) and avoid skin contact with victims until decontamination has been carried out (4,19).

As soon as possible victims should be removed from the contaminated place, and decontamination must be initiated. Antidotes should be given at the onset of effects as appropriate (e.g. autoinjector containing atropine, obidoxime and diazepam). For unconscious or severely intoxicated patients, priorities must

follow the ABCs of resuscitation. Oxygen administration and assisted ventilation should be undertaken as soon as possible in those with respiratory distress. Because atropine will reverse bronchoconstriction within minutes, one might hesitate to intubate a dyspneic, conscious patient who probably will improve quickly. However, in a severely poisoned ,unconscious, apneic patient, endotracheal intubation with assisted ventilation should be undertaken as quickly as possible.

Airway resistance may be very high initially, causing some mechanical ventilators to malfunction, but it will return toward normal after atropine administration. Frequent airway suctioning may be required for copious bronchial secretions. Supplemental oxygen through an endotracheal tube with positive end-expiratory pressure is indicated for severely hypoxic patients. It is important to improve tissue oxygenation before atropine administration to minimize he risk of ventricular fibrillation. Advanced life support, including IV line placement, should be provided to all victims with evidence of respiratory compromise or other signs of severe exposure (4).

Decontamination

Decontamination must be carried out at the earliest opportunity to limit skin absorption of the agent and prevent contamination of the rescuers. Thorough decontamination is essential before casualties enter an emergency department or other site of medical care to avoid contamination of staff and other patients.

If the eyes have been exposed, they should be irrigated as soon as possible with running water or saline. Skin decontamination should be done by pouring on large amounts of a chlorine-liberated solution such as 5.0% hypochlorite solution (household bleach) followed by copious water rinsing. If bleach is not available, the skin should be blotted gently (without rubbing) with generous amounts of alkaline soap and water followed by a water rinse. Generous amounts of water alone can be used if nothing else is available; water will dilute and physically wash away the agent, but it will not hydrolyze it. Contaminated clothing and jewelry should be

removed, and the underlying skin thoroughly decontaminated. Care should be taken to clear under the nails, intertriginous areas, axillae, groin, and hair (4).

Fetal bovine serum acetylcholinestrase (FBS-AChE) protected mice from multiple LD_{50} doses of OP nerve agents (20). Butyrylcholinestrase purified from human plasma (HuBchE) was also effective both *in vitro* and *in vivo* mice and rats as a single prophylactic antidote against the lethal effects of nerve agents (21).

Addition of the oxime HI6 to FBS-AChE as a pre-treatment drug, amplified the efficacy of enzyme as a scavenger of nerve agents (22).

Recombinant DNA-derived AchEs revealed a great improvement over wild-type AChE as bioscavengers; they can be used to develop effective methods for the safe disposal and stored OP nerve agents and potential candidates for pre or post-exposure treatment for OP toxicity (23). By the utilization of cell immobilization technology, immobilized Escherichia coli with surface-expressed organophosphorous hydrolase was made to detoxify nerve agents (24). By protein engineering techniques one butyrylcholinestrase mutant G117H was made to hydrolyze V and G-agents but reacts much slowly (25).

Organophosphate acid hydrolyses (OPAA) from 2 species of Ateronomas were cloned and sequenced to detoxify G agents, which was effective (26). Cholinesterase were covalently linked to a polyurethane matrix can effectively be used to remove and decontaminate nerve agents from surface biological (skin or wounds) or otherwise (clothing or medical equipments) or the environment. This could protect medical personnel from secondary contamination while attending chemical casualties, and civilians exposed to highly toxic nerve agents (27).

A reactive skin decontamination (RSD) lotion active against classical nerve agents and mustard was developed. Inactivation process was time and agent dependent and also related to ratio of OP to RSD (28).

Pretreatment

In animal studies, pre-treatment with reversible carbamate acetylcholinestrase inhibitors, such as pyridostigmine and physostigmine, enhances the

efficacy of post-exposure treatment of soman exposure or soman poisoning with atropine and pralidoxime chloride and permits survival at higher agent challenges. This protection apparently is due to the fact that the more lethal nerve agents cannot attack acetylcholinestrase molecules bound by carbamates. Carbamylation of 20% to 40% of the erythrocyte ChE is associated with antidotal enhancement. Carbamate pre-treatment will not reduce the effects of the agents, and by themselves carbamates provide no benefit. Pretreatment is not effective against sarin and VX challenge and should not be considered a panacea for all nerve agents. It is of value for soman intoxication when agent challenge is followed by atropine and an oxime. Pretreatment is ineffective unless standard therapy is administered after the exposure.

Because physostigmine is toxic at the amounts required, pyridostigmine is the drug of choice for pretreatment. The standard dosage is 30 mg orally every eight hours for impending nerve agent attack. Because pyridostigmine does not cross the blood-brain barrier, it causes no central nervous system toxicity of nerve agents. Carbamates must never be used after nerve agent exposure; in that setting, carbamate administration will worsen, rather then protect from, toxicity. Excessive doses cause many of the same toxic effects as do the nerve agents, and the recommended amounts caused annoying side effects in more than half of the population in a war zone. Eptastigmine treatment given I.V. protected mice better then physostigmine against soman exposure (29).

Pretreatment with a drug mixture (Pyridostigmine, benactyzine and trihexyphenydil), and antidotal treatment (HI6 + Benactyzine) was investigated in rats. This cholinergic-anticholinergic pretreatment restores respiratory and circulatory changes induced by soman (30).

Antidotes

Available antidotes (atropine, oximes) do not necessarily prevent respiratory failure or incapacitation (31). However, early aggressive medical therapy with antidotes and intensive care management are the keys to prevention of morbidity and mortality associated with nerve agent poisoning.

Atropine

Atropine should be titrated with the goal of the therapy being drying secretions and resolution of bronchoconstriction and bradycardia (32). Thus there is no actual dose for atropine. The dose (2 mg) of atropine available in auto injector is not adequate for the moderate to severe exposure to nerve agents. In fact, atropine should be given intravenously in doses to produce mild to moderate atropinisation (dryness of tongue, oropharyngeal and bronchial tree, tachycardia, mydriasis and flushing) as soon as possible. At least the same amount as the initial atropinisation dose should be infused in 500 dextrose 5% constantly to sustain the atropinisation and repeat it as needed until the patient becomes asymptomatic. Continuous infusion of atropine effectively antagonizes the muscarinic effects and some of the central nervous system effects of nerve agent poisoning, but has no effect on skeletal muscle weakness, seizures, unconsciousness or respiratory failure (4). Large doses of atropine requires higher concentration of atropine preparation (e.g. 100mg/10 ml made in Germany) or at least a vast amount of atropine (10—100mg) in dextrose 5% solution, ready made for I.V. infusion in severely nerve agent intoxicated patients. However, based on clinical experience of the first author, much lower atropine doses are required for nerve agents than for the severe OP-pesticides poisoning.

Atropine should not be given I.V. to a hypoxic patient. If the patient is hypotensive, atropine can be given through an endotracheal tube or intratracheally for more rapid absorption through the peribronchial vessels (4). Aerosolized atropine has also been used and can be administered quickly by inhalation. Studies suggest that in addition to the local effects in the lungs, it is also absorbed systemically (33).

Oximes

Oximes are mainly pyridinium compounds, which are divided into mono and bispyridium oximes.

Although oximes have been designed to reactivate the inhibited acetylcholinestrase. Clinical experience has indicated that they are not always effective as reactivators and at this moment, none of them can be regarded as a

broad-spectrum antidote (34). The choice of oximes presently based on the data presently available may well also be dependent on factors other than protection against lethality, such as cost and availability of the oxime and it's side effects, Obidoxime (Toxogonin) is likely to cause more toxic effects (particularly with high doses) than pralidoxime and HI-6[62]. HI-6 is the least toxic, but is less unstable in solution and is not commercially available in many parts of the world.

Pralidoxime (PAM-2Cl), HI6 and HGG-12 were used in dogs with soman and tabun poisoning. PAM-2Cl (in conjunction with atropine and diazepam) revealed the best protective in soman-poisoned dogs, with the respective protective indices of 9, 6.3 and 3.5. None of them were effective against tabun poisoning (36). Efficacy of two other oximes, HLo-7 and pyrimidoxime in 3x LD_{50} dose of sarin, soman and GF and 2x LD_{50} of tabun were tested in mice. HLo-7 produced significant (P<0.05) reactivation of phosphorylated acetylcholinestrase, resulting in 47,38,27 and 10 % reactivation of sarin, GF, soman and tabun inhibited mouse diaphragm acetylcholinestrase, respectively (37). In a comprehensive study, the order of effectiveness against soman was HI-6, HLo-7 and pyrimidoxime. HLo-7 was very effective against tabun poisoning, while HI-6 and pyrimidoxime were of moderate value. Against GF, HI6 and HLo-7 were extremely effective, obidoxime was moderately effective and PAM-2Cl and pyrimidoxime were the least effective (38).

In soman –intoxicated guinea pigs, HI6 was therapeutically slightly more effective than HLo-7. HLo-7 was more effective against tabun intoxication than HI-6 (39).

Pharmacokinetics and effects of HI6 in blood and brain of soman-intoxicated rats were studied. High doses of HI6 can reach the brain in sufficient amount to reactivate inhibited brain acetylcholinestrase. Signs of soman poisoning correlated positively to acetylcholinestrase inhibition and negatively to the concentration of inbound HI6 in the brain and that soman intoxication significantly decreased uptake of HI-6 into the brain (40). Reactivating potency of Obidoxime, pralidoxime, HI6 and HLo7 in human erythrocyte acetylcholinestrase inhibited by soman, sarin, cyclosarin and VX were studied in vitro. After soman, sarin, cyclosarin and VX, the reactivating potency decreased in the order of HLo7>HI6>obidoxime>pralidoxime (41). Dose response effects of atropine and HI6 treatment in soman and tabun poisonings were studied in guinea pigs. Atropine had a large effect on the efficacy of HI6 against both the nerve agents. They were also more effective against soman than against tabun. Adjunctive treatment with diazepam enhanced the efficacy of HI6 and atropine against soman (42).

The effects of common oximes in different nerve agent poisoning are summarized in table 1.

ProPAM, the tertiary amine analog of pralidoxime penetrates the CNS more readily than pralidoxime. Consequently, proPAM would be expected to have greater beneficial effect in nerve agent poisoning than Pralidoxime. This expectation has not in general been realized in experimental studies.

Dosage regimen of oximes

In spite of many oximes tested in animal experiments, the human experience either in

Table 1. Relative effects of oximes in OP nerve agents poisoning:

Oximes	GA Sarin	GB Soman	GD Tabun	GF	VX
Pralidoxime	+ + +	+ +	+	+	+ + +
Pyrimidoxime	+ +	+ +	+ +	+	+ +
Obidoxime	+ +	+ + +	+ +	+ +	+ + +
HI-6	+ + +	+ + + +	+ +	+ + + +	+ + +
HLo-7	+ + + +	+ + +	+ + + +	+ + + +	+ +
HGG-12	N/A	+ + +	+	N/A	N/A

Key: N/A= No data available   + = Least effective   + + = Partially effective   + + + =Moderately effective   + + + + = Most effective

war or terrorism limited to Pralidoxime and Obidoxime. Pralidoxime should be administered intravenously at a dose of 30mg/kg initially over 30 minutes followed by constant infusion of 8 mg/kg/hr in dextrose 5%. It could be continued until the full recovery or until atropine is required. Obidoxime was hepatotoxic at high recommended doses of 8 mg/kg initially and 3 mg/kg/hr (43). It may be given at a dose not more than 500mg initially and about 750 mg-1000mg per day. Liver function tests should be checked regularly during obidoxime therapy.

Diazepam

Behavioral efficacy of diazepam against nerve agents in rhesus monkeys was studied. The results revealed that diazepam would be an excellent adjunct to the traditional nerve agent therapy to facilitate behavioral recovery from nerve agent intoxication that might be encountered by the medical military personnel on the battlefield (44).

Despite the introduction of diazepam as a symptomatic anticonvulsant, a number of studies have been performed which indicate that the effects of diazepam may be more specific. These studies have mainly investigated the effects on cholinergic and GABAergic systems.

New Additional Medications

Gacyclidine

Gacyclidine is an anti-glutamatergic compound that was studied as a complement to the available emergency therapy in organophosphate poisoning. It was used in conjunction with atropine, pralidoxime and diazepam in nerve agent poisoning in primates.

Gacyclidine prevents the mortality observed after early administration of the above classical emergency medication above. E.E.G. recordings and clinical observations also revealed that gacyclidine prevented soman induced seizures and motor convulsions. It also markedly accelerated clinical recovery of soman challenged primates. Gacyclidine prevented the neuropathology observed three weeks after soman exposure in animals (45). In case of severe nerve agent poisoning, gacyclidine represented a promising adjuvant therapy to the currently available

polymedication to insure optimal management of OP nerve agent poisoning in man. This drug is currently being evaluated in human clinical trial for different neuroprotective indications (46).

Sodium bicarbonate

Effects of sodium bicarbonate in OP pesticide poisoning were investigated in patients with moderate to severe intoxication. It was aimed to make an alkalinisation to reach and sustain the arterial blood pH between 7.45 and 7.55. Sodium bicarbonate was administered I.V. firstly to correct the metabolic acidosis and then 3-5 mg/kg/24h as constant infusion until recovery or until atropine was required. Arterial blood gas analysis was performed in certain intervals to adjust the dosing. The preliminary results were promising (47). It was thus aimed to investigate higher doses of sodium bicarbonate. Infusion of high doses of sodium bicarbonate (5 mEq/kg in 60 min. followed by 5-6 mEq/kg/day to obtain arterial blood pH of 7.45 to 7.55) was appeared to be effective in treatment of patients with OP pesticide poisoning. It may thus be an aid and could be added to the treatment regime of OP poisoning (48).

Since alkalinisation products of nerve agents particularly soman are less toxic, it seems that administration of IV infusion of sodium bicarbonate to produce moderate alkalinisation, may be even more effective in nerve agent poisoning.

Magnesium sulphate

Intravenous magnesium sulfate in a dose of 4 g only on the first day after admission reduced hospitalization days and mortality in 8 patients with acute OP poisoning (49).

Antioxidants

In addition to acetyl cholinesterase inhibition, the toxicity of OP compounds is mediated by generation of nitric oxide and other free radicals. These toxic molecules can be counteracted by antioxidants such as vitamins C and E, spin traps, melatonin and low molecule weight thiols. The latter compounds can also increase the synthesis of glutathione, which can both ameliorate the OP-induced oxidative stress and enhance OP detoxification (50,51).

Conclusion

Sodium bicarbonate, Magnesium sulfate and the antioxidants should be added to the standard treatment of OP poisonings.

References

(1) Dunn MA and Sidell FR. Progress in Medical defense against nerve agents. *JAMA* (1998) 262: 649-652

(2) Sidell FR and Borak J. Nerve agents. *Ann. Emerg. Med.* (1992) 21: 865-871

(3) Rickell DJ, Glenn JF and Houston WE. Medical defense against nerve agents: New direction. *Milit. Med.* (1987) 152: 35-41

(4) Sidell FR and Borak J. Nerve agents. *Ann. Emerg. Med.* (1992) 21: 865-871

(5) Morita H, Yanagisawa N, Nakajima T, Shimizu M, Hirabayashi H, Okudera H, Nohara M, Midorikawa Y and Mimura S. Sarin poisoning in Matsumoto, Japan. *Lancet* (1995) 346: 290-293

(6) Liu DD, Watanabe HK, Ho IK and Hoskins B. Acute effects of soman, sarin and tabun on cyclic nucleotide metabolism in rat stratium. *J. Toxicol. Environ. Health* (1986) 19: 23-32

(7) Cao CJ, Mioduszewski RJ, Menking DE, Valdes JJ, Katz EJ, Eldefrawi ME and Eldefrawi AT. Cytotoxicity of organophosphate anticholinesterases. *In Vitro Cell Dev. Biol. Anim.* (1999) 35: 493-500

(8) Ohbu S, Yamashina A, Takasu N, Yamaguchi T, Murai T, Nakano K, Matsui Y, Mikami R, Sakurai K and Hinohara S. Sarin poisoning on Tokyo subway. *Southern Med. J.* (1997) 90: 587-593

(9) Grob D. The manifestations and treatment of poisoning due to nerve gas and other organic phosphate anticholinesterase compounds. *Arch. Intern. Med.* (1956) 98: 221-239

(10) Siddell FR. Soman and sarin: Clinical manifestations and treatment of accidental poisoning by organophosphates. *Clin. Toxicol.* (1974) 7: 1-17

(11) Lockridge O and Masson P. Pesticides and susceptible populations: people with butyrylcholinestrase genetic variants may be at risk. *Neurotoxicology* (2000) 21:113-126

(12) Mulchandani P, Mulchandani A, Kaneva I and Chen W. Biosensor for direct determination of organophosphate nerve agents. 1. Potentiometric enzyme electrode. *Biosens. Bioelectron.* (1999) 14: 77-85

(13) Mulchandani A, Pan S and Chen W. Fiber-optic enzyme biosensor for direct determination of organophosphate nerve agents. *Biotechnol. Prog.* (1999) 15:130-134

(14) Polhuijs M, Langenberg JP and Benschop HP. New method for retrospective detection of exposure to organophosphorous anticholinesterases:application to alleged sarin victims of Japanese terrorists. *Toxicol. Appl. Pharmacol.* (1997) 146: 156-161

(15) Nagao M, Takatori T, Matsuda Y, Nakajima M, Iwase H and Iwadate K. Definitive evidence for the acute sarin poisoning diagnosis in the Tokyo subway. *Toxicol. Appl. Pharmacol.* (1997) 144: 198-203

(16) Nozaki H, Aikawa N, Fujishima S, Suzuki M, Shinozawa Y, Hori S and Nogawa S. A case of VX poisoning and the difference from sarin. *Lancet* (1995) 346: 698-699

(17) Klette KL, Levine B, Dreka C, Smith ML and Goldberger BA. Cholinesterase activity in postmortem blood as a screening test for organophosphate/chemical weapon exposure. *J. Forensic Sci.* (1993) 38: 950-955

(18) Pope C, Dilorenzo K and Ehrich M. Possible involvement of a neurotrophic factor during the early stages of organophospahte-induced delayed neurotoxicity. *Toxicol. Lett*. (1995) 75: 111-117

(19) Munro N. Toxicity of the organophosphate chemical warfare agents GA, GB, and VX: Implications for public protection. *Environ. Health Perspect.* (1994) 102: 18-37

(20) Wolfe AD, Rush RS, Doctor BP, Koplovitz I and Jones D. Acetylcholinestrase prophylaxis against organophosphate toxicity. *Fundam. Appl. Toxicol.* (1987) 9: 266-270

(21) Raveh L, Grunwald J, Marcus D, Papier Y, Cohen E and Ashani Y. Human butyrylcholinesterase as a general prophylactic antidote for nerve agent toxicity. *In vitro* and *in vivo* quantitive characterization. *Biochem. Pharmacol.* (1993) 45: 2465-2474

(22) Caranto GR, Waibel KH, Asher JM, Larrison RW, Brecht KM, Schutz MB, Raveh L, Ashani Y, Wolfe AD, Maxwell DM and Doctor BP. Amplification of the effectiveness of acetylcholinesterase for detoxification of organophosphorous compounds by bis-quartenary oximes. *Biochem. Pharmacol.* (1994) 47: 347-357

(23) Saxena A, Maxwell DM, Quinn DM, Radic Z, Taylor P and Doctor BP. Mutant acetylcholinestrase as potential detoxification agents for organophosphate poisoning. *Biochem. Pharmacol.* (1997) 54: 269-274

(24) Mulchandani A, Kaneva I and Chen V. Detoxification of organophosphate nerve agents by immobilized *Escherichia coli* with surface expressed organophosphate hydrolase. *Biotechnol. Bioeng.* (1999) 63: 216-223

(25) Broomfield CA, Lockridge O and Millard CB. Protein engineering of a human enzyme that hydolyzes V and G nerve agents: design, construction and characterization. *Chem. Biol. Interact.* (1999) 119-120: 413-418

(26) Cheng TC, DeFrank JJ and Rastogi VK. Alteromonas prolidase for organophosphorous G-agent decontamination. *Chem. Biol. Interact.* (1999) 119-120: 455-462

(27) Gordon RK, Feaster SR, Russell AJ, LeJeune KE, Maxwell DM, Lenz DE, Ross M and Doctor BP. Organophosphate skin decontamination using immobilized enzymes. *Chem. Biol. Interact.* (1999) 119-120: 463-470

(28) Sawyer TW, Parker D, Thomas N, Weiss MT and Bide RW. Efficacy of an oximate-based skin decontaminant against organophosphate nerve agents determined *in*

vivo and *in vitro. Toxicology* (1991) 67: 267-277

(29) Tuovinen K and Hannien O. Protection of mice against soman by pre-treatment with eptastigmine and physostigmine. *Toxicology* (1999) 139: 233-241

(30) Kassa J and Fusek J. The positive influence of a cholinergic-anticholinergic pretreatment and antidotal treatment on rats poisoned with supralethal doses of soman. *Toxicology* (1998) 128: 1-7

(31) Munro NB, Watson AP, Ambrose KR and Griffin GD. Treating exposure to chemical warfare agents: implications for health care providers and community emergency planning. *Environ. Health Perspect.* (1990) 89: 205-215

(32) Holstege CP, Kirk M and Sidell FR. Chemical warfare. Nerve agent poisoning. *Crit. Care Clin.* (1997) 13: 923-942

(33) Orma PS and Middleton RK. Aerosolized atropine as an antidote to nerve gas. *Ann. Pharmacother.* (1992) 26: 937-938

(34) Van Helden HP, Busker RW, Melchers BP and Bruijnzeel PL. Pharmacological effects of oximes: how relevant are they? *Arch. Toxicol.* (1996) 70: 779-786

(35) Dawson RM. Review of oximes available for treatment of nerve agent poisoning *J. Appl. Tox.* (1994) 14: 317-331

(36) Boskovic B, Kovacevic V and Jovanovic D. PAM-2, HI-6 and HGG-12 in soman and tabun poisoning. *Fundam. Appl. Tox.* (1984) 4: S106-115

(37) Clement JG, Hansen AS and Boulet CA. Efficacy of HLo-7 and pyrimidoxime as antidotes of nerve agent poisoning in mice. *Toxicology* (1992) 66: 216-219

(38) Lundy PM, Hansen AS, Hand BT and Boulet CA. Comparison of several oximes against poisoning by soman, tabun and GF. *Toxicology* (1992) 72, 99-105

(39) Melchers BP, Philippens IH and Wolthuis OL. Efficacy of HI-6 and Hlo-7 in preventing incapacitation following nerve agent poisoning. *Pharmacol. Biochem. Behav.* (1994) 49: 781-788

(40) Cassel G, Karlsson L, Waara L, Ang KW and Goransson-Nyberg A. Pharmacokinetics and effects of HI-6 in blood and brain of soman-intoxicated rats: a microdialysis study. *Eur. J. Pharmacol.* (1997) 332: 43-52

(41) Worek F, Widmann R, Knopff O and Szinicz L. Reactivating potency of obidoxime, pralidoxime, HI 6 and Hlo7 in human erythrocyte acetylcholinestrase inhibited by highly toxic organophosphorous compounds. *Arch. Toxicol.* (1998) 72: 237-243

(42) Kopolovitz I, Menton R and Matthews C. Dose-response effects of atropine and HI-6 treatment of organophosphorous poisoning in guinea pigs. *Drug Chem. Toxicol.* (1995) 18: 119-136

(43) Balali-Mood M and Shariat M. Treatment of organophosphate poisoning. Experience of nerve agents and acute pesticide poisoning on the effects of oximes. *J. Physiology (Paris)* (1998) 92: 375-378

(44) Castro CA, Larsen T, Finger AV, Solana RP and McMaster SB. Behavioral efficacy of diazepam against nerve agent exposure in rhesus monkeys. *Pharmacol. Biochem. Behav.* (1992) 41: 159-164

(45) Lallement G, Clarencon D, Masqueliez C, Baubichon D, Galonnier M, Burckhart MF, Peoc'h M and Mestries JC. Nerve agent poisoning in primates: antilethal, anti-epileptic and neuroprotective effects of GK-11. *Arch. Toxicol.* (1998) 72: 84-92

(46) Lallement G, Clarencon D, Galonnier M, Baubichon D, Burckhart MF and Peoc'h M. Acute soman poisoning in primates neither pretreated nor receiving immediate therapy; value of gacyclidine (GK-11) in delayed medical support. *Arch. Toxicol.* (1999) 73: 115-122

(47) Balali-Mood M, Salimifar H and Shariate M. Effects of Sodium Bicarbonate in Human Organophosphate Poisoning. *Proceedings of the 3rd International Chemical and Biological Medical Treatment Symposium.* May 7-12 2000, Switzerland (2000)

(48) Balali-Mood M, Ayati MH and Ali-Akbarian H. Effects of high doses of sodium bicarbonate in organophosphorous poisoning. *J. Toxicol. Clin. Toxicol.* (2005) 43: 571-574

(49) Pajoumand A, Shadnia S, Rezaie A, Abdi M and Abdollahi M. Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorous insecticides. *Human Exp. Toxicol.* (2004) 23: 565-569

(50) Ranjbar A, Solhi H, Mashayekhi FJ, Susanabdi A, Rezaie A and Abdollahi M. Oxidative stress in acute human poisoning with organophosphorous insecticides: a case control study. *Environ. Toxicol. Pharmacol.* (2005) 20: 88-91

(51) Pena-Llopis S. Antioxidants as potentially safe antidotes for organophosphorous poisoning. *Curr. Enzyme Inhib.* (2005) 1: 147-156

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