TOXICOLOGY REVIEW

Sarin: guidelines on the management of victims of a nerve gas attack

A P Volans

Abstract
Sarin is now a weapon of the terrorist. Its acute effects are primarily due to unrestricted cholinergic activity at both muscarinic and nicotinic receptors. Treatment is based on the use of large doses of atropine and pralidoxime which may lead to practical problems of sufficient drug supplies for the average hospital. Ventilation may be necessary and present problems. Victim decontamination involves use of bleach, soap and water. Staff handling casualties need protection with respirators and butyl rubber boots and gloves.
(*J Accid Emerg Med* 1996;13:202–206)

Key terms: sarin; organophosphates; terrorist attack; management

Organophosphate pesticides are used extensively in the agricultural and horticultural industry. Worldwide there are estimated to be three million cases of poisoning and about 40 000 deaths per year, mostly in the developing world, from misuse of these chemicals.[1][2] There are many standard texts to advise on the management of such patients.[3]

Recently, the organophosphate nerve gas, sarin, has been used by terrorists against civilians in Japan. The military have experience in the treatment of such cases and in this review I aim to bring the lessons learnt in military medicine to the audience of civilian emergency medicine.

The risk
Organophosphate nerve agents are relatively easy to make in an impure form, easy to distribute, can cause large numbers of casualties, especially in enclosed spaces, and their effects are frightening. They also have a malevolence that simple explosive devices seem not to have and consequently are an ideal terror weapon. The fact that they carry a significant risk to the perpetrator may have reduced, until recently, their acceptability as a weapon for the urban terrorist.

In Japan, there is evidence that sarin was used by an "Armageddon" based religious sect which is preparing for the imminent end of the world.[4-6] Whereas in Britain we have little evidence of such sects, Europe is not immune to such beliefs, for example the simultaneous mass suicide of a Templar based Armageddon

sect in Switzerland and Canada in 1994, and the death of British subjects at the Davidian cult centre at Wako, USA. With the oncoming millennium, we might well see more such cults, and now that a precedent exists, copy-cat attacks are a possibility.

Even without Armageddon cults, the phenomenon of the suicide bomber is not unknown in Europe.

Recent press coverage[6][7] has, with more or less detail, described the manufacture of sarin and stressed the simplicity of the process.

The agent
The agent responsible for the two Japanese attacks was sarin. This organophosphate was first produced in Germany along with tabun and soman in the late 1930s by the agrochemical industry in their quest for pesticides.[1][8][9] Sarin and tabun, which are long acting potent neurotoxins, were both identified as potential chemical weapons but were not used in the military field by the Nazis, possibly for fear of retaliation. They are currently restricted to a "no first use" policy under the 1925 Geneva protocol[1][8] but were used during the Iran-Iraq war of the 1980s.

The agents differ from the organophosphate pesticides in that they are fluorinated, volatile, and more potent. They are otherwise similar in structure and mode of action.[2]

Of the three agents, tabun and sarin are volatile liquids and are absorbed as vapour or liquid through mucous membranes and breaks in the skin. Because of their volatility the military classify these as non-persistent agents.

The agents smell slightly of paint, although this odour is not detectable by significant proportions of the population.[8][9]

Soman is classified as semi-persistent. It may be prepared as a solid form, from which the agent volatilises; it can also penetrate the skin, and because of its persistence can contaminate the environment, entering the food chain. It is more potent, more toxic, and more rapidly acting than tabun and sarin.

One agent, VX, was developed in the United Kingdom. It is persistent, highly toxic and skin penetrating, and is environmentally contaminating. Little is known of its actions in man.[9]

Chemical agents may be delivered in binary form. This is militarily useful with nerve agents because of their toxicity. The weapon is transported as separate non-toxic constituents

Department of Accident and Emergency, Accident and Emergency Department, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF
A P Volans

Correspondence to:
Mr A P Volans,
Senior Registrar in Accident and Emergency

which are only mixed at the target to produce the active agent. In military delivery systems, the mixed agent is then distributed in droplet form by an explosion.

Sarin can be readily produced by mixing isopropyl alcohol with two purchasable halogenated methyl-phosphonates. When mixed these develop an exothermic reaction producing sarin and hydrochloric acid. The yield is contaminated (1–10% sarin) and to stockpile the chemical requires a very dangerous distillation.[7] In consequence the binary mode is more common and was the mode of delivery in the Japanese attacks, the agent being distributed as a vapour rather than in droplet form.[2 7]

Chemical weapons are not necessarily designed to kill, rather they should incapacitate the soldier and tie up resources in his care.[8 9]

Toxicity
The organophosphate nerve agents, like the less potent insecticides, act acutely by binding to and inactivating the enzyme cholinesterase. The agent crosses the blood-brain barrier and acts at both muscarinic and nicotinic receptors. With the enzymatic blockade, the level of acetylcholine rises at the postsynaptic receptor and stimulation becomes persistent. The symptoms of acute poisoning therefore reflect acetylcholine's activities in the body (table 1).

The first clinical evidence of exposure to an organophosphate vapour is usually pupillary meiosis and blurred vision due to muscarinic activity within the iris. Mydriasis can occur in 10% of cases because of presynaptic nicotinic activity.[1 3] Meiois occurs with sublethal exposure levels in the order of 15 mg per minute per mm^3 (aerosol concentration in air) of sarin.[8 9] The balance of effects then depends on the route of entry.

Inhaled sarin toxicity has a rapid onset, with respiratory symptoms and salivation predominating; if taken orally the onset is slower and gastrointestinal symptoms are more apparent. Where the skin is intact, absorption is very limited; however, in the presence of wounds, absorption will result in localised muscle fasciculation at an early stage of toxicity, and eye signs may be absent.

The LD$_{50}$ for sarin is 1 mg absorbed; however, significant poisoning occurs at much lower levels of exposure and the victim may require intensive medical support to reverse the symptoms.

Table 1   Organophosphate toxicity

Peripheral muscarinic	Peripheral nicotinic	Central muscarinic
Bronchosecretion	Fasciculation	Confusion
Bronchoconstriction	Weakness	Restlessness
Pulmonary oedema	Tachycardia	Headache
Cyanosis	Hypertension	Tremor
Sweating	Hyperglycaemia	Ataxia
Salivation	Pallor	Hypotension
Nausea + vomiting	Mydriasis (rare)	Respiratory depression
Cramps		Convulsions
Diarrhoea		
Incontinence		
Bradycardia		
Hypotension		
Meiosis		
Blurred vision		

As well as the acute cholinergic crisis, organophosphates are known to have late sequelae, with an intermediate syndrome described,[11] developing 24 to 48 hours after poisoning and possibly due to postsynaptic effects, and a late syndrome due to demyelination, developing two to three weeks after exposure.[2 11 12] These are discussed later.

Diagnosis
Nerve agent poisoning is diagnosed clinically, based on exposure to an agent with resulting meiosis and blurred vision with bronchospasm and salivation. More severe cases may lead to respiratory failure secondary to pulmonary oedema and respiratory muscle paralysis. Muscle fasciculation with abdominal cramps and urinary and faecal incontinence may also be a feature.[1 8 9]

With the organophosphate insecticides, it is typical to find bradycardia and excess salivation as presenting features. In the reports of the Tokyo poisonings, tachycardia and hypertension, a nicotinic, presynaptic effect, was common and excess secretions were only seen in the most severely poisoned patients.[13 14]

General management
In the military situation, at risk personnel are issued with nuclear, chemical and biological warfare (NCB) suits. Oral pyridostigmine is taken prophylactically if a real risk of attack is perceived and "combo pens" of atropine (2 mg) and pralidoxime (4 g) are issued for self treatment on exposure to a nerve agent.[5 8 9] Soldiers are trained in symptom recognition and agent identification as well as safe procedures in the presence of such agents. In civilian life this level of preparedness is unlikely.

DECONTAMINATION
In a civilian incident, the fire brigade is responsible for on-site safety and chemical identification. A cordon is established around a chemical incident. All casualties would then leave the cordon through a control point where decontamination by washing or application of the adsorbent Fuller's earth would occur, depending on advice from the paramedic services and the National Chemical Emergency Centre at Harwell.

Patients may also be contained rather than decontaminated and could be transported with their bodies enclosed within heavy plastic casualty pouches (personal communication, Assistant Divisional Officer, Trent Fire and Rescue Service, Sheffield). Within each region, there are designated hospitals, which have accident and emergency (A&E) departments deemed capable of managing contaminated patients. The hospital major accident plan (MAJAX) should carry these lists.

Sarin permeates clothing, leather, and wood and then exudes as a liquid or evaporates into the air, putting rescue and medical staff at risk of inhalation. Its skin penetrating capacity is poor on intact skin but it is well absorbed through wounds and passes with ease through latex rubber (for example, surgical gloves).[8 9]

Protection for attending staff where there is only a vapour hazard, such as in a receiving A&E department, is considered adequate with respirators and butyl rubber gloves and boots. At the incident full protection with NCB suits or their equivalent is necessary.[5] [8] [9]

Sarin and other nerve agents are highly soluble in lipids, moderately soluble in water, and rapidly broken down by strong alkali and chlorinated compounds.

After initial resuscitation the patient should be stripped and ideally cleaned with a hypochlorite bleach and water which will denature the agent, followed by soap and water cleansing. Care must be taken with disposal of removed clothing and used Fuller's earth which may give off gas.[8]

If absorbed orally, gastric lavage and instillation of charcoal to absorb the agent, or 5% sodium bicarbonate to enhance its hydrolysis, is recommended, although benefit is not proven.[3] [11]

Laboratory diagnosis

Red cell cholinesterase is used as a monitor of total body cholinesterase activity. This test is performed on an EDTA sample[1] and the test is available in most hospital laboratories. In less severe levels of poisoning, and with less toxic agents, the residual activity can be used as guidance for treatment (table 2) and in severe cases can be used to monitor the success of enzyme reactivation.

Specific treatments

ATROPINE

Atropine is used primarily to reverse salivation and bronchospasm. The military guidelines are an initial dose of 2 mg atropine intravenously or intramuscularly, repeated every 15 minutes until atropinisation has been achieved. Signs of an adequate response are an increase in heart rate to more than 90 beats per minute, a dry mouth, and dry skin. Resolution of meiosis is not a reliable guide as it may not respond to parenteral atropine.[1] [3] [8] [9] During the Tokyo poisoning the majority of mildly affected victims responded well to topical atropine as a treatment of their ocular symptoms.[13]

The military guidelines suggest that for sarin, doses of 100 mg or more of atropine may be needed to achieve a full response, and in severe cases it may be necessary to maintain full atropinisation over several days, until symptoms resolve and enzyme levels show recovery.

The Japanese experience, so far reported,[14] describes a total dose requirement of 15 mg of atropine over 24 hours in one case requiring ventilation.

Atropine only has significant action on the muscarinic effects of the agent. At high doses, cardiac arrhythmias such as supraventricular tachycardia and heart block[8] are significant complications, particularly if the patient becomes hypoxic.

PRALIDOXIME MESYLATE

Atropine blocks some postsynaptic activity. It does not release the enzyme from the organophosphate and has minimal activity at the neuromuscular junction. If release is not achieved within 24 hours, then premature aging of the enzyme occurs. Once this has happened, reactivation cannot occur and recovery is dependent on regeneration of the enzyme, a process that may take several weeks. With the agents tabun and sarin, the enzyme can be reactivated by pralidoxime mesylate given intravenously, concurrently with atropine, at an initial dose of 1–2 g at 0·5 g/min, repeated at one hour and then every eight hours until evidence of recovery is seen at the nicotinic sites.[1] [8] [9]

The Japanese case so treated[14] showed rapid recovery within 24 hours of both the clinical picture and the plasma cholinesterase level.

As pralidoxime reverses enzyme blockade, the need for atropine declines and patients should be monitored closely for the unmasking of atropine toxicity.[8]

BENZODIAZEPINES

Benzodiazepines (diazepam, clonazepam) are used for the control of convulsions as well as of the centrally generated anxiety attributed to the agent, which is not relieved by pralidoxime. Doses of diazepam of 10–20 mg repeated as required are advised.[1] [8] [9]

VENTILATION

Ventilation may be required to control hypoxia. The severely poisoned patient is suffering from paralysis of their respiratory muscles, severe bronchospasm, marked bronchosecretion, and pulmonary oedema. In addition, treatment with high dose atropine will sensitise the heart to arrhythmias in the presence of hypoxia.

When paralysing the patient for ventilation, suxamethonium is contraindicated because of its postsynaptic depolarising activity and its degradation by cholinesterase.[11] A non-depolarising relaxant is the drug of choice, although the dose is likely to be difficult to predict because of its competitive action.

With severe bronchoconstriction and increased secretions, high ventilation pressures (>65 cm H_2O)[9] are to be expected.

It is advisable to use a filter on the ventilators to prevent contamination of the equipment.[5]

Drug interactions

Drugs reported as contraindicated in severe organophosphate poisoning are morphine,

Table 2   Red cell cholinesterase activity and severity of poisoning (after Minton and Murray[1])

Severity	Clinical features	RBC esterase	Treatment
Subclinical	No symptoms/signs	>50%	Observation
Mild	Tiredness, dizziness, nausea, headache, salivation, wheeze	20–50%	Atropine 1 mg iv/im Pralidoxime 1 g iv/im
Moderate	+Meiosis, weakness, ataxia, fasciculation, dysarthria	10–20%	Atropine 2 mg every 15 min Pralidoxime 1–2 g repeat at 1 hour then 8 hourly
Severe	+Coma, flaccid paralysis, cyanosis, pulmonary oedema, respiratory distress, severe mieosis	<10%	Atropine 4–5 mg iv, every 15 min Pralidoxime 1–2 g iv as above

iv, intravenous; im, intramuscular.

aminophylline, theophylline, and chlorpromazine.[11]

Logistical problems

Hospital trusts are not kept on a war footing. Although all hospitals have a major accident plan, very few will have rapid access to decontamination and protection systems suitable for a nerve gas attack. Individual departments will have to seek appropriate sources of respirators and training in their use. Standard fire brigade compressed air units would not be appropriate for use by untrained personnel (personal communication, Assistant Divisional Officer, Trent Fire and Rescue Service, Sheffield). NHS Document HSG(93)38 describes in general the role of the district health authority and regional health authority in the response to a chemical incident, with further details in the Department of Health document *Emergency planning in the NHS*, HC(90)25. What is not clear is the suggested location of a source of respirators and the appropriate training.

Butyl rubber based gloves and boots should be obtained and included in the major accident equipment stores. Other body protection is not considered necessary outside of the attack area.[6 8 9]

Atropine is used at high dosage and for prolonged periods in severe poisoning. If a large number of casualties are to be treated, then hospital stocks are likely to be run down rapidly. Personal inquiry from several city centre hospital pharmacy departments revealed available stocks of between 200 mg and 2000 mg of atropine, normally as 1 mg preloaded syringes. Military guidelines suggest that doses of 50 to 100 mg per patient in the first 24 hours are unremarkable.

Pralidoxime was not universally available in all hospitals contacted. It is held at designated centres, a list of which is available from the Department of Health and through the regional poisons centres. Our hospital, a designated centre, carries 20×1 g vials of pyridostigmine. These are manufactured for the Department of Health and stores are held centrally in Middlesex. The drug has a long shelf life but is rarely used. Part of a unit's preparations must include the update of stocks. In the event of mass casualties, the anticipated response is to collect extra supplies from surrounding designated sites and to obtain resupply from the Department of Health through the central vaccine unit.

The use of this drug is important; there is a window of opportunity for its use of 24 hours for sarin and tabun.[1 8 9]

Prognosis

These weapons, although potentially lethal, injure far more victims than they kill. In the first attack at Matsumoto, Japan,[12] there were seven deaths (2%) among the 311 victims injured by an open air night time attack. In the most recent Japanese attack, 10 victims (2%) died out of 600 admitted to hospital, with 5000

minimally affected.[6 13] It is possible that the low mortality in these terrorist attacks was due to the delivery as a vapour rather than an explosively distributed droplet. However, during the Iran-Iraq war, the mortality among 3500 identified victims of tabun attack was also 2% (70 deaths).[14]

Deaths from severe poisoning usually occur within the first 24 hours in untreated cases and within 10 days in treatment failure and are generally due to hypoxia.[8 9 13–15]

Symptoms may recur if reactivation is not seen to occur with treatment, and there is the risk of delayed release of the agent from fatty tissues due to the agent's lipid solubility. Consequently the patient should be monitored until stable both clinically and by enzyme levels.

In the Japanese attacks, the majority of those affected had eye symptoms only, presumably from low levels of vapour exposure, and were successfully treated with atropine eye drops.[13]

Late sequelae

INTERMEDIATE SYNDROME

An intermediate syndrome has been described[10] with organophosphate insecticide poisoning. Ten patients suffered a typical acute cholinergic response that was treated along the suggested guidelines with apparent resolution of all cholinergic symptoms. These patients then deteriorated 24 to 48 hours after poisoning, with cranial nerve palsies and marked proximal muscle weakness. Seven patients showed signs of respiratory failure which required ventilation in four. Death occurred in three patients. Recovery in the survivors took 5–15 days. One of these patients went on to develop the typical late sequelae.

LATE SYNDROME

This is a peripheral neuropathy with a mixed sensorimotor pattern. The pathology is a primary axonal degeneration with secondary demyelination.[2 11] The risk of development is believed to be related to the inherent toxicity of the agent and the dose received.[16]

Clinically, the symptoms start peripherally and progress centripetally with tingling and burning of the legs with weakness and ataxia.[1 14 16] Onset is typically two to three weeks after poisoning, and recovery – if it occurs – takes 6–12 months.

Neuropsychiatric disorders are recognised.[1 8 9 16] Psychomotor performance is disturbed, memory, speech and mood can be affected, and features of depression, anxiety, and irritability are recorded. Weakness and fatigue may persist for several months.

The report on the Matsumoto attack[12] includes follow up data on 85% of survivors. In the majority of patients, symptoms had resolved by one month, although 1% still suffered from headache at three months. The predominant symptoms at one month were of dysaesthesiae, eye discomfort with altered

vision, rhinorrhoea, and fatigue. These symptoms were correlated with lower levels of erythrocyte anticholinesterase and residual meiosis. None of these survivors had developed the typical late sequelae of peripheral neuropathy.

Conclusions

Organophosphates have been freely available in the agrochemical industry for many years and tend to have caused isolated episodes of poisoning. There is now the risk of terrorist use of sarin, a potent neuroactive organophosphate poison, against large populations.

Treatment of sarin poisoning can require extremely large doses of atropine, far above those of normal clinical experience, but dosage may be controlled by titration against simple clinical signs.

If large numbers of casualties occur, there may be a risk of a hospital running out of atropine, and emergency sources of both atropine and pralidoxime should be identified within any major incident plan developed to deal with such an event.

Decontamination of patients should be performed using a regimen including bleach as well as soap and water.

Staff dealing with casualties need protection with respirators and butyl-rubber boots and gloves rather than latex rubber garments. Sources of respirators and training in their use should be included in any major incident plan.

Severely poisoned patients need ventilation. Suxamethonium should not be used for intubation, and ventilation will be difficult because of bronchospasm and pulmonary secretions. Several other common drugs are also contraindicated in poisoned patients.

Despite their inherent toxicity and fearful reputation, exposure to nerve gases has a low mortality if treated aggressively.

Contact numbers

National Chemical Emergency Centre, Harwell
01235 82111 Ext 3249

Department of Health Central Vaccine Unit (office hours only)
0171 972 4476 and 4477
Fax: 0171 972 4468

Emergency supplies of pralidoxime (out of office hours):
Pasteur Merrier MSD 01836 503649

---

1 Minton NA, Murray VSG. A review of organophosphate poisoning. *Med Toxicol* 1988;3:350–75.
2 Jamal GA. *Adverse Drug React Toxicol Rev* 1995;14:83–5.
3 Proudfoot AT. *Acute poisoning: diagnosis and management*, 2nd ed. Oxford: Butterworth-Heinemann, 1993:166–72.
4 Murder on the metro. *Nature* 1995;374:392.
5 World MJ. Toxic gas trauma. *Lancet* 1995;346:260–1.
6 Terror in Tokyo. *The Economist* 1995; March 25:87–8.
7 Sarin savagery. *The Economist* 1995; March 25:132–3.
8 *JSP312: Medical manual of defence against chemical weapons*, 6th ed. MOD D/Med(F&S)(2)/10/1/1. London: HMSO, 1987
9 Nato. *Handbook of the medical aspects of NBC defensive operations*. AMedP-6 Part III – Chemicals, 1986: chapter 2. London: Combined Services MOD HMSO.
10 Karalliedde L, Senanayake N. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med* 1987;316:761–3.
11 Abou-Donia MB, Lapadula DM. Mechanisms of organophosphorus ester-induced delayed neurotoxicity: type I and type II. *Annu Rev Pharmacol Toxicol* 1990; 30:405–40.
12 Jamal GA. Long term neurotoxic effects of organophosphate compounds. *Adverse Drug React Toxicol Rev* 1995;14:85–99.
13 Suzuki T, Morita H, Ono K, Maekawa K, Nagai R, Yazaki Y. Sarin poisoning in Tokyo subway [letter]. *Lancet* 1995;345:980.
14 Nozaki H, Aikawa N, Shinozawa Y, Hori S, Fujishima S, Takuma K, et al. Sarin poisoning in the Tokyo subway [letter]. *Lancet* 1995;345:980–1.
15 Morita H, Yanagiawa N, Nakajima T, Shimizu M, Hirabayashi H, Okudera H, et al. Sarin poisoning in Matsumoto, Japan. *Lancet* 1995;346:290–3.
16 Abbas F. Report of the specialists appointed by the Secretary General of the United Nations to investigate allegations by the Islamic Republic of Iran concerning the use of chemical weapons. Proceedings of the first World Congress on Biological and Chemical Warfare. *Arch Bel de Medic Sociale, Hygiene Medicine du Travail et Medicin Legal(suppl)* 1984:302–31.