

A review article on nerve agents

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The incidence of Tokyo subway attack by the Aum Shinrikyo cult in 1995 had raised the concern of the use of nerve agent as a weapon in terrorist attack. The recent event in World Trade Centre in New York city had further brought our attention to the possibility of terrorist attacks using these agents. In view of the high possibility of nerve agents being used as chemical weapon, medical personnel should have a clear knowledge of these agents. This article aim to provide a detailed discussion of these agents. (*Hong Kong j.emerg.med.* 2002;9:83-89)

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Introduction

Hazmat incident is defined as an accident, which involves contamination of victim(s), by toxic chemical, biological or radiological agents. According to the FM 8-285 classification, nerve agents are classified as one of the lethal chemical agents.¹ Nerve agents include GA (Tabun), GB (Sarin), GD (Soman), GF and VX. GA, GB, GD and GF are also called "G-agents". Nerve agents are hazardous in their vapour and liquid states. Nerve agents can be dispersed from rockets, bombs, missiles, spray tanks and other large munitions.

History

Nerve agents were developed in Germany before the World War II. Schrader synthesized what today is known as tabun in 1936.^{2,3} Over a year later, Schrader synthesized a second organophosphorus compound and named it as sarin.² Germany had synthesized ten

to thirty thousand tons of tabun and smaller quantities of sarin and put into munitions during the World War II, but these agents were never used. Soman was synthesized by Richard Kuhn of Germany in 1944.³ In early 1950s, VX was first synthesized for industrial use in United Kingdom. It was then given to United States for military development.^{1,3} Besides, the United States also began to produce sarin for potential military use.

The use of nerve agents in battlefield was known in the Iraq-Iran conflict.¹ In addition, sarin was also used in terrorist attacks. In June 1994, the members of Japanese Aum Shinrikyo cult released sarin in Matsumoto. This event resulted in almost 300 casualties and the death of 7 casualties. However, this event was not well publicized. Another attack happened in March 1995 in Tokyo subway. This event resulted in almost 5500 casualties and 12 casualties died.⁴⁻⁶

Physicochemical characteristics

Nerve agents are liquids in temperate conditions, thus the term nerve gas is a misnomer. In their pure state, they are clear, colourless and tasteless. GA has been reported to have a faint, slightly fruity odour and soman have an ill-defined odour. GB and VX are apparently odourless. "G-agents" are more volatile

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than VX. The more volatile agents will constitute a vapour hazard when dispersed. The less volatile agents will mainly constitute a liquid hazard. Among the "G-agents", GB (sarin) is the most volatile while GF is the least volatile.¹

Toxicokinetics

Nerve agents in vapour form are absorbed from the respiratory tract and the liquid form will penetrate the skin. Small absorbed dose will cause local effects but larger doses will have systemic effects and the agent will be distributed to brain, heart and other organs.

Nerve agents undergo a large number of metabolic reactions inside the body. The main reaction is the Phase I reactions in the liver which include oxidative desulfuration, oxidative dealkylation and dearylation, aromatic ring hydroxylation and hydrolysis. Most of these metabolites are eliminated in the urine without Phase II conjugative reactions.

Toxicity

For nerve agents in vapour form, the toxicity is measured as the product of concentration-time, which refers to concentration multiply by time. LC_{t50} means the quantity of the agent which will predictably cause lethal effect in 50% of the given population. For nerve agents in liquid form, the toxicity is measured as lethal dosage. LD₅₀ refers to the quantity of the agent which will predictably causes lethal effect in 50% of the given population. The toxicity of nerve agents in their vapour and liquid form are shown in Table 1.¹ The immediately dangerous to life and health (IDLH) concentrations of nerve agents are 0.0001 mg/m³ for GA, GB, GF and VX. IDLH for GD is 0.0003 mg/m³.¹

Toxicodynamics

Nerve agents are organophosphorus cholinesterase inhibitors. They inhibit the acetylcholinesterase at

cholinergic receptor in tissue, butyrylcholinesterase in plasma and the acetylcholinesterase in the erythrocyte.^{7,8} The clinical effects are caused by excessive acetylcholine. Organs with cholinergic receptor sites include smooth muscle, skeletal muscle, exocrine glands, central nervous system, cranial efferent and ganglionic afferent cholinergic nerves. There are two types of cholinergic receptors, the muscarinic receptor and the nicotinic receptor.

Organs with muscarinic receptors include smooth muscle and exocrine glands. Organs with nicotinic receptors include skeletal muscle and ganglia. Central nervous system contains both receptors. Atropine mainly block the effects of excess acetylcholine at muscarinic sites rather than the nicotinic sites.

The binding of the nerve agents to the cholinesterase (enzyme) is essentially irreversible unless removed by therapy. Erythrocyte enzyme activity returns at the rate of erythrocyte turnover, usually at a daily rate of 1%. Plasma and tissue enzyme activities return with the synthesis of new enzymes. However, the rate of return are variable among different tissues.⁹

Oxime possesses the functions of removing the nerve agents from the enzymes and reactivating the enzymes unless "aging" has occurred. "Aging" is a biochemical reaction between the agent and the enzyme complex. Once "aging" has occurred, the agent-enzyme complex becomes refractory to the oxime reactivation. Different nerve agents have different aging time. The aging time for GD (soman) is 2 minutes whereas GB (sarin) is 3 to 4 hours. Other nerve agents have a longer aging time. This reflects that oxime is not useful for GD poisoning if two minutes has elapsed.^{1,10,11}

Table 1. Vapour and liquid toxicity.

Agent	Vapour toxicity LC _{t50} (Mg-min/m ³)	Liquid toxicity LD ₅₀ amount
VX	10-50	10 mg
GF	Unknown	30 mg
GD	50-70	50-350 mg
GB	100	1700 mg
GA	400	1000 mg

Clinical effects

The clinical effects of exposure to nerve agents depend on the route of administration and the dosage. Exposure to a sublethal amount of nerve agent vapour will cause effects in eyes, nose and airway. Exposure to a sublethal amount of nerve agent liquid on the skin will cause effect in the gastrointestinal tract (GI) initially. On the other hand, exposure to lethal amount of vapour or liquid nerve agents will cause a rapid cascade of events. Victims will collapse and fit within one to two minutes, followed by apnoea and muscle flaccidity in the next few minutes.

Nose

Rhinorrhoea may be the first symptom of nerve agent vapour exposure. The severity is dose dependent.

Eye

Miosis is a characteristic sign of nerve agent vapour exposure. Exposure to nerve agent liquid will not cause miosis unless the amount is lethal or the droplet of liquid is close to the eye. Miosis will begin within seconds or minutes after exposure.^{12,13} It is bilateral but occasionally unilateral due to the leakage from the mask in a masked person.

Victims usually complained of pain, dim vision, blurred vision, conjunctival injection, nausea and vomiting. Topical eyedrops like atropine or homatropine can relieve miosis and its associated symptoms.

Airways

Exposure to nerve agent vapour causes bronchoconstriction and increase airway secretions. Apnoea can occur within minutes on exposure to large amount of nerve agent. The apnoea may be mediated through the central nervous system although peripheral factors like bronchoconstriction or intercostal muscle weakness may contribute.^{1,14,15}

Gastrointestinal tract (GI)

Exposure to nerve agents causes an increase in the GI tract secretions and its motility. Therefore, victims will experience nausea, vomiting, abdominal cramp,

diarrhoea and fecal incontinence. Nausea and vomiting are early signs of nerve agents liquid exposure while diarrhoea usually occurs when victims are in contact with large amount of agents. Increased GI tract secretions can occur after systemic absorption of the agents by either routes.

Glands

Exposure to nerve agents vapour will increase secretions from lacrimal, nasal, salivary and bronchial glands. Exposure to liquid agent on the skin will cause localised sweating. Generalised sweating is common after a high dose of vapour or liquid exposure.

Skeletal muscle

Excessive acetylcholine on nicotinic receptors will cause muscle fasciculation and twitching. This will be followed by muscle flaccidity and weakness if exposed to a high dose of nerve agent. However, muscle flaccidity is never the first sign of nerve agent poisoning in neuromuscular system.

On exposure to a droplet of liquid agent, localised fasciculation usually occurs at the site of exposure. Generalised fasciculations are common after high dose exposure.

Cardiovascular system

The heart rate can be slow, normal or fast in nerve agent poisoning. Bradycardia is due to the stimulation of vagus nerve. Tachycardia can be due to the stimulation of nicotinic receptors in the pre-ganglionic sites and other factors like hypoxia and anxiety. Therefore, heart rate is not a good indicator for diagnostic and prognostic purposes. Blood pressure may be elevated from adrenergic stimulation but is usually normal until the terminal decline.

Central nervous system (CNS)

On exposure to large amount of nerve agents, victims will have loss of consciousness, seizure and apnoea. These clinical effects begin within one minute on exposure to large amount of vapour. There may be an asymptomatic period of one to thirty minutes after skin contact with large amount of liquid agent.

On exposure to small amount of nerve agents, the CNS effects vary and are non-specific. These include forgetfulness, depression, failure to concentrate, insomnia, bad dreams, irritability and impaired judgement.^{16,17}

Summary of clinical effects

The symptoms and signs on nerve agents poisoning depend on the amount and route of exposure. These are summarised in Tables 2 and 3.

Detection

Detectors of nerve agents attack and poisoning include M256A1, CAM, M8 paper, M9 paper, M8A1 and M8 alarm system. The liquid "G-agents" turn M8 paper a "yellowish gold" colour and VX turns M8 paper a "verdant" or "olive green" colour. Liquid nerve

agents and vesicants turn M9 paper pink, red, reddish-brown or purple. However, this colour change in M9 paper cannot identify the class of agent.¹

Laboratory findings

As discussed above, nerve agents inhibit the cholinesterase activity in erythrocyte, plasma and tissue. Therefore, the estimation of this enzyme activity is useful in detecting nerve agent exposure. The erythrocyte enzyme activity is more sensitive in detecting acute nerve agent exposure than plasma enzyme activity.

It must be emphasized that the amount of erythrocyte enzyme inhibition does not correlate well with the severity of exposure. In one extreme, normal or nearly normal erythrocyte enzyme activity may be present

Table 2. Effects on vapour exposure.

	Mild	Severe
Symptoms and signs	Nose: rhinorrhoea Mouth: salivation Eyes: miosis, dim vision Lungs: chest tightness	Symptoms and signs as in mild exposure plus Muscle twitching, weakness or flaccid paralysis Seizure Severe breathing difficulty or apnoea Loss of consciousness Urinary and fecal incontinence
Time of onset	Seconds to minutes after exposure	Seconds to minutes after exposure
Self-aid	One MARK I	None Casualty is unable to help himself
Buddy-aid	Stand by	Three MARK I and diazepam

Table 3. Effects of skin exposure by liquids.

	Mild/Moderate	Severe
Symptoms and signs	Nausea, vomiting Weakness Muscle fasciculation and sweating at the site of exposure	Symptoms and signs as in mild/moderate exposure plus Muscle twitching, weakness or flaccid paralysis Seizure Severe breathing difficulty or apnoea Loss of consciousness Urinary and fecal incontinence
Time of onset	10 minutes to 18 hours after exposure	Minutes to an hour after exposure
Self-aid	One to two MARK I	None Casualty is unable to help himself
Buddy-aid	Stand by	Three MARK I and diazepam

with moderate toxic effects in these organs. However, at the other extreme, the erythrocyte enzyme may be inhibited up to 70% when rhinorrhoea and miosis are the only signs of exposure.¹⁸

Other laboratory findings are related to complications. Acidosis may occur after prolonged hypoxia. Electrolyte imbalance may occur from sweating and GI tract disturbance.

Medical management

Management of nerve agents poisoning consists of (I) termination of exposure and resuscitation (II) antidotes and drug administration, (III) decontamination, (IV) ventilation and supportive therapy. The clinical conditions of a patient will determine the order and the need for each of these procedures.

(I) Termination of exposure and resuscitation

Medical personnel should be protected with Personal Protective Equipment (PPE) when handling these casualties. It is essential to terminate the exposure of nerve agents and provide basic life support for airway, breathing and circulation. General supportive treatments include oxygen, fluid resuscitation, correction of acid-base imbalance and the monitoring of cardiac arrhythmia.

(II) Antidotes and drugs administration

Atropine

Atropine is an anticholinergic drug. It is very effective in blocking excessive acetylcholine in muscarinic sites. Therefore, it dries the secretions from exocrine glands and reduces smooth muscle constriction. The initial dosage is 2 mg and can be given intravenously, intramuscularly or through the endotracheal tube. It can be given repeatedly every 5 to 10 minutes until the secretion dries up or the ventilation improve. In general, 15-20 mg atropine may be required to achieve these effects.¹⁹⁻²¹ Moreover, atropine will not help miosis and has no effect on skeletal muscle.

Atropine may cause side effects when given to people not exposed to nerve agents. These side effects are

common when more than 10 mg atropine is given. Side effects include delirium, inhibition of sweating which results in heat related illness.

Pralidoxime chloride

Pralidoxime chloride is an oxime. Its mechanism of action is to break the nerve agent-enzyme bond so as to restore the enzyme activity. It mainly acts on the nicotinic sites to improve the strength of the skeletal muscle. Its effect on the muscarinic sites is not apparent clinically. In addition, it is less useful when aging has occurred.^{10,11,17} The initial dosage is 1 g given intravenously, over 20-30 minutes. Another dose can be repeated 1 hour later.²⁰

MARK I kit

MARK I kit is an auto-injector composed of 2 mg atropine (0.7 ml) and 600 mg 2-PAMCl (600 mg).^{1,20} Each military member are given 3 MARK I kit to carry.

The appropriate number of MARK I kit to be injected depends on the severity of exposure. A casualty with miosis and rhinorrhoea should be given one MARK I only if rhinorrhoea is severe. A casualty with mild to moderate dyspnoea should be given one to two MARK I, depending on the severity of respiratory distress. A severe casualty is defined as one with miosis, copious secretions, severe breathing difficulty or apnoea, cyanosis, muscle fasciculation or twitching, seizure and loss of consciousness. Three MARK I and diazepam should be given immediately. Atropine should then be given until the secretions dry and the ventilation improves.¹

The casualty with skin exposure to liquid is far more difficult to manage than vapour exposure. GI effects are expected to start at 30 minutes to 18 hours after exposure to liquid nerve agents. If the GI effects occur in the first few hours, two MARK I are usually required. If the GI effects occur late, only one MARK I is required. If the casualty has clinical effects similar to the severe casualty in vapour exposure, three MARK I and diazepam should be administered.¹

Diazepam

Diazepam is an anticonvulsant drug. Each military personnel carries one auto-injector containing 10 mg

diazepam for his buddy. The current military practice is to give diazepam with three MARK I to severe casualty, whether or not seizure is among those clinical effects.¹

(III) Decontamination

Decontamination is performed to prevent further absorption of the nerve agent by the casualty and to prevent the contamination of the nerve agent to others. In order to reduce the damage to the casualty, decontamination must be performed within minutes. If the agent is vapour, casualty should be moved to an environment free of vapour and a protective mask should be put on. Skin decontamination is not necessary after exposure to nerve agent vapour but clothing should be removed as it may contain trapped vapour.

On exposure to liquid nerve agents, clothing should be removed immediately. Water is a decontaminant, which can remove and dilute the chemical agents when used in large amount. Apart from water, 0.5% hypochlorite solution can also be used to remove and neutralize the chemical agents. Some decontamination kits are also available. These include M291 decontamination kit which contain charcoal and resin and M258A1 decontamination kit which contain two moistened towelettes.²²⁻²⁴

(IV) Ventilation

Ventilatory support is an essential therapy for a casualty with severe respiratory compromise. The effectiveness of antidotes is increased with the addition of ventilation. The methods of ventilation depends on the equipment available. Airway resistance is usually high (50-70 cm water) due to the copious secretions and broncho-constriction.^{1,15} In reported cases of severe exposure, ventilation were required from half an hour to three hours.

Triage

Immediate: A casualty who presented with loss of consciousness, convulsion or post-ictal drowsiness, difficulty in breathing, apnoea or flaccid paralysis will survive with appropriate therapy if the circulation is still intact.

Delayed: A casualty recovering from a severe exposure after receiving large amounts of antidotes and has been ventilated.

Minimal: A casualty with minimal symptoms and can walk and talk.

Expectant: A casualty in circulatory failure with no heart beat.

Antidote enhancement

Pyridostigmine is a carbamate drug which is used to treat myasthenia gravis. It binds to the acetylcholinesterase for a few hours by the reaction called carbamylation. While the enzyme is carbamylated, it will be protected from attack by compounds like nerve agents. Therefore, pyridostigmine is used as a pre-exposure enhancement for nerve agent exposure. This is also commonly called "pretreatment".^{1,10,11}

The dosage regimen for antidote enhancement is pyridostigmine 30 mg every 8 hours.¹ To start or stop using the drug is a military command decision and not an individual decision.

It was found that in soman exposure, the use of pyridostigmine increased the LD₅₀ by several folds and the survival rate increased as well.^{1,11} However, the use of pyridostigmine provided no additional benefit in GB or VX poisoning. Current data are inadequate to evaluate the effectiveness of pyridostigmine on GA and GF poisoning.

Pyridostigmine is not an antidote. It should not be taken after soman exposure. It will be ineffective if the standard MARK I therapy is not used properly.

Summary

Nerve agents are the most toxic chemical agents. This is a popular chemical agent used in terrorist attacks. Although Hazmat incidents are uncommon, nerve agents can cause clinical effects within seconds and death within minutes if not managed immediately. Therefore, medical personnel should have a basic

knowledge about the toxicity, clinical effects and the management of the nerve agents. Moreover, staff personal protection and their safety when handling these casualties should not be undervalued.

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