

Pharmacology and Toxicology of Chemical Warfare Agents

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Abstract

Toxic chemicals have been used as weapons of war and also as means of terrorist attacks on civilian populations. The main classes of chemical weapons are: a) nerve agents, b) vesicant agents and c) blood agents. If an exposure to nerve agents is anticipated, prophylactic pyridostigmine may be used. Once exposure has occurred, the management strategy is to reduce cholinergic activity through the use of atropine as well as to attempt to regenerate acetylcholinesterase with pralidoxime. Convulsions may be managed using diazepam. Exposure to vesicant agents may be reduced through the use of protective gear, but once exposure has occurred, no specific treatment is available. Treatment remains symptomatic and supportive. Lethal atmospheric concentrations of hydrogen cyanide gas, a blood agent, is seldom achieved except in enclosed spaces. Sub-lethal exposure to hydrogen cyanide may be managed using sodium nitrite, sodium thiosulphate and VitB₁₂.

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Introduction

The recent terrorist *sarin* attacks in the subways of Tokyo and Matsumoto City in Japan have drawn considerable public attention to the public threat of chemical agents. These events have been particularly worrying as they had been directed against civilian populations during peace time. Coupled with recent developments within Iraq, the media presentations of the *sarin* attacks have conveyed the false impression that the use of chemical weapons is a relatively new phenomenon that will quickly supercede more conventional methods in warfare.

The use of chemicals can be traced back as far as 400 BC when, during the Peloponnesian war, burning sulphur was used to generate noxious sulphur dioxide fumes upwind from the besieged city of Plataea. Ironically the same method was used 2300 years later in the same vicinity against guerrillas hiding out in caves.^{1,2}

The first systematic large scale use of chemicals during wartime was seen during the First World War.^{1,2} In 1915, the Germans unleashed 180 tonnes of *chlorine* against the Allied forces at Ypres producing 15 000 casualties, 5000 deaths and a 8-km breach in the defence. But the phenomenal success of the chemical attack was totally unexpected and the Germans were unable to capitalise on the defensive breach. This was quickly followed up with attacks using *phosgene* and later *mustard gas* but by this time, the allied forces had

already not only learnt how to deal with such attacks but were also able to launch some of their own. Chemical weapons claimed a total of 1.3 million casualties during World War I with an estimated fatality rate of about 7%.³

Although initially impressive, the use of chemical weapons did not eventually contribute significantly to the outcome of the war. The level of technology on either side of the conflict equalised rapidly thus negating any early advantage chemical weapons might have conferred. By the end of the war, both had learnt to protect themselves against the threat of irritant gases through the use of gas masks. But while both sides were able to manufacture and use vesicant (blister) agents, neither knew how to neutralise the threat.

A third class of chemicals was added to the arsenal in the 1930s when the German pharmaceutical group Bayer discovered the organophosphorous *tabun*. Originally developed as an insecticide, it rapidly became adapted for battlefield use. Soon after, related compounds such as *sarin* and *soman* were added to the arsenal.

Despite these developments, the period leading into, as well as that during the Second World War, was conspicuous in the relatively low use of chemical weapons. In more recent times however, reports of alleged use of chemicals weapons in regional conflicts have increased. The recent subway attacks in Tokyo confirm the ease by which the technology has migrated from the military superpowers into the hands of terrorist groups.

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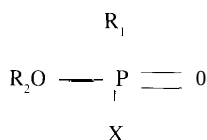
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Types of Chemical Warfare Agents

Although there are literally thousands of poisonous chemicals available, only about 70¹ have been found in stockpiles around the world. Of these, only a few have real utility as chemical weapons. The main classes of chemical agents used are: a) nerve agents; b) vesicants and c) blood agents.

Nerve Agents

These are essentially derivatives of the cholinesterase inhibitor insecticides. All are organophosphorus compounds with the basic chemical structure as shown in Figure 1. The initial three compounds, tabun, sarin and soman, were given the military codes GA, GB and GD respectively.^{1,4} Highly toxic, they are also stable, volatile and easily dispensable. Toxicity is produced mainly through inhalation and percutaneous absorption. The high volatility of these agents mean that they do not persist long enough to pose a threat to invading troops when used during offensive operations. The down side is that the effects of these agents are not very persistent. Of the three agents, tabun is the least volatile and sarin the most. In 1958 VX (*O*-ethyl *S*-diisopropyl-aminomethyl methylphosphonothiolate) was introduced which had a much lower volatility and higher toxicity than the pre-existing agents.^{1,4} A thick viscous liquid, VX has a tendency to cling to everything it come into contact with and presents the most insidious threat of all the nerve agents.



Nerve agent X		R ₁	R ₂
Tabun GA	-CN	-N(CH ₃) ₂	-C ₂ H ₅
Sarin GB	-F	-CH ₃	-CH(CH ₃) ₂
Soman GD	-F	-CH ₃	-CH(CH ₃)C(CH ₃) ₃
VX	-S(CH ₂) ₂ N(CH(CH ₃) ₂) ₂	-CH ₃	-C ₂ H ₅

Fig. 1. Chemical structure of nerve agents.

The nerve agents are readily hydrolysed at the P-I bond to a harmless phosphoric acid product.^{1,4} Hydrolysis occurs in water but is accelerated with the addition of alkali. More rapid hydrolysis can be achieved by increasing the temperature or by adding bleaching powder. Being relatively volatile, areas contaminated by G agents tend to self-decontaminate within a few days. V agents however, tend to remain on the ground and are much more resistant to water and alkali hydrolysis.^{1,4,5}

All nerve agents produce their toxicity through irre-

versibly inactivating acetylcholinesterase at nerve endings. The accumulation of the neurotransmitter acetylcholine results in overstimulation of the cholinergic nervous system. Toxicity manifests rapidly as increased oro-nasal and bronchial secretions, bronchoconstriction, abdominal cramps, vomiting, involuntary defaecation, respiratory paralysis, muscular weakness, tremors, convulsions and death. Mild and early symptoms include weakness, runny nose, chest tightness, slurred speech, nausea, impaired short range vision and painful accommodation.^{1,4}

The treatment modalities for nerve agent poisoning can be classified as follows: i) prophylaxis, ii) antidote, iii) acetylcholinesterase regenerators and iv) anti-convulsants.

Prophylaxis: Prophylaxis against nerve agent toxicity makes use of the reversible binding of carbamate cholinesterase inhibitors, such as *pyridostigmine*, to acetylcholinesterase.^{1,4} While the acetylcholinesterase is bound to *pyridostigmine*, it is protected against the irreversible attack by nerve agents. Since only a small amount of acetylcholinesterase is required for normal nerve transmission, toxicity is prevented by the constant release of active enzyme from its binding with *pyridostigmine*.

Troops in high risk situations may routinely be given oral prophylactic doses of *pyridostigmine*.^{1,4,6} These doses are relatively small and are generally devoid of unpleasant effects. During the recent Persian Gulf War however, exposure-related complaints suggest that the routine use of *pyridostigmine* may in fact sensitise individuals to the combined effects of the insect repellent DEET (*N,N*-diethyl-*m*-toluamide) and the insecticide *permethrin*.⁷ It has been proposed that *pyridostigmine* may inhibit the plasma esterases that bind to DEET and *permethrin*, leaving larger amounts of the latter to penetrate the central nervous system.⁷

Pyridostigmine itself is metabolised rapidly in the liver to an *N*-demethylated product, 3-dimethyl-amino-carbonyloxy-pyridine.⁸ A recent study in rats has implicated the cytochrome P450 2D1 (CYP2D1) as the main isozyme responsible for the detoxification of *pyridostigmine*.⁸ Although similar studies in man have not been carried out, the human equivalent of CYP2D1 is the genetically polymorphic CYP2D6 isozyme. In a white Caucasian population, about 5% to 10% of individuals have genetic deficiency of the CYP2D6 isozyme.⁹ Whether this deficiency may account for higher risk of adverse effects associated with routine *pyridostigmine* usage remains to be established. Although the genetic deficiency is uncommon (<1%) amongst Chinese and Malays,¹⁰ approximately 44% of Chinese subjects carry at least one copy of another mutant allele which codes for a less efficient isozymic form.^{11,12} The mutant allele has been named D6-J and occurs amongst Chinese at a

frequency of 0.6.¹² Should it be shown that Chinese subjects detoxify *pyridostigmine* less efficiently compared to Caucasians, it may be necessary to re-evaluate current dosage schedules for prophylactic *pyridostigmine*.

Antidote: Once poisoning has occurred, the antidote of choice is the pharmacological cholinergic antagonist *atropine*. *Atropine* may be administered intramuscularly by an autoinjector and can be titrated against signs and symptoms of cholinergic excess.^{1,6} Peripheral muscarinic effects can be effectively controlled through appropriate use of *atropine* but central nervous system effects are relatively unaffected. Maximum therapeutic benefit is therefore seen only when *atropine* is combined with assisted ventilation.⁶

Regenerators: Oximes such as *pralidoxime* (PAM) block the binding of nerve agents to acetylcholinesterase and reactivate the enzyme at nerve endings.^{1,4} To be effective, PAM has to be given early after exposure. This is because acetylcholinesterase bound to nerve agents tends to “age” with time and become unresponsive to PAM. In the field, PAM may be administered by an intramuscular autoinjector upon suspicion of exposure.^{1,6} Its effectiveness in the presence of nerve agents is about 1 to 2 hours after the standard autoinjector dose.

Other oximes such as HI-6 and *obidoxime* are available for use.⁷ All are suitable against sarin. *Soman* is the most difficult to manage and can only be treated using HI-6. As the oximes penetrate the brain poorly, they are most effective against the peripheral toxicity produced by nerve agents.

Anticonvulsants: Central nervous system effects are difficult to manage because many of the drugs used penetrate the blood-brain barrier poorly. Consequently while the patient's cardio-respiratory functions following exposure can be normalised fairly easily, central nervous system effects persist for some time. Convulsions are particularly troubling as they herald the onset of organic brain damage. The prevailing opinion is that if convulsions can be prevented, residual brain damage is not likely to occur.^{1,6}

The benzodiazepine anticonvulsant *diazepam* is often given by autoinjector upon suspicion of exposure.^{1,6} *Diazepam* effectively blocks and terminates nerve agent-induced convulsions. Centrally acting muscarinic drugs tend to be effective only in the early stages of poisoning, and high doses are required for late or recurrent convulsions.⁶

Vesicants

Otherwise known as blistering agents, the vesicants are corrosive chemicals that produce contact skin lesions resembling burns and blisters. Similar lesions are produced upon contact with the eyes, respiratory tract

and internal organs.

Mustard HD is a colourless and odourless liquid with low volatility.⁴ Early production methods resulted in a mustard-smelling chemical contamination from which its name was derived. The earliest of its class, mustard is also one of the easiest to manufacture. It produces its toxicity through nucleophilic attacks on the nitrogen and sulphhydryl moieties of nucleic acids, proteins and peptides. Cellular and tissue damage is not usually obvious immediately and it may take up to 24 hours before clinical evidence of exposure is apparent.

Nitrogen mustard ND is modified from the original mustard through substitution of the sulphur core by a nitrogen.⁴ *Lewisite L* belongs to a family of arsenicals whose basic chemical structure is based on the chloroarsine molecule.⁴ Phosgene CX is derived from a basic chemical structure containing an NOH⁺⁺ radical.⁴ It differs from the other vesicants in that it is highly corrosive, producing cutaneous and tissue lesions immediately upon contact.

It is difficult to protect against attacks by vesicants. Protective suits are effective barriers but substantially restrict functional capabilities of the soldier. No pharmacological antidote is currently available to treat casualties exposed to vesicant agents. Tissue resistance to these chemicals depend to some extent on the availability of naturally occurring scavengers of reactive radicals produced by vesicants. Tissue stores of *glutathione* for example, may serve as a readily available pool of such scavengers that may modulate toxicity produced by the sulphonium radicals of *mustard*.¹ This reaction is mediated by a family of enzymes called glutathione S transferase (GST). The GST family is mediated by at least 7 genetic loci.¹³ Of these, the μ isozyme is the most ubiquitous and studied. The θ isozyme is found substantially in erythrocytes and is involved in the conjugation of glutathione with natural and synthetic haloalkanes.

A genetic polymorphism exists for the μ and θ isozymes of glutathione S transferase so that a sizeable proportion of individuals in a given population are homozygous for either or both GST gene deletion. Amongst the Chinese, approximately 63% and 58% have the null phenotype for GST- μ and GST- θ respectively.¹⁴ The frequencies in the Malay population is similar (64%) for GST- μ but much lower (38%) for GST- θ .^{15,16} By contrast, the frequencies amongst Indians are both relatively low (32% and 18%, respectively).^{15,16} Correspondingly, approximately 37% and 22% of the Chinese and Malay population respectively may have neither of the GST isozymes. In contrast, only 5% of the Indian population may be expected to have neither of the GST isozymes. Among Caucasian populations, the frequency of the null GST- μ and GST- θ genotypes are about 48%¹⁷ and 37%,¹⁸ respectively. Correspondingly, about 18% of

Caucasians may be expected to have neither isozymes. No information is currently available on whether individuals who are genetically deficient in these GST isozymes might have increased susceptibility to vesicant agents.

After decontamination, treatment of casualties exposed to vesicant agents is largely symptomatic, relying on conventional means to alleviate pain and discomfort as well as to prevent infections. At a later stage, plastic surgery may be required.⁹

Blood Agents

The main agent in the class of chemical weapons is *hydrogen cyanide* (HCN). Apparently no documented reports of its use in warfare exist although the Iraqis were suspected to have used it against the Kurds during the 1980s.¹

The problem with HCN is that it is highly volatile and lethal concentrations are difficult to achieve except in confined spaces. *Cyanide* is essentially a respiratory poison, binding avidly to haem containing enzymes such as cytochrome oxidase. Deprived of this enzyme, cellular functions cease and the casualty literally suffocates.¹

HCN may be detoxified in the liver through the actions of the enzyme rhodanase which, in the presence of sulphur, converts HCN to *thiocyanate*. The reaction can be accelerated by providing sulphur moieties through *sodium thiosulphate*. As cyanide ions bind readily to Fe⁺⁺⁺ in methaemoglobin, detoxification can also be encouraged by using *sodium nitrite* to oxidise normal haemoglobin to methaemoglobin. VitB₁₂ provides cobalt which also binds to the free CN ions.^{1,6}

Conclusion

The mass use of chemicals as weapons of war is not a new stratagem. Although largely undocumented and unverified, chemical weapons have probably been used for as long as there has been any kind of human conflict. In recent years however, international interest in these weapons have heightened because their technology is within easy reach of developing countries. Any nation capable of producing fertilisers in bulk will be able to synthesise these chemical agents. Chemical weapons have unfortunately become the Third World's alternative to nuclear arms. In recognition of this alarmingly growing threat to world security, the United States, as well as a number of other developed countries have publicly disavowed interest in developing offensive chemical capabilities. Furthermore, increasing pressures are placed on developing countries to become signatories of an international ban on chemical weapons. While the intent is laudable, it is widely acknowl-

edged that verification is almost impossible. To make matters worse, the recent events in Japan show that chemical weapons technology has filtered underground and is now in the hands of terrorist groups. It is therefore clear that even peaceful countries need to develop a strategy to counter the potential threat of chemical weapons. The initial step in the process is to understand the toxicology and therapeutics of poisoning by these chemical agents.

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