

## Nerve Agents

### Introduction

The nerve agents (NA) are a group of particularly toxic chemical warfare agents. They were developed just before and during World War II. Although chemically related to the organophosphorus insecticides, their clinical presentation and medical management may differ. The principal nerve agents are: GA (tabun), GB (sarin), GD (soman), GF (cyclosarin) and VX (methylphosphonothioic acid). In some countries the "V" agents are known as "A" agents.

### Physical and Chemical Properties

Nerve agents are organophosphorus esters. The "G" agents tend to be non-persistent whereas the "V" agents are persistent. Some agents may be thickened in order to increase their persistence, and therefore the total amount penetrating intact skin.

At room temperature, GB is a comparatively volatile liquid and therefore non-persistent. GD is also significantly volatile, as is GA though to a lesser extent. VX is a relatively non-volatile liquid and therefore

persistent. It is regarded as presenting little vapour hazard to people exposed to it. In the pure state nerve agents are colourless and mobile liquids. In an impure state, nerve agents may be encountered as yellowish to brown liquids. Some nerve agents have a faint fruity odour.

In general, nerve agents are moderately soluble in water with slow hydrolysis, highly soluble in lipids, and are rapidly inactivated by strong alkalis and chlorinating compounds.

### Detection

Nerve agents may be detected by a variety of means. Single and three colour detector papers are available for individual issue to detect liquid nerve agent. Area detectors and monitors of various sensitivities are available (Figures 9,10,11). Highly sensitive and specific water testing kits are also available.

### Protection

To prevent inhalation of an incapacitating or lethal dose, it is essential that the breath is held and the respirator put on at the first warning of the presence, or suspected



Fig 9. Lightweight Chemical Agent Detector (LCAD) shortly to enter service. It uses ion mobility spectrometry to detect CW agents.



Fig 10. Man-Portable Chemical Agent Detector (MCAD) shortly to enter service.



Fig 11. Nerve Agent Immobilised-Enzyme and Detector (NALAD). This was the world's first biologically-based nerve agent detector.

presence, of a nerve agent. In addition, it is recommended that the eyes are shut whilst masking.

Normal clothing is penetrated by these agents whether contact is with liquid or vapour and specialised clothing including a respirator, NBC suit, gloves and foot protection are required when liquid agent is present. The respirator protects the eyes, mouth and respiratory tract against nerve agent spray vapour and aerosol. Nerve agent

vapour at field concentrations is generally not a percutaneous hazard over short periods of time, so that where a vapour hazard exists alone, the respirator may provide adequate respiratory and eye protection without the use of an NBC suit.

### Decontamination

The importance of early skin decontamination cannot be over emphasised. Decontamination of the skin should be



Table 3. Likely Signs and Symptoms of GB (Sarin) Poisoning Shown in Terms of Vapour Exposure and Approximate Blood Acetyl-cholinesterase Depression.

Short term Ct mg.min.m <sup>-3</sup>	Approximate AChE depression	Symptoms and signs*	
		Vapour	Systemic exposure only eyes protected
<2	<5%	Incipient miosis (miosis produced at Ct=2, t=30 min), slight headache	Nil
5	20% + 10%	Increased miosis, headache, eye pain, rhinorrhoea, conjunctival injection, tightness in chest	Tightness in chest
5-15	20-50% +10%	Eye signs maximal, Bronchospasm and all the effects already described	Symptoms beginning to appear. Bronchospasm
15	50% +10%	Bronchospasm and all the effects already described	Wheezing, alivation, eye effects, nausea, vomiting. (Local sweating and fasciculation in liquid contamination of the skin).
40	80% ± 10%	Symptoms and signs as for systemic	Weakness, defecation, urination. Paralysis, convulsions
100	100%	Respiratory failure, death	Respiratory failure, death

\* All symptoms and signs will be subject to very considerable inter-subject variation

accomplished immediately after exposure to liquid agent if it is to be fully effective. However, a late degree of protection is provided by late decontamination. Liquid agent may be removed by an adsorbant, such as Fullers' Earth, or chemically inactivated by the use of reactive decontaminants. Decontamination personnel should use a respirator and full protective equipment. If combat clothing is contaminated, it should be removed as soon as possible. Once a casualty has been decontaminated or the agent fully absorbed, no further risk of contamination exists. The casualty's body fluids, urine or faeces do not present a CW hazard.

## Mechanism of Action

### Absorption

Nerve agents may be absorbed through any body surface. When dispersed as a spray or an aerosol, agents can be absorbed through the skin, eyes and respiratory tract. When dispersed as a vapour at expected field concentrations, the vapour is primarily absorbed through the respiratory tract and is also a direct hazard to the eye. If enough agent is absorbed, local effects are followed by generalised systemic effects. The rapidity with which effects occur is directly related to the amount of agent absorbed in a given period of time.

### Inhibition of Cholinesterases

The effects of the nerve agents are mainly due to their ability to inhibit acetylcholinesterase throughout the body. Since the normal function of this enzyme is to hydrolyse acetylcholine wherever it is released, such inhibition results in the accumulation of excessive concentrations of acetylcholine at its various sites of action. These sites include the endings of the parasympathetic nerves to the smooth muscle of the iris, ciliary body, bronchial

tree, gastrointestinal tract, bladder and blood vessels; to the salivary glands and secretory glands of the gastrointestinal tract and respiratory tract; and to the cardiac muscle and endings of sympathetic nerves to the sweat glands.

The accumulation of acetylcholine at these sites results in characteristic *muscarinic* signs and symptoms. The accumulation of acetylcholine at the endings of motor nerves to voluntary muscles and in some autonomic ganglia results in *nicotinic* signs and symptoms. The accumulation of excessive acetylcholine in the brain and spinal cord results in characteristic *central nervous system* symptoms - see Table 3. The inhibition of cholinesterase enzymes throughout the body by nerve agents may be irreversible and its effects prolonged.

### Location of Acetylcholinesterase

Acetylcholinesterase is found associated with the post-junctional membrane at the neuromuscular junction and in the cell bodies and processes of cholinergic neurons. The concentration is particularly high in some central nervous system neurons. The location of acetylcholinesterase in autonomic ganglia is less well understood than that at the neuromuscular junction. Acetylcholinesterase is also found at sites where, as yet, no functional role has been identified: the musculotendinous junction, red blood cells, platelets and the placenta.

## Pathology

Aside from the decrease in the activity of cholinesterase enzymes throughout the body (which may be detected by chemical methods or by special staining), no specific lesions are detectable by gross examination. At post-mortem examination there is usually capillary dilatation, hyperaemia and oedema of the lungs; there may be similar changes in the brain and the remaining organs.

Neuropathological changes have been reported in animals following severe intoxication. During the acute phase these include damage within the central nervous system and at the neuromuscular endplate. Following severe exposure to some nerve agent, lesions to the peripheral motor nerves may be identified subsequently.

## CLINICAL AND PHARMACOLOGICAL EFFECTS

### Signs and Symptoms

The order in which signs and symptoms appear and their relative severity depend on the route of exposure and whether the casualty has been exposed to liquid agent or vapour. The local effects of vapour and liquid exposure are described below, followed by a description of the systemic effects which occur after significant absorption of agent via any route.

### Effects of Nerve Agent Vapour

#### *Absorption*

The lungs and the eyes absorb nerve agents rapidly. Changes occur in the smooth muscle of the eye (resulting in miosis) and in the smooth muscle and secretory glands of the bronchi (producing bronchial constriction and excessive secretions in the upper and lower airways). In high vapour concentrations, the nerve agent is carried from the lungs throughout the circulatory system; widespread systemic effects may appear in less than 1 minute.

#### *Local Ocular Effects*

These effects begin within seconds or minutes after exposure, before there is any evidence of systemic absorption. The earliest ocular effect which follows minimal symptomatic exposure to vapour is miosis (Figure 12). This is an invariable sign of ocular exposure to enough vapour to produce symptoms. It is also the last ocular manifestation to disappear. The pupillary constriction may be different in each eye. Within a few minutes after the onset of exposure, there also occurs redness of the eyes due to conjunctival hyperaemia, and a sensation of pressure with heaviness in and

behind the eyes. Usually, vision is not grossly impaired, although there may be a slight dimness especially in the peripheral fields or when in dim or artificial light.

Exposure to a level of a nerve agent vapour slightly above the minimal symptomatic dose results in miosis, pain in and behind the eyes attributable to ciliary spasm (especially on focusing), some difficulty of accommodation and frontal headache. The pain becomes worse when the casualty tries to focus the eyes or looks at a bright light. Some twitching of the eyelids may occur. Occasionally there is nausea and vomiting which, in the absence of systemic absorption, may be due to a reflex initiated by the ocular effects. These local effects may result in moderate discomfort and some loss of efficiency but may not necessarily produce casualties.

Following minimal symptomatic exposure, the miosis lasts from 24 to 72 hours. After exposure to at least the minimal symptomatic dose, miosis is well established within half an hour. Miosis remains marked during the first day after exposure and then diminishes gradually over 2 to 3 days after moderate exposure but may persist for as long as 14 days after severe exposure. The conjunctival erythema, eye pain, and headache may last from 2 to 15 days depending on the dose.

#### *Local Respiratory Effects*

Following minimal exposure, the earliest effects on the respiratory tract are a watery nasal discharge, nasal hyperaemia, sensation of tightness in the chest and occasionally prolonged wheezing expiration suggestive of bronchoconstriction or increased bronchial secretion. The rhinorrhoea usually lasts for several hours after minimal exposure and for about 1 day after more severe exposure. The respiratory symptoms are usually intermittent for several hours duration after mild exposure and may last for 1 or 2 days after more severe exposure.

### Effects of Liquid Nerve Agent

#### *Local Ocular Effects*

The local ocular effects are similar to the effects of nerve agent vapour. If the concentration of the liquid nerve agent contaminating the eye is high, the effects will be instantaneous and marked. If the exposure of the two eyes is unequal, the local

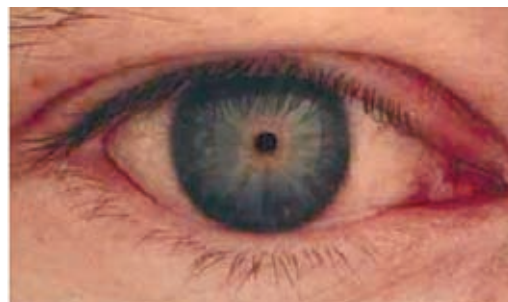


Fig 12. Miosis (right) from a very low dose of nerve agent.

manifestations may be unequal. Hyperaemia may occur but there is no immediate local inflammatory reaction such as may occur following ocular exposure to more irritating substances (for example, Lewisite).

#### *Local Skin Effects*

Following cutaneous exposure, there is localised sweating at and near the site of exposure and localised muscular twitching and fasciculation. However, these may not be noticed, causing the skin absorption to go undetected until systemic symptoms begin.

#### *Local Gastrointestinal Effects*

Following the ingestion of substances containing a nerve agent (which is essentially tasteless), the initial symptoms include abdominal cramps, nausea, vomiting and diarrhoea.

### **Systemic Effects of Nerve Agent Poisoning**

The sequence of symptoms varies with the route of exposure. Respiratory symptoms are generally the first to appear after inhalation of nerve agent vapour, although gastrointestinal symptoms are usually the first after ingestion. Following comparable degrees of exposure, respiratory manifestations are most severe after inhalation, and gastrointestinal symptoms may be most severe after ingestion. Otherwise, the systemic manifestations are, in general, similar after any exposure to nerve agent poisoning by any route. If local ocular exposure has not occurred, the ocular manifestations (including miosis) may initially be absent. Following systemic absorption mydriasis may occur due to a nicotinic effect on the superior cervical ganglion.

The systemic effects may be considered to be nicotinic, muscarinic or central. The predominance of muscarinic, nicotinic or central nervous system effects will influence the amount of atropine, oxime or anti-convulsant which must be given as therapy. These effects will be considered separately.

Acute or delayed (up to 50 hours) pulmonary oedema has been described during the course of pesticide poisoning. Its exact mechanism is not known and may be due to a direct cardiac effect, haemodynamic modifications or both. Soman and other organophosphates have been reported to produce histopathological changes in the myocardium. Similar effects may thus occur with nerve agents.

### **Muscarinic Effects**

Tightness in the chest is an early local symptom of respiratory exposure. This symptom progressively increases as the nerve agent is absorbed into the systemic circulation, whatever the route of exposure. After moderate or severe exposure, excessive

bronchial and upper airway secretions occur and may become very profuse, causing coughing, airway obstruction and respiratory distress. Audible wheezing may occur, with prolonged expiration and difficulty in moving air into and out of the lungs, due to the increased bronchial secretion or to bronchoconstriction, or both. Some pain may occur in the lower thorax and salivation increases.

Salivation may be so profuse that watery secretions run out of the sides of the mouth. Bronchial secretion may be thick and tenacious. If postural drainage or suction is not employed, these secretions may add to the airway obstruction. Laryngeal spasm followed by collapse of the hypopharyngeal musculature may also obstruct the airway. The casualty may gasp for breath, froth at the mouth, and become cyanotic.

If the upper airway becomes obstructed by secretions, laryngeal spasm or hypopharyngeal musculature collapse, or if the bronchial tree becomes obstructed by secretions or bronchoconstriction, little ventilation may occur despite respiratory movements. As hypoxaemia and cyanosis increase, the casualty will fall exhausted and become unconscious.

Following inhalation of nerve agent vapour, the respiratory manifestations predominate over the other muscarinic effects; they are likely to be most severe in older casualties and in those with a history of respiratory disease, particularly bronchial asthma. However, if the exposure is not so overwhelming as to cause death within a few minutes, other muscarinic effects appear. These include sweating, anorexia, nausea and epigastric and sub-sternal tightness with heartburn and eructation. If absorption of nerve agent has been great enough (whether due to a single large exposure or to repeated smaller exposures), there may follow abdominal cramps, increased peristalsis, vomiting, diarrhoea, tenesmus, increased lachrymation and urinary frequency. Cardiovascular effects can include bradycardia, hypotension and cardiac arrhythmias. The casualty perspires profusely and may have involuntary defecation and urination; this may lead to circulatory collapse and cardiorespiratory arrest followed by death.

### **Nicotinic Effects**

With the appearance of moderate muscarinic systemic effects, the casualty begins to have increased fatigue and mild generalised weakness which is increased by exertion. This is followed by involuntary muscular twitching, scattered muscular fasciculations and occasional muscle cramps. The skin may be pale due to vasoconstriction and blood pressure moderately elevated (transitory) together with a tachycardia, resulting from cholinergic stimulation of sympathetic



ganglia and possibly from the release of epinephrine. If the exposure has been severe, the muscarinic cardiovascular symptoms will dominate and the fascicular twitching (which usually appear first in the eyelids and in the facial and calf muscles) becomes generalised. Many rippling movements are seen under the skin and twitching movements appear in all parts of the body. This is followed by severe generalised muscular weakness, including the muscles of respiration. The respiratory movements become more laboured, shallow and rapid; then they become slow and finally intermittent. Later, respiratory muscle weakness may become profound and contribute to the respiratory depression.

### Central Nervous System Effects

In mild exposures, the systemic manifestations of nerve agent poisoning usually include tension, anxiety, jitteriness, restlessness, emotional lability, and giddiness. There may be insomnia or excessive dreaming, occasionally with nightmares.

If the exposure is more marked, the following symptoms may be evident:

- Headache.
- Tremor.
- Drowsiness.
- Difficulty in concentration.
- Impairment of memory with slow recall of recent events.
- Slowing of reactions.

In some casualties there is apathy, withdrawal and depression. With the appearance of moderate symptoms, abnormalities of the EEG occur, characterised by irregularities in rhythm, variations in potential, and intermittent bursts of abnormally slow waves of elevated voltage similar to those seen in patients with epilepsy. These abnormal waves become more marked after one or more minutes of hyperventilation which, if prolonged, may occasionally precipitate a generalised convulsion.

If absorption of nerve agent has been great enough, the casualty becomes confused and ataxic. The casualty may have changes in speech, consisting of slurring, difficulty in forming words, and multiple repetition of the last syllable. The casualty may then become comatose, reflexes may disappear and respiration may become Cheyne-Stokes in character. Finally, generalised seizures may ensue, but not all of these may be associated with convulsive activity.

With the appearance of severe central nervous system symptoms, central respiratory depression will occur (adding to the respiratory embarrassment that may already be present) and may progress to respiratory arrest. However, after severe exposure the casualty may lose consciousness and convulse within a minute without other

obvious symptoms. Death is usually due to respiratory arrest and anoxia, and requires prompt initiation of assisted ventilation to prevent death. Depression of the circulatory centres may also occur, resulting in a marked reduction in heart rate with a fall of blood pressure some time before death.

### Cumulative Effects of Repeated Exposure

Repeated exposure to concentrations of a nerve agent insufficient to produce symptoms following a single exposure, may result in the onset of symptoms. Continued exposure, possibly over several days, may be followed by increasingly severe effects.

After symptomatic exposure, increased susceptibility may persist for up to 3 months (the body synthesises acetylcholinesterase at a rate of approximately 1% new enzyme activity per day). A period of increased susceptibility occurs during the enzyme regeneration phase which could last from weeks to months, depending on the severity of the initial exposure. During this period the effects of repeated exposures are cumulative. Increased susceptibility is not limited to the particular nerve agent or other cholinesterase inhibitors initially absorbed.

### Potential Long Term Effects

Minor EEG changes have been noted more than a year after a clinically relevant, symptomatic nerve agent exposure; averaged EEGs in a group of people who had been exposed to a nerve agent were compared to a control group. Since changes could not be identified in individual EEGs, the clinical relevance is unknown. Neuropsychiatric changes have been noted in individuals for weeks to months after insecticide poisoning. Polyneuropathy, reported after organophosphate insecticide poisoning, has not been reported in humans exposed to nerve agents. It has been produced in animals only at doses of nerve agents so high that survival would be unlikely. The Intermediate Syndrome (polyneuropathy in the medium term – weeks) has not been reported in humans after nerve agent exposure, nor has it been produced in animals by nerve agent administration. Muscular necrosis has been produced in animals after high dose nerve agent exposure but resolves within weeks; it has not been reported in humans.

### Cause of Death

In the absence of treatment, death is caused by asphyxia resulting from airway obstruction, paralysis of the muscles of respiration and central depression of respiration. Airway obstruction is due to pharyngeal muscular collapse, upper airway and bronchial secretions, bronchial constriction and occasionally laryngospasm and paralysis of the respiratory muscles.

Respiration is shallow, laboured, and rapid and the casualty may gasp and struggle for air. Cyanosis increases. Finally, respiration becomes slow and then ceases. Unconsciousness ensues. The blood pressure (which may have been transitorily elevated) falls. Cardiac rhythm may become irregular and death may ensue.

If assisted ventilation is initiated via cricothyroidotomy or endotracheal tube and airway secretions are removed (by postural drainage and suction, and diminished by the administration of atropine), the individual may survive several lethal doses of a nerve agent, albeit with a potential for severe irreversible brain damage. However, if the exposure has been overwhelming, amounting to many times the lethal dose, death may occur despite treatment as a result of respiratory arrest and cardiac arrhythmia.

When overwhelming doses of the agent are absorbed quickly, death occurs rapidly without orderly progression of symptoms.

Figure 13 shows victims in Halabja, Iraq from the probable use of GB in March 1998 (although UN Inspectors consider that the deaths may have resulted from the use of hydrogen cyanide).



Fig 13. Dead in Halabja, Iraq, probably from GB.

## MANAGEMENT OF NERVE AGENT POISONING

### Introduction

The medical management of nerve agent poisoning consists of pre-treatment, diagnosis and treatment with a combination of pharmacological, respiratory and other general supportive measures, as dictated by the condition of the casualty.

The life-threatening effects of acute nerve agent poisoning occur much more rapidly and for a generally shorter duration than those produced by organophosphate (OP) insecticides. Following pre-treatment, successful post-exposure treatment relies on the rapid recognition of effects and the

equally timely administration of necessary therapeutic measures. Urgent skin decontamination and continued respiratory protection must be applied alongside the administration of autoinjectors for self and buddy aid, all of which must be maintained during rapid evacuation to medical care. Triage priorities must be reviewed frequently, with subsequent delivery of appropriate drug therapy and continued respiratory support, where necessary. This must be administered in a timely and confident manner if emergency medical management is to be successful and the ultimate prognosis favourable. Field medical management may have to be conducted initially in a contaminated environment, requiring practised procedures to avoid cross-contamination and unnecessary exposure of the already compromised casualty.

### Pre-treatment

Poisoning by nerve agents which form rapidly ageing complexes may be particularly difficult to treat. Ageing is the biochemical process by which the agent-enzyme complex becomes completely resistant to oxime reactivation. In the case of soman (GD), the agent-enzyme complex ages within minutes. These difficulties have been mitigated, in part, by the use of carbamates as pre-treatment. The terms pre-treatment or prophylaxis are differentiated thus:

- Pre-treatment: the administration of drugs in advance of poisoning designed to increase the efficacy of treatment administered post-poisoning.
- Prophylaxis: the administration of drugs in advance of the poisoning designed to make post-poisoning therapy unnecessary.

Current pretreatments utilise carbamate anticholinesterases, for example, pyridostigmine, which may be used either alone or in combination with other anticholinergic drugs (Figure 14). They bind cholinesterases *reversibly*, preventing the organophosphate binding to the enzyme. The term *reversible* is used here comparatively: the carbamate-acetylcholinesterase complex breaks down fairly rapidly, while organophosphate-acetylcholinesterase complexes break down very slowly. In comparison, the aged organophosphate acetylcholinesterase complex is stable.

When carbamates are used as pre-treatments, carbamoylation of acetylcholinesterase prevents phosphorylation, but later the carbamate-acetylcholinesterase complex dissociates, freeing active enzyme. Current pre-treatment regimen (pyridostigmine, 30 mg 8 hourly) are designed to give 20 – 40% binding of peripheral acetylcholinesterase, thereby allowing the carbamate to protect a proportion of the acetylcholinesterase against binding by nerve



Fig 14. Nerve Agent Pre-treatment Set (NAPS) – Pyridostigmine.

agent. There are no significant signs and symptoms associated with this level of inhibition since:

- the process of inhibition of the enzyme is slower than that due to nerve agent.
- there is negligible inhibition of central acetylcholinesterase.

In conjunction with post exposure therapy, good protection against lethality is obtained within 2 hours of the first dose, but is enhanced by continued intake of pyridostigmine pre-treatment, according to the accepted dosage regimen.

Pyridostigmine pre-treatment should be stopped when the symptoms of nerve agent poisoning following a chemical warfare attack are observed; post exposure therapy must be started immediately. Pyridostigmine is not an antidote, and it should not be taken after nerve agent exposure. Its continued use post-exposure may well enhance the effects of nerve agent poisoning. It is ineffective unless standard therapy is also used in the appropriate manner.

The recognised side effects of prolonged use of pyridostigmine include gastrointestinal changes including increased flatus, loose stools, abdominal cramps and nausea. Other reported effects are urinary urgency, headache, rhinorrhoea, diaphoresis and tingling of the extremities. However, several studies have concluded that these side effects are tolerable by most personnel and lead to negligible degradation of military performance – symptoms due to pyridostigmine may be ameliorated by taking the tablets with food, and Pyridostigmine pre-treatment was discontinued on medical advice in less than 0.1% of individuals, generally because of intolerable nausea and diarrhoea.

When taken in excess of the recommended

dosage, symptoms of carbamate poisoning will occur. These include diarrhoea, gastrointestinal cramps, tight chest, nausea, rhinorrhoea, headache and miosis. Good compliance is required if optimal protection is to be obtained. The importance of Pyridostigmine pre-treatment should therefore be stressed during training.

Medical officers must be aware of potential drug interactions and contraindications when dealing with personnel on pre-treatment. This is of particular relevance with respect to some muscle relaxants used in anaesthesia. Pyridostigmine has been used in clinical situations for up to 50 years. At this time there is no evidence of long term side effects.

Note that the national policy for the use of pre-treatment varies within NATO; it cannot be assumed that allied casualties will have received pre-treatment.

## Diagnosis and Therapy of Nerve Agent Poisoning

### Symptoms

Nerve agent poisoning may be identified from characteristic signs and symptoms. If exposure to vapour has occurred, the pupils will be very small, usually pin-pointed. If exposure has been cutaneous or has followed ingestion of a nerve agent in contaminated food or water, the pupils may be normal or, in the presence of severe systemic symptoms, slightly to moderately reduced in size. In this event, the other manifestations of nerve agent poisoning must be relied on to establish the diagnosis. No other known chemical agent produces muscular twitching and fasciculations, rapidly developing pin-point pupils, or the characteristic muscarinic, nicotinic and central nervous system manifestations.



### *Differential Diagnosis*

The effects caused by a mild vapour exposure, namely rhinorrhea and tightness in the chest, may easily be confused with an upper respiratory malady or an allergy. Miosis, if present, will help to distinguish these, but the eyes must be examined in very dim light to detect this. Similarly, GI symptoms from another illness may be confused with those from nerve agent, and in this instance there will be no useful physical signs. A history of possible exposure will be helpful, and laboratory evidence (decreased RBC-Cholinesterase activity) will be useful to distinguish the two. The diagnosis is easier in the severely intoxicated patient. The combination of miosis, copious secretions and generalised muscular fasciculations in a gasping, cyanotic and convulsing patient is characteristic.

### *Symptom Differentiation*

It is important that individual service members know the following MILD and SEVERE signs and symptoms of nerve agent poisoning. Servicemen and servicewomen who have most or all of the symptoms listed below must IMMEDIATELY receive first aid (self-aid or buddy aid respectively). Casualties with severe symptoms will not be able to treat themselves and must receive prompt buddy aid and subsequent medical treatment if they are to survive.

#### *MILD Poisoning (Self-Aid)*

Casualties with MILD symptoms may experience most or all of the following:

- Unexplained runny nose.
- Unexplained sudden headache.
- Sudden drooling.
- Difficulty in seeing (dimness of vision and miosis).
- Tightness in the chest or difficulty in breathing.
- Localised sweating and muscular twitching in the area of the contaminated skin.
- Stomach cramps.
- Nausea.
- Bradycardia or tachycardia.

#### *MODERATE Poisoning*

Casualties with MODERATE poisoning will experience an increase in the severity of most or all of the MILD symptoms. Especially prominent will be an increase in fatigue, weakness and muscle fasciculations. The progress of symptoms from mild to moderate indicates either inadequate treatment or continuing exposure to agent.

#### *SEVERE Symptoms (Buddy Aid)*

Casualties with SEVERE symptoms may experience most or all of the MILD symptoms, plus most or all of the following:

- Strange or confused behaviour.

- Wheezing, dyspnoea, and coughing.
- Severely pin-pointed pupils.
- Red eyes with tearing.
- Vomiting.
- Severe muscular twitching and general weakness.
- Involuntary urination and defecation.
- Convulsions.
- Unconsciousness.
- Respiratory failure.
- Bradycardia.

### **Post-Exposure Therapy**

The main principles of post exposure treatment for nerve agent poisoning are based on early drug therapy in combination where necessary with measures to support respiration and provide general supportive care.

### **Pharmacological Treatment of Nerve Agent Poisoning**

The pharmacological treatment of nerve agent poisoning involves the use of:

- Anticholinergics to antagonise the muscarinic effects.
- Oximes to reactivate inhibited enzyme and antagonise the nicotinic effects.
- Anticonvulsants to prevent seizure activity and protect against subsequent CNS damage.

The effects of drugs used in nerve agent poisoning are described below.

#### **Anticholinergic - Atropine**

Atropine sulphate is an essential drug in the treatment of nerve agent poisoning. It acts by blocking the effects of acetylcholine at muscarinic receptors and so produces relief from many of the symptoms previously listed. Some therapeutic effects are also produced within the central nervous system; at high doses (> 6 mg) atropine may help reduce central respiratory depression, and if administered early after poisoning (5 – 10 minutes), may have some beneficial anticonvulsant action.

#### *Dose Regimen*

Immediate treatment with atropine in cases of systemic nerve agent poisoning is essential, and the absolute requirement will depend on both the severity of effects and whether pre-treatment has been used. Following autoinjector therapy for first aid (Figure 15,16), doses should be repeated regularly until signs of successful atropinisation are noted. Intervals of 5 – 15 minutes may be required for continuing but non life-threatening effects of poisoning; the intravenous route of administration is preferred.

In cases of severe poisoning, higher doses may well be required. Atropine is given intravenously at a rate of 2 mg every 3-5 minutes until the casualty is atropinised. Subcutaneous or intramuscular routes of



Fig 15. NAPS, and Combopen Autoinjectors.



Fig 16. Self-injection using a ComboPen.

administration are alternatives, and recommended until significant hypoxia is corrected, as in such cases intravenous administration of atropine may precipitate life-threatening ventricular arrhythmias. In the Iran-Iraq War, intravenous infusion of atropine at 2 mg/min for over an hour was administered with considerable success for casualties severely poisoned by nerve agent vapour who had not received pre-treatment. In severe cases that have previously received pre-treatment, it is estimated that 30 – 50 mg of atropine in total may be required to achieve atropinisation.

Signs of successful atropinisation include decreased bronchospasm, reduced airways resistance, the drying-up of bronchial and salivary secretions, reduced sweating and a stabilisation in the heart rate to around 90 beats per minute. The effect of atropine in drying bronchial secretions may make the removal of mucus more difficult, so suction is likely to be necessary.

After the emergency field treatment, atropinisation should be maintained for at least 24 hours by intramuscular injection or slow intravenous infusion of 1 to 2 mg of atropine per hour as required.



### *Complications*

Atropine, especially in the presence of hypoxia, may render the myocardium more susceptible to arrhythmias. Correction of hypoxia, and ECG monitoring if available, is essential during atropinisation. Overdosage may produce euphoria, hallucinations, anxiety, and delirium. Close observation is necessary and sedation of casualties may be required. Bladder dysfunction may necessitate catheterisation. By the reduction of sweating, atropine increases the risk of heat stress.

### *Inappropriate Administration*

If atropine is administered in the absence of nerve agent poisoning, the following effects may be noted:

- dryness of the mouth and pharynx
- decreased sweating
- slight flushing and tachycardia
- some hesitancy of micturition
- slightly dilated pupils
- mild drowsiness
- impaired memory and recall
- blurring of near vision

After 2 mg, these symptoms should not interfere with ordinary activity except in the occasional person, in hot environments or at high work rates. Higher doses, or repeated doses, will produce more marked symptoms which may become totally incapacitating, particularly in warm environments or high work rates. The effects of atropine are fairly prolonged, lasting 3 to 5 hours after one or two injections of 2 mg and 12 to 24 hours after significant over-atropinisation.

The traditional antidote for atropine overdose is physostigmine. This is a carbamate anticholinesterase, like pyridostigmine, but crosses the blood brain barrier. As physostigmine acts by inhibiting anticholinesterase, it must be used with caution in treating over-atropinisation following nerve agent poisoning, where the levels of enzyme may be reduced below normal. In such cases, the risk of repeated cholinergic effects is greater. Its use should therefore be reserved only for those cases with severe symptoms of atropine overdose, refractive to general supportive measures.

### *Atropine For Eye Effects*

Atropine given parenterally has comparatively little effect on nerve agent induced miosis. The local application of cycloplegics (homatropine or similar eye drops) to the eye reduces both the degree of miosis, eye pain and associated nausea, vomiting and headache. However, expert opinion on the value of atropine-containing eye drops in the management of nerve agent induced miosis remains divided. It is believed by some that problems of accommodation may be made worse by the application of the drops and that, overall, little benefit may be produced.

### *Other Anticholinergics*

On the basis of experimental data, other anticholinergic drugs are considered to be beneficial in the treatment of nerve agent poisoning. Anticholinergics with pronounced central antimuscarinic effects (e.g. benactyzine, biperiden, trihexyphenidyl, scopolamine) have the potential to suppress seizure activity without further anticonvulsant therapy, if administered early after poisoning. Drug combinations with atropine (e.g. benactyzine and atropine) have been introduced by some nations in specific clinical situations, but caution must be exercised when using these regimen.

## **Oximes**

### *Toxicity*

While atropine blocks the cholinergic effects of nerve agent poisoning at muscarinic sites, it has little effect upon the nicotinic effects at skeletal neuromuscular junctions and the autonomic ganglia. Amelioration of nerve agent effects at these sites and also at muscarinic sites can, however, be obtained by the reactivation of inhibited AChE by means of oximes.

Three oximes are available in autoinjectors for self- or buddy-administration and these are:

- N-methyl derivative of 2-pyridine-2-aldoxime (pralidoxime) as the methane-sulphonate; methyl sulphate and chloride salt.
- toxogonin (obidoxime) dichloride.
- HI-6 chloride.

Note that atropine and oximes are synergistic in their effects and the administration of atropine and oxime in combination has been shown experimentally to raise the LD50's of some nerve agents by a factor in excess of 20.

### *Enzyme Reactivation*

The relative potency of the different oximes in reactivating inhibited AChE varies according to the nature of the nerve agent. The choice of oxime (if more than one is available) is not only dependent on the identity of the nerve agent responsible for the poisoning; the effectiveness of a given oxime is also dependent on whether the casualty has received pyridostigmine pre-treatment and the administration of other anticholinergic and anticonvulsant drugs.

In the field, immediate post-exposure therapy consisting of atropine, oxime and diazepam will be given by intramuscular injection from an autoinjector device on the appearance of the first significant signs of nerve agent poisoning. Following the use of the autoinjector, if casualties remain symptomatic, they will require further doses of oxime (and atropine) to alleviate the clinical situation and reactivate inhibited enzyme. Opinion remains divided as to the

Table 4. Intravenous Bolus Dosing of Oximes.

Degree of Poisoning	Pralidoxime Chloride	Pralidoxime Methanesulphonate	Obidoxime	HI-6
Mild	1000 mg.	400 mg.	250 mg.	500 mg.
Moderate	1000 mg. <sup>(1)</sup>	400 mg. <sup>(2)</sup>	250 mg. <sup>(3)</sup>	500 mg.
Severe	1000 mg. <sup>(1)</sup>	500 mg. <sup>(2)</sup>	250 mg. <sup>(3)</sup>	500 mg. <sup>(3)</sup>

(1). Dose repeated every 8–12 hours.

(2). Second dose of 400–500 mg 30 minutes after the initial dose followed by further doses of 200–400 mg every 4–12 hours.

(3). Second dose administered 2 hours after the initial dose and followed by a further dose every 6–12 hours.

Table 5. Theoretical Loading Doses and Infusion Rates For Intravenous Oxime Administration.

Oxime	Loading Dose (mg.kg <sup>-1</sup> ) <sup>(1)</sup>	Total Dose (mg) <sup>(2)</sup>	Infusion Rate (mg.kg <sup>-1</sup> .h <sup>-1</sup> ) <sup>(3)</sup>	Total Rate (mg.h <sup>-1</sup> ) <sup>(2)</sup>
2-PAM	4.2	300	2.2	160
P2S	4.4	310	2.1	150
Obidoxime	0.8	56	0.5	34
HI-6	1.6	110	0.8	54

Key: 2-PAM = Pralidoxime chloride P2S = Pralidoxime methanesulphonate

(1) Loading dose = Therapeutic Plasma Concentration  $\times$  Volume of Distribution.

(2) The total dose and total rate of infusion have been calculated assuming a man weighing 70 kg.

(3) Infusion Rate = Therapeutic Plasma Concentration  $\times$  Renal Clearance.

most appropriate way of achieving therapeutic blood levels of oxime.

The intravenous injection of bolus doses of oxime is probably the only practical solution on the battlefield; doses are shown in Table 4. Under field conditions, single bolus doses can also be given by intramuscular injection.

An alternative method of administering therapeutic doses of oxime is by intravenous infusion. Sundwall reported experimentally that a plasma concentration of 4  $\mu\text{g.mL}^{-1}$  pralidoxime methanesulphonate was needed to counteract the neuromuscular block, bradycardia, hypotension and respiratory failure caused by organophosphate anticholinesterases. This concentration has been assumed since then to be the minimum concentration of oxime required to counteract nerve agent intoxication in man. Based on this assumption, it is possible to calculate the loading and maintenance doses for the intravenous administration of oximes that will achieve this level. The calculated dosing regimen for various oximes are summarised in Table 5.

There is only limited experience in human poisoning by organophosphorus nerve agents but it is generally accepted that the persistence of clinically relevant amounts of nerve agent in the blood is shorter than that of insecticides or pesticides. However, as a result of ageing of the inhibited AChE (which may be very rapid following poisoning with GD), it is suggested that in the absence of clinical improvement, administration of oxime for periods in excess of 24–48 hours is unlikely to achieve further reactivation of the enzyme.

### Anticonvulsants

In severe poisoning by nerve agent, atropine protects only partially against seizure activity and the resulting brain damage; other anticholinergics vary in this ability. Early

administration of anticonvulsants should be mandatory.

Experimental evidence shows that the early administration (5 – 10 min) of the benzodiazepines antagonises the seizure activity of nerve agent. The addition of this class of drugs to the basic treatment regimen greatly improves morbidity and mortality, in addition to its anti-seizure effect. Currently Diazepam is the most widely fielded and should be administered as a 5 – 10 mg dose initially and further doses should be given frequently enough to control seizures. This may require additional injections, at intervals ranging from a few minutes to several hours.

In the absence of anticonvulsant therapy, irreversible brain damage may result; this is exacerbated by periods of hypoxia.

### Respiratory Supportive Care

#### Airway management

A patent airway should always be maintained, with postural drainage and suction. In an unconscious casualty, adequate atropine should be administered to reduce airway resistance. Cricothyroidotomy and/or endotracheal intubation may be needed.

#### Respiratory support

Dyspnoeic casualties may require respiratory support; this should be started at the lowest possible level. In a casualty that is dyspnoeic, the respirator should be removed and replaced with a casualty hood which will reduce the ventilatory resistance.

#### Positive pressure ventilation

Assisted ventilation may range from mouth-to-mouth ventilation (in the absence of a liquid or vapour hazard and after appropriate decontamination) to the use of an automatic ventilator. Manual or automatic ventilators must be capable of delivering uncontam-



inated air, with supplementary oxygen (if available). Atropine will be required to reduce airway resistance and endotracheal atropine should be considered in difficult cases. Assisted ventilation with supplementary oxygen may be needed for some hours.

#### *Oxygen*

Dyspnoeic casualties should receive oxygen at the lowest possible level. This may result in a high demand for oxygen. If available, oxygen saturation should be monitored.

### **General Supportive Care**

Although pre- and post-exposure therapy will reduce lethality, casualties may still be incapacitated. A patient severely poisoned by an anticholinesterase is a critical medical emergency and may require intensive care for days or weeks. General supportive care such as restoring fluid and electrolyte balance, correction of acid base balance, control of body temperature and control of infection should follow normal medical practice. Special precautions should be taken when using muscle relaxants in patients poisoned by nerve agents.

### **Emergency Field Therapy**

#### *Self Aid (or Buddy Aid)*

This comprises first aid measures which the soldier can apply to help him- or herself. The rapid action of nerve agents calls for immediate self treatment. Unexplained nasal secretion, salivation, tightness of the chest, shortness of breath, constriction of pupils, muscular twitching, or nausea and abdominal cramps call for the immediate intramuscular injection of 2 mg of atropine, combined if possible with oxime. From 1 to 3 automatic injection devices, each containing 2 mg atropine or mixture of atropine, oxime and/or anticonvulsant, are carried by each individual.

One device should be administered immediately when the symptoms and/or signs of nerve agent poisoning appear. This may be done by the casualty or by a buddy, the injection being given perpendicularly through the clothing into the lateral aspect of the middle of the thigh. Further devices, up to a total of 3, should be administered by the casualty or by his or her buddy during the following 30 minutes if the symptoms and/or signs of poisoning fail to resolve.

The timing of these further injections and whether they are given at one time or separately may depend on the casualty's condition (and on instructions promulgated by individual NATO nations).

Note that if automatic injectors are used in the absence of exposure to agent, the following signs and symptoms may be seen: dry mouth, dry skin, fast pulse (>90 beats per minute), dilated pupils, retention of urine

and central nervous system disturbance. Susceptibility to heat exhaustion or heat stroke is increased, particularly in closed spaces or whilst wearing protective clothing.

#### *First Aid by Trained Personnel*

This comprises the emergency actions undertaken to restore or maintain vital bodily functions in a casualty. Wherever the casualty is not masked, the respirator must be adjusted for him or her by the nearest available person. Attention should be given to decontamination at the earliest possible moment and any skin contamination must be removed with a personal decontamination kit.

After nerve agent poisoning, the administration of atropine is repeated at intervals until signs of atropinization (dry mouth and skin and tachycardia >90 per minute) are achieved. Miosis from vapour exposure is not relieved by systemic atropine.

Mild atropinization should be maintained for at least 24 hours by intramuscular injection of 1-2 mg of atropine at intervals of 1/2 to 4 hours, as required. There is a danger of ventricular arrhythmias arising from atropinization if the casualty is anoxic.

Assisted ventilation is required for severely poisoned individuals as they will have:

- Marked bronchoconstriction.
- Copious secretions in the trachea and bronchi.
- Paralysis of the respiratory muscles.
- Central respiratory depression, hypoxia, and convulsions.

#### *Assisted Ventilation*

Positive pressure resuscitation should be undertaken but the pressure necessary to overcome the bronchoconstriction may be more than 65 cm H<sub>2</sub>O and if possible, intubation is highly desirable. In the absence of a liquid or vapour hazard, assisted ventilation may be attempted by the standard mouth-to-mouth method after decontamination of the casualty's face and mouth. In the presence of a liquid or vapour hazard, ventilation may be given by a portable resuscitator with NBC filter attached.

In a medical care facility, mechanical resuscitation of the positive pressure type may be used with endotracheal intubation or tracheostomy; artificial respiration must be continued until the casualty is breathing normally or the medical personnel have pronounced the casualty dead. Due to the production of copious secretions, regular suction will be required.

### **Return To Duty**

As with all other injuries in military operations, return to duty depends on the clinical recovery of the casualty, his military assignment, and the tactical situation. In

principle, the soldier with reduced cholinesterase activity may be at a higher risk if re-exposed to any cholinesterase inhibitor. The use of pre-treatment is not advised in these cases, until recovery of cholinesterase activity can be confirmed. If cholinesterase activity cannot be measured, then a period of at least 4 weeks without pre-treatment is recommended.

Most individuals triaged as minimal could return to duty within several hours if the tactical situation required all available manpower. The lingering ocular and CNS effects may be limiting factors in these cases. These individuals might be able to fire a rifle, but their performance on a tracking screen might be severely disturbed because of both visual problems and difficulty in concentrating. These prolonged effects must be thoroughly evaluated before the casualties are returned to duty.

A casualty who has had severe effects might be walking and talking after 6 to 24 hours but will still be unfit for most duties. Ideally, he should be kept under medical observation for a week or longer and not returned until recovery of cholinesterase activity. However, the tactical situation may lead to modification of these guidelines.

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