

Nerve Agents

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Abstract

Nerve agents are one of the most lethal chemical materials. They may be used as weapons of mass destruction in terrorist attacks or in the battlefield. Successful management is composed of many close organized steps. Early detection, field triage, decontamination, primary survey, resuscitation, and early antidote use are imperative in the acute stage of poisoning. Basic pharmacological therapy includes antidote (atropine and pralidoxime) and anticonvulsant therapy. We review the basic physical properties, the pathophysiology, and the acute management of nerve agents poisoning. (*Ann Disaster Med.* 2005;4 Suppl 1:S29-S34)

Key words: Nerve Agent; Poisoning; Resuscitation; Chemical Warfare

Introduction

For developing best pesticides, nerve agents were synthesized by German scientists in the 1930s. These agents are relatives of organophosphate insecticides and are very toxic. Internationally they have North Atlantic Treaty Organization (NATO) codes and common chemical names. Abbreviations are used include GA (tabun), GB (sarin), GD (soman), GF (cyclosarin) and VX. The G agents are named for Germany, and the VX was first synthesized in the British.

Pathophysiology

The classic nerve agents are esters of phosphoric acid, namely organophosphates. Recalling phosgene and chloride, the first chemical agents in World War I, are gases at standard temperature and pressure. The term “nerve gas” or “poi-

son gas” is a historic misnomer for nerve agents. At standard pressure and temperature, they are liquids, with melting points range from -42°C (soman) to -39°C (VX).¹ They can be volatile spontaneously at room temperature. Thus one need not really contact the nerve agents to be affected by their vapors.

All the nerve agents have vapor densities greater than 1, that means their vapors are heavier than air and tend to sink lower to the ground. Besides, the rates of vaporization and the volatility determine the hazardous effects of these agents. Sarin is the most volatile agent, and the VX, oily by contrast, is the least volatile agent of all. Therefore, though sarin poses greater vapor hazard, VX tends to persist in the environment longer.

Nerve agents can induce life-threatening cholinergic crisis by acting as cholinesterase

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inhibitors, as do the organophosphates. Nerve agent forms a covalent binding with the acetylcholinesterase (AChE), which has only one active site, causing irreversible inhibition of this enzyme. The accumulating neurotransmitter acetylcholine (ACh) in the synaptic cleft, which cannot be hydrolyzed by AChE, will in turn activate the postsynaptic cholinergic receptors. This can happen in the peripheral and central nervous systems, at both muscarinic and nicotinic receptors. In our human body, our erythrocyte cholinesterase activity correlates better with that in the nervous system than plasma cholinesterase, which we often called pseudocholinesterase or butyrylcholinesterase.²⁻⁴ However, the presenting symptoms are not correlate with the erythrocyte cholinesterase inhibition very well.

Clinical Manifestation

The routes of exposure determine somewhat the order and onset timing of the presenting symptoms. In terrorist or battlefield scenarios, most victims are affected via vapor route. The pupillary muscles are the most accessible cholinergic synapses. Thus miosis may be the first symptom in these patients. Nozaki et al reported that pupil size less than 3mm is a sensitive and simple method for sarin exposure detection.⁵ In the sarin subway attack in Japan, the patients complained of dim and blurred vision. They described that everything seemed dark at that time.⁶ Rhinorrhea and salivation can be the next presenting symptoms in the vapor exposure. This can also be a systemic effect. The severity is dose-related.^{4,7} With the vapor inhalation, nerve agents induce bronchorrhea and bronchoconstriction of the respiratory tract. When the nerve agents enter the body, they

penetrate into the circulating blood and cause systemic effect. The gastrointestinal effects of nerve agents include increased bowel movement, nausea, vomiting, diarrhea, and abdominal cramping pain.

The cardiac effects vary since sympathetic and parasympathetic inputs to the heart are somewhat different in each individual. Besides, nerve agents can activate both muscarinic and nicotinic receptors in the cardiovascular systems. As a result, the blood pressure and heart rate are relatively unpredictable in exposed patients.

In the peripheral neuromuscular systems, cholinergic nicotinic activation causes fasciculations and then twitching. This can be differentiated from seizure by electroencephalogram. When adenosine triphosphate (ATP) is depleted late in the course, flaccid paralysis follows. Remember in botulinium intoxication, flaccid paralysis occurs earlier in the course due to presynaptic inhibition of ACh release by the toxin. The neuromuscular effects of nerve agents can compromise respiratory function if the respiratory muscles are involved.

Human brain has a number of pathways contain acetylcholine, including neurons in the neostriatum, the medial septal nucleus, and the reticular formation. Nerve agents can cause great hazard here. Loss of consciousness, multifocal seizures and apnea due to central respiratory center suppression will occur.

Nerve agents can be absorbed through the skin. Volatility determines the topical dose the nerve agents need to produce toxicity. Less volatile nerve agents need fewer dose and time to be absorbed. VX is the least volatile agent and it can be absorbed into the skin well after a small contact time.⁸ The dermal LD50 of liquid VX is 6 mg for a 70-kg adult, and that of liquid

sarin is much larger, about 1960mg. (LD50: the dose needed to kill 50% of the patients exposed).^{3,4,7,9} Relative large proportion of sarin and tabun evaporate before they can be absorbed, since they are more volatile nerve agents. In Marrs et al's study, the symptoms can onset 18 hours after dermal exposure to liquid nerve agent.⁸ Delayed presentation may be due to continuous penetration of the already absorbed nerve agent into the blood circulation, though the skin has been decontaminated.^{8,10} In general, the more delayed onset of the symptoms, the less severe the effects will be. With a drop of nerve agent, it may cause localized sweating, localized fasciculation, however, these may be subtle if the patients are not aware of them. Then the nerve agents enter the bloodstream through the well vascularized subcutaneous tissue or muscles. Miosis will occur much later in the course by this route of exposure, because the nerve agents have to cross many barriers and diffuse into the aqueous humor to reach the receptors of the papillary muscles. Commonly, the cholinergic effects of liquid nerve agent exposure take more time to reach peak than vapor exposure. Thus, much longer time for treatment and close monitoring is needed if liquid exposure cannot be excluded.

Nerve agent intoxication-related death usually is respiratory failure. This can result from bronchospasm, bronchorrhea, respiratory muscle paralysis, and central inhibition of the respiratory center.

Delayed neurobehavioral syndrome are noted in some patients survived the nerve agent attack. Some patients have difficult in concentrating, sleeping, or working. Mood disturbance, headache, and personality change have been reported in the Japan subway attack

patients. This delayed neurobehavioral syndrome in some patients, if not at all, may be posttraumatic stress disorder.^{11,12} In others, it may due to hypoxic encephalopathy.^{13,14} The pathophysiology is still unclear now.

Treatment

The patients' clinical condition and the exposed pathway should be kept in mind in the management of nerve agent hazard.

Decontamination

Decontamination should be considered in the management of nerve agent victims. Simply by taking off the clothes or the garments and brief decontamination can remove most of the toxins. Nerve agents can be absorbed through the skin. Therefore, unrecognized contamination or inadequate decontamination may cause secondary injury to the healthcare workers.

The nerve agents can be inactivated by alkaline solutions. The US Army recommend 0.5% sodium hydrochloride (household bleach: water= 1:9) can be used. Detergent and water are used in the most situations, however.

Atropine

Atropine is highly selective for muscarinic receptors, but it can not distinguish between the M1, M2, and M3 subgroups of muscarinic receptors. Its potency at nicotinic receptors is much lower than that at muscarinic receptors. Atropine causes reversible blockade of the actions of acetylcholine. This can be overcome by a larger amount of AChs by competition with atropine at the binding site of muscarinic receptors.

Initially, administer 2 mg for adults and 0.02mg/kg for children intravenously is

considered. Intramuscular (IM) route via an IM autoinjector can be used in the field treatment. In a severely nerve-agent-poisoned adult, treatment begins with three IM autoinjectors or 6mg of atropine, then to retreat every 5 to 10 minutes if needed.¹⁵ Nerve agent-induced bronchospasm and bronchorrhea could make ventilation-only ineffective in a severely poisoned patient. In a severely poisoned patient who still has pulse, it could be better to give an IM atropine autoinjector before taking time to intubate.¹⁵ Dunn reported that in the first 2 or 3 hour of management, a cumulative dose of 10-20 mg will provide adequate control in the acute stage.¹⁶ Sometimes a maintenance intravenous therapy is needed for 2 to 3 days.¹⁷ Generally the endpoint of atropine treatment is when the patient can breath without the complication of respiratory secretions. Clement reported that atropine can counteract soman-induced hypothermia in a mice study.¹⁸

Pralidoxime chloride

Pralidoxime chloride (2-PAM-Cl) is a cholinesterase regenerator. It can regenerate the active enzyme from the organophosphorous-cholinesterase complex. Its oxime group (=NOH) has high affinity for the phosphorous atom. 2-PAM-Cl can hydrolyze the phosphorylated enzyme if the complex is not "aged". Cholinesterase "aging" half-time varies for different kinds of nerve agents. The "aging" half-time of VX and tabun is reported longer than 40 hours. Soman has relatively short "aging" half-time of about 2 minutes.⁴ 2-PAM-Cl is most effective in the management of nerve-agent associated neuromuscular junction poisoning. However, because of its positive charge, it cannot cross the blood-brain barrier. It is ineffective in re-

versing the central effects of nerve agents.

2-PAM-Cl is administered by intravenous infusion, 1- to 2-g given over 15-30minutes, for a 70-kg adult. A maximum single dosage of 2000mg or 30mg/kg per hour is currently accepted in United States.^{19,20} Higher doses (e.g., 4g) may be needed in severe poisoned patients.²¹ In excessive doses, 2-PAM-Cl has potential adverse effects, such as dangerous hypertension and neuromuscular weakness. Elevated blood pressure can persist for hours, and it may be minimized by prolonging the infusion time.⁴ Data of 2-PAM-Cl use in nerve-agent poisoned children is limited. One recommended begin by slow intravenous infusion with a dose of 15-20 mg/kg for children.²² A typical dose of 2-PAM-Cl in organophosphate-poisoned children is 20 to 50 mg/kg to a maximum of 2000mg/h.²³ Repeated doses or continuous intravenous infusion may be needed in severe cases.

Anticonvulsant

Nerve agent-related status epilepticus may be multicentric in origin, since the cholinergic neurotransmission in the brain is widely distributed. Benzodiazepines are effective in nerve agent-related seizures. In the field medicine, 10-mg IM autoinjectors is preferred. It is better changed to intravenous route for the unpredictable absorption of IM autoinjectors. Although diazepam is the FDA approved benzodiazepine for seizure, midazolam showed a broad spectrum against nerve agents at lowest blood concentration and more rapid in an animal study.²⁴ It may be needed to use EEG for seizure evaluation since convulsion can be masked by the paralysis effect of the nerve agents. Prolonged seizure is considered to dam-

age neurons.

Other

Pyridostigmine bromide

Pyridostigmine bromide antagonize nondepolarizing neuromuscular blockademainly by inhibiting the acetylcholinesterase, resulting in increasing the acetylcholine at the neuromuscular synapses. To a lesser extent, it can also increase release of neurotransmitter from the motor nerve terminal. The FDA approved pyridostigmine bromide as a pretreatment for the rapid aging soman attack in the field in February 2003. The pretreatment dose is 30 mg every 8 hours while it is started 60 mg every 8 hours in myasthenia gravis patients.

Conclusions

Management of nerve agent poisoning is composed of close linked steps. Early detection, field on-site triage (set priority), decontamination (if appropriate), primary survey, resuscitation, and early antidote use are clearly important in the acute stage of poisoning. Intensive care by a well-trained team is needed. The success of nerve agent poisoning management depends on how well we have prepared.

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