Chemical warfare agents

James Geoghegan MB ChB FRCA
Jeffrey L Tong MB ChB FRCA RAMC

Chemical warfare (CW) agents are chemical substances that have a direct toxic effect on plants, animals and humans. Classified according to their physiological effects, agents effective against humans include nerve agents, blistering agents (vesicants), blood agents, choking agents and toxins. Incapacitating, vomiting, psychoactive and riot control agents (e.g. CS gas) also exist.

All personnel in contact with contaminated casualties must wear the appropriate level of chemical personal protective equipment (CPPE) until adequate decontamination is assured or the need for decontamination is eliminated. Decontamination limits agent absorption and prevents cross-contamination. Over the past 20 yr, civilian populations around the World have been exposed to numerous CW agents (Sarin, Tabun, VX, Mustard gas, Hydrogen cyanide and Kolokol-1), and the possibility of a major CW incident occurring within the UK cannot be excluded. It is essential that anaesthetists have an understanding of the pharmacology and toxic clinical effects of the common CW agents as well as treatment strategies.

Nerve agents

Nerve agents are amide or ester derivatives of phosphonic acid and are structurally related to organophosphate insecticides. They are highly potent inhibitors of acetylcholinesterase (AChE) and classified as G or V agents. They include Tabun or GA (ethyl N,N-dimethylphosphoramidocyanate), Sarin or GB (isopropyl methylphosphonofluoridate) and VX (O-ethyl-S-2-diisoproplaminoethyl-methylphosphonothioate). The GV-series nerve agents combine the properties of both classes.

AChE inhibition

The primary mechanism of toxicity of nerve agents is the inhibition of AChE. It has two active sites: anionic and esteratic. Nerve agents inactivate AChE by alkyl phosphorylation of a serine hydroxyl group at the esteratic site of the enzyme. The inactive phosphorylated enzyme is very stable and, as spontaneous hydrolysis of nerve agent intermediates does not occur, ACh accumulates at nicotinic, muscarinic and central nervous synapses. The nerve agent eventually loses (non-enzymatically) an alkyl side chain and the stability of the enzyme–nerve agent complex is enhanced. This process is known as ageing. Enzyme inactivation is irreversible and recovery mainly depends on synthesis of new enzyme. The ageing half-time (time for half of involved cholinesterase to age) varies from 2 min for Soman, to >40 h for VX and Tabun.

Other cholinesterases

In addition to AChE, nerve agents also inhibit erythrocyte cholinesterase and butyrylcholinesterase (plasma cholinesterase). Erythrocyte cholinesterase is a sensitive indicator of nerve agent toxicity and confirms exposure to nerve agent. The inactivation of neuropathy target esterase (NTE) may be responsible for the delayed polyneuropathy associated with organophosphate exposure.

Physical properties

Nerve agents are predominantly liquids at room temperature, with high lipid solubility, low molecular weight and low volatility. Sarin is the most volatile with a vapour pressure similar to water. This facilitates rapid and effective absorption via inhalation and the transdermal route. Penetration of the central nervous system readily occurs. V agents are persistent and remain in the environment. Persistence depends on density, volatility and stability on exposure to light and water.

Latency and toxicity

Latency describes the delay between nerve agent exposure and the onset of clinical effects. It is determined by the absorption and distribution characteristics, route and dose of the agent.
agent. Symptoms of inhalation toxicity develop rapidly (30–120 s), but clinical severity depends on vapour concentration and length of exposure. After transdermal exposure, systemic toxicity is delayed as the agent diffuses through the skin. The ambient temperature, dose and anatomical area (rapid absorption occurs where the dermal layers are thin, e.g. ears and eyelids) also affect latency.

Pharmacological properties

Nerve agents cause excessive stimulation of the cholinergic system, with stimulation of muscarinic receptors at autonomic effector organs, stimulation then depression of skeletal muscle and autonomic ganglia, and stimulation of cholinergic receptors in the CNS (Table 1). They also bind to nicotinic, cardiac muscarinic and glutamate NMDA (N-methyl-D-aspartate) receptors directly and antagonize GABA (γ-aminobutyric acid) neurotransmission.

Clinical manifestations

The classical presentation of nerve agent poisoning is a cholinergic toxic syndrome (toxidrome) (Table 1). The ‘DUMBELS’ mnemonic describes the muscarinic features as follows: Diarrhoea, Urination, Miosis, Bronchorrhoea, bronchoconstriction and bradycardia, Emesis, Lacrimation, Salivation. The most prevalent indicator of poisoning after the Tokyo sarin attack was miosis (>90%). Heart rate was an unreliable sign as patients presented with bradycardia or tachycardia.

After organophosphate poisoning, a triphasic clinical syndrome is seen. In human nerve agent poisoning, the initial cholinergic phase occurs (without the intermediate and third phases) and lasts for 1–2 days. It is associated with depolarizing neuromuscular block (because of prolonged and high intrasynaptic concentrations of ACh). The scoring systems that assess the severity of organophosphate poisoning, for example, Peradeniya Organophosphate Poisoning (POP) Scale, are not validated for nerve agents and the severity of nerve poisoning is clinically classified.

Treatment

The first priority is ABC because airway, respiratory and cardiac support is necessary in severe poisoning. Death is from bronchoconstriction, vocal cord paralysis, bradycardia or convulsions. Patients require organ support, intensive care and early administration of antidotes.

Non-depolarizing neuromuscular blocking agents cause prolonged paralysis and once AChE is irreversibly inactivated, reversal with carbamate esters (neostigmine) is ineffective. Succinylcholine causes prolonged paralysis because butyrylcholinesterase is inhibited. Ketamine increases oropharyngeal secretions and should be used with caution.

Pyridostigmine

This is a reversible competitive carbamate ester antagonist of AChE. Pre-treatment with 30 mg orally tds, acts as an antidote enhancer, improving survival after nerve agent exposure. Carbamylation of AChE binding sites produces a reservoir of temporarily inactivated AChE. Subsequent dissociation reactivates AChE which, combined with pralidoxime and atropine, reduces the incidence of cholinergic crises. It cannot cross the blood brain barrier (quaternary amine) or prevent CNS symptoms, but the peripheral effects are limited. Pre-treatment alters neuromuscular blocking agent pharmacodynamics so that less succinylcholine (phase I block) and more non-depolarizing relaxants are required to produce paralysis.

Atropine

Atropine antagonizes the muscarinic effects of excess acetylcholine but nicotinic receptors are unaffected and muscle weakness or paralysis does not improve. ‘Atropinization’ requires 2 mg i.v. every 3–5 min. Infusion doses for resistant bradycardia are large (e.g. 120 mg h−1 during Iran/Iraq war) but rarely required after 24 h. The therapeutic endpoints of atropinization (antimuscarinic effect) are drying of pulmonary secretions, reversal of bronchoconstriction and correction of bradycardia (>80 beats min−1). Pupillary response, tachycardia and skin colour are not useful measures. Ocular pain and miosis is treated with 0.5% tropicamide. Atropine or homatropine ophthalmic solutions are used, but they exacerbate visual impairment.

Pralidoxime

A member of the monopyridinium group, pralidoxime reactivates AChE by competitively binding with its active sites (Fig. 1), reversing nicotinic receptor dysfunction and reducing paralysis. Early administration disrupts the covalent bond between nerve agent and enzyme before it becomes irreversible (aged). Pralidoxime 15–30 mg kg−1 is given through i.v. and a slow injection minimizes adverse effects (laryngospasm, muscle rigidity and tachycardia). It is rapidly excreted by the kidneys (unchanged) and maintaining a therapeutic blood concentration of 4 μg ml−1 requires a continuous infusion of

### Table 1 Nerve agent poisoning. The clinical and associated receptor effects of the cholinergic toxic syndrome (toxidrome)

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td></td>
</tr>
<tr>
<td>Acetylcholine, GABA, NMDA</td>
<td>Headache, anxiety, irritability, ataxia, fatigue, amnesia, hyperthermia, lethargy, unconscionness, central respiratory depression, convulsions, coma</td>
</tr>
<tr>
<td>Muscarinic synapses</td>
<td>Miosis, eye pain, glandular hypersecretion (salivatory, bronchial and lachrymal), sweating, bradycardia (QT prolongation or atrioventricular block), bronchoconstriction, vomiting, diarrhoea, urination</td>
</tr>
<tr>
<td>Nicotinic synapses</td>
<td>Tachycardia, hypertension (adrenal medulla)</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Fasciculations, weakness, muscular paralysis, rhabdomyolysis, depressed ventilation</td>
</tr>
</tbody>
</table>
Oxime therapy is continued for 24 h after symptoms resolve. Diazepam I.V. diazepam is indicated in moderate to severe poisoning and 2–5 mg should be i.v. titrated to effect (10 mg i.m.) to prevent seizures and minimize secondary brain injury.

Novel treatments
Clonidine is used to control central nervous cholinergic symptoms and magnesium reduces pre-synaptic acetylcholine release. At an experimental level, Hagedorn oximes (e.g. HI-6) have increased ability to reactivate aged AChE and direct antimuscarinic and antinicotinic actions. In addition, anti-nerve agent human monoclonal antibodies that scavenge nerve agents and prevent them binding to AChE are under investigation.

Blistering agents (vesicants)
The two main classes of blistering agents are arsenicals (lewisite) and mustard agents, which include nitrogen mustards and sulphur mustards (H). Vesicants constitute a vapour and liquid threat.

Mustard gas (H)
Mustard gas [bis (2-chloroethyl) sulphide] is an oily yellow liquid which smells of garlic or mustard. Its olfactory threshold is below concentrations associated with toxicity providing early warning of exposure, but olfactory fatigue does occur. Mustard gas has low volatility and water solubility but has a high persistence. It is lipophilic and is readily absorbed transdermally. Approximately 10% of the mustard dose binds to the skin as reacted (fixed) mustard, the remainder enters the circulation as unreacted (free) mustard. Mustard is eliminated in the urine as a byproduct of alkylation.

The toxicity of mustards depends on rapid covalent binding to biological molecules and the formation of reactive cyclic ethylene sulphonium ions which alkylate amino and sulphhydryl groups in nucleic acids and peptides. Mustards also bind to and deplete glutathione, leading to enzyme inactivation, loss of calcium homeostasis, lipid peroxidation, cellular membrane disruption and death.

Clinical manifestations
A variable latency period occurs (2–12 h) between exposure and the development of systemic symptoms. Vapour exposure causes >80% of casualties, but the mortality rate is <5%.

Eyes
Ocular symptoms occur in 85% of casualties and include eye pain, lachrimation, conjunctival oedema and blepharospasm. Treatment involves saline irrigation and petroleum jelly to limit eyelid closure. Long-term complications include corneal opacification and panophthalmitis.

Skin
Superficial chemical burns occur over exposed skin causing oedema, extreme pain and intense pruritus. Liquefactive necrosis of the epidermal basal cell keratinocytes causes vesicles and bullae. Full thickness burns with spreading vesication follows high-dose exposure, requiring surgical debridement and antibiotics. Fluid loss predominantly occurs during blister formation and fluid replacement should follow protocols for burn injuries. Healing is delayed in blistered areas because of alkylation of cell DNA, which also increases the incidence of skin carcinogenesis.

Respiratory
Respiratory symptoms occur in 70% of casualties. A chemical tracheobronchitis occurs with bronchospasm, respiratory epithelial necrosis, pulmonary oedema and haemorrhage, leading to respiratory failure. Pseudomembrane formation can cause obstruction. Long-term complications include permanent lung damage, tracheal stenosis and respiratory tract carcinogenesis.
**Systemic**
High-dose exposure causes bone marrow suppression; an initial polymorphic leucocytosis is followed by leucopenia, thrombocytopenia and anaemia. Death is from secondary infection and bone marrow failure.4

**Lewisite**
Lewisite (2-chlorovinyl dichloroarsine) has an irritating odour and is more volatile than mustard agents. The clinical manifestations of exposure are similar to mustard agents.

**Treatment**
There are no specific systemic or topical antidotes to mustard agents. Systemic lewisite toxicity may be treated with i.m. dimercaprol (3 mg kg⁻¹), which combines with the arsenic group in lewisite forming a water soluble compound.13

**Blood agents**
These are metabolic poisons and include hydrogen cyanide (AC) and cyanogen chloride (CK). They are delivered as vapours and a lethal dose results in rapid death.

**Hydrogen cyanide**
This is a colourless liquid that smells of bitter almonds and is highly volatile. The vapour rapidly disperses to sublethal concentrations and exposed casualties frequently survive to reach hospital.4

Cyanide inhibits the catalytic function of cytochrome oxidase enzymes in the final step of the electron transport chain, by binding to the trivalent iron ion in the porphyrin moiety of cytochrome a₃. The subsequent interruption in mitochondrial function and cellular oxygen utilization causes histotoxic hypoxia.

**Clinical manifestations**
Inhalation exposure to high-dose cyanide causes tachypnoea, confusion and dizziness, which is rapidly followed by convulsions, coma and cardiorespiratory arrest. Exposure to low concentrations can cause nausea, vertigo, muscular weakness and prolonged coma. Arterial blood gas analysis shows a metabolic acidosis with increased lactate and decreased arteriovenous oxygen difference, because of decreased tissue oxygen uptake.

**Treatment**
Organ supportive therapy, intensive care and specific antidotes are required. Antidotes include 300 mg of i.v. sodium nitrite over 5–10 min, which converts haemoglobin to methaemoglobin and binds cyanide. This is given with 12.5 g of i.v. sodium thiosulphate over 10 min, which provides sulphur groups and increases the detoxification of cyanide by hepatic rhodanase to thiocyanate.

Second-line treatment includes i.v. dicyclopent edetate 300–600 mg over 1 min, with 50 ml of 50% glucose, which combines with cyanide forming inert compounds, restoring cytochrome function. Adverse effects include hypertension, tachycardia and vomiting.13

**Choking agents**
Chlorine and phosgene (COCl₂) are irritant gases widely used in industry. They are denser than air and accumulate close to the ground.

Chlorine is a green–yellow gas with an acrid smell. The olfactory threshold is below toxic levels, providing early warning of exposure.4 It is an oxidizing agent that reacts with water to form hydrochloric acid, hypochlorous acid and oxygen free radicals, which directly damage lung tissue.13

Phosgene is a colourless gas that smells of newly mown hay. Its odour provides insufficient early warning of exposure, as toxic effects occur at concentrations below the olfactory threshold.4 Olfactory fatigue occurs with high concentration exposure. Phosgene contains a highly reactive carbonyl group attached to two chloride atoms and reacts slowly with water to form carbon dioxide and hydrochloric acid, causing extensive cellular damage to terminal airways and the alveolar-capillary membrane.13

**Clinical manifestations**
The clinical effects of choking agents are dose-dependent. Low to moderate dose exposure causes eye pain, lachrimation, cough, dyspnoea and bronchospasm. High concentrations induce laryngospasm. The extensive tissue necrosis and serum leakage from alveolar capillaries (upto 1 litre h⁻¹), rapidly produces non-cardiogenic pulmonary oedema and respiratory failure.4 Secondary infection and ARDS contribute to tissue ischaemia leading to multiple organ failure. The radiological changes after phosgene inhalation lag behind clinical changes.4

**Treatment**
There are no specific antidotes to choking agents. Management involves respiratory support with bronchodilators, high-dose corticosteroids and prophylactic antibiotics.14 Diuretics have a limited role in phosgene induced pulmonary oedema. Leukotriene inhibitors and antioxidants such as glutathione offer little clinical benefit. Bed rest after low-dose exposure is essential, as minimal exertion can expose asymptomatic pulmonary damage, causing dyspnoea and pulmonary oedema.3

**Toxins**
Toxins are defined as potent toxic chemicals produced by living organisms (e.g. ricin and botulinum toxin) that inhibit protein synthesis causing severe cytotoxic effects. Of the hundreds known, fewer than 20 have been used as weapons.
Ricin

Derived from beans of the castor plant, ricin is composed of two haemagglutinins and two toxins (RCL III and RCL IV). The toxins consist of two polypeptide chains (A and B), joined by a disulfide bond. The B chain binds to cell surface glycoproteins; the A chain acts on the 28S ribosomal RNA, which inhibits protein synthesis causing cell death. High-dose inhalation is rapidly fatal; lower doses result in death within 3 days.4

Botulinum toxin

Clostridium botulinum produces the most toxic chemical known. Seven serologically distinct neurotoxins exist (A to G, with three subtypes of A) and structurally they consist of two polypeptide chains. A dose of 200–300 pg kg⁻¹ of Neurotoxin A is lethal. All serotypes of the toxin permanently inhibit the pre-synaptic release of ACh, blocking neurotransmission at peripheral cholinergic synapses (including the NMJ), post-ganglionic parasympathetic synapses and peripheral ganglia. Recovery occurs after the formation of new terminal boutons. Trivalent antitoxins are effective for several serotypes and pentavalent antitoxin is under development.4

Incapacitating agents

These are non-lethal agents designed to temporarily remove the ability to perform tasks because of quantifiable physical or mental impairment, for example, Kolokol-1, BZ (3 quinuclidinyl beuzilate).1,3

Kolokol-1

Used by the security forces in Moscow in 2002, kolokol-1 is an extremely potent opioid-based agent containing carfentanil. It is 100 times more potent than fentanyl and inhalation exposure causes rapid unconsciousness (in seconds), lasting for several hours. Life threatening side-effects such as airway obstruction and apnoea are easily reversed with opioid antagonists.

References


Please see multiple choice questions 12–16.