Pathophysiological and clinical aspects of combat anticholinesterase poisoning

Avi A. Weinbroum
Post-Anaesthesia Care Unit, Tel Aviv Sourasky Medical Centre and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Nerve agents are organophosphate compounds similar to those used as pesticides but with much higher toxicity. They all block the activity of the enzyme acetylcholine esterase. Victims are intoxicated by absorption of the toxin via exposed skin or, more commonly, via inhalation of the poisonous gas. The resultant clinical picture is of hyperstimulation of both the nicotinic and muscarinic cholinergic system, which, if not promptly treated, leads to severe muscle paralysis, cardiac brady-asystole, hypersecretion from secretory glands, respiratory failure, seizures, coma and death. If antidotal drugs are promptly administered, the clinical severity of the poisoning is attenuated or complete abortion of symptoms is obtained. The main therapeutic strategies include atropine and oximes that counteract the nerve-agent-induced muscarinic and nicotinic cholinergic symptoms, respectively. Anticonvulsants and sedatives are used to treat central nervous system acetylcholine esterase disarray. This review summarizes the biochemistry and pathophysiology of anticholinesterase poisoning, the relevant clinical manifestations and the currently available therapeutic strategies.

Introduction

Nerve agents (NAs) are organophosphate-like compounds (Fig. 1) which are irreversible acetylcholine esterase (AChE) inhibitors. The earliest recorded use of chemically related compounds as poisons was the use of the Calabar bean in African witchcraft ceremonies; an extract was later synthesized and in 1864 its active ingredient was identified as physostigmine (Fig. 2).1 The first organophosphate compound to be synthesized in the laboratory was probably tetraethyl pyrophosphate by Wurtz in 1854.2 In the following 80 years, the organophosphate chemistry continued to be developed, but more recently the production of a number of well-known deadly organophosphates has been abandoned (Fig. 3). Before the Second World War only the
reversible AChE inhibitors were available (reversible and irreversible refers to the duration of binding to AChE). The former included physostigmine and neostigmine, which were used mainly for the treatment of glaucoma and intestinal stimulation and in compounds counteracting...
Fig. 3 Chemical formulae and classification of organophosphorus-like compounds. All compounds are based on the general formula (Fig. 1) with radical X replaced by different chemical groups. The four A compounds (isofluorophate, tabun, sarin and soman) are irreversible inactivators of acetylcholine esterase. The two B compounds are active metabolites of parathion and malathion, respectively. The three C compounds are extremely toxic agricultural insecticides that will soon be banned. Both B and C compounds are organophosphates with dissimilar anticholinesterase inactivation potentials.
the symptoms of myasthenia gravis. Later, neostigmine became the drug of choice for reversing neuromotor block induced by non-depolarizing muscle relaxants. Irreversible AChE inhibitors are potentially highly toxic because of their chemically irreversible inactivation of AChE, resulting in an excess of acetylcholine (ACh) which affects the cholinergic system throughout the body. Hence these compounds act as NAs.

The first report on the extremely toxic potential of organophosphates appeared in 1932 when the effect of vapours of dimethyl- and diethyl-phosphorofluoridate vapours was characterized. Shortly before the Second World War, German scientists who were attempting to develop superior pesticides based on existing organophosphate compounds synthesized new compounds. Tabun was the first to be synthesized, followed by sarin and soman, which were produced at the end of 1944 (Fig. 3). The Allied forces coded these as GA, GB and GD, for tabun, sarin and soman, respectively, after they occupied Germany. Another lethal type of NA, O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothiolate, was known as VX and was one of the numerous V-agents. This was originally produced in the United States, but its production was halted by President Nixon.

The use of NA weapons of mass destruction has become a real threat since the Iraq–Iran war in the late 1980s and the terrorist attacks against civilians in Japan in 1994 and 1995. As NAs are relatively cheap and easy to synthesize, they are expected to be readily available to terrorist groups, thus becoming an actual threat to humankind. The physical and military aspects of anticholinesterase compounds are beyond the scope of this article, but further details can be obtained elsewhere.

Clinical aspects of exposure to NAs

The route of exposure to the NA and the amounts of absorption are important factors in determining the pathophysiological course of NA intoxication. NAs can enter the body via contact with the skin or mucous membranes or by inhalation of vapour. Inhalation is the most rapid means of absorption of these agents because of the large surface area of the lung. Respiratory symptoms (shortness of breath, wheezing, bronchorrhoea etc., which are all muscarinic effects) are the early clinical manifestations of vapour exposure and are followed by progressive muscle weakness, leading to cardiovascular and respiratory collapse and death within minutes. Dermal exposure leads mainly to nicotinic effects which, depending upon the amount of exposure, can lead to local
twitching that evolves into muscle fasciculation, weakness, and delayed, but progressive, complete muscular paralysis. Although dermal exposure generally produces a more gradual accentuation of respiratory symptoms than inhalation exposure, it constitutes a significant risk to health care personnel if they are in direct contact with contaminated clothing and skin. However, whatever the route of exposure, respiratory failure develops and may ultimately lead to the patient’s death.

Biochemistry of NAs

NAs are chemical derivatives of phosphoric acid (Figs 1 and 3). They differ from each other by the type of chemical group replacing the [OH−] radical on the acid–base structure. All compounds formed by such replacements are capable of inhibiting AChE reversibly (organophosphate-based insecticides) or irreversibly (NAs) (Fig. 3). They are colourless and odourless volatile liquids in their basic state, and their vapours are heavier than air so that they tend to sink to the ground (Table 1). Tabun (GA; ethyl N-dimethylphosphoramidocyanidate), sarin (GB; isopropyl-methylphosphonofluoridate) and soman (GD; 1,2,2-trimethyl-propyl-methyl-phosphonofluoride) are halogen-, cyanide- and thiocyanate-containing organophosphates (Fig. 3). The V-agents are sulphur-containing organophosphates, which are less volatile and more enduring, and constitute mainly a liquid contact hazard.

AChE belongs to the class of enzymes called esterases, which catalyse the hydrolysis of esters. It has a high affinity for choline esters. Although there are several types of choline ester, ACh, which is the neurotransmitter of the cholinergic portion of the nervous system, is most relevant to

Table 1 Toxicological data for various NAs

<table>
<thead>
<tr>
<th></th>
<th>Tabun (GA)</th>
<th>Sarin (GB)</th>
<th>Soman (GD)</th>
<th>VX</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC50 (mg/min/m3)</td>
<td>400</td>
<td>100</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>LD50 (mg)</td>
<td>1000</td>
<td>1700</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>T1/2 (min) for ageing</td>
<td>420</td>
<td>150</td>
<td>5</td>
<td>Long</td>
</tr>
<tr>
<td>Volatility at 25°C (mg/m3)</td>
<td>610</td>
<td>220</td>
<td>3900</td>
<td>10.5</td>
</tr>
<tr>
<td>Freezing point (°C)</td>
<td>−5</td>
<td>−56</td>
<td>−42</td>
<td>−51</td>
</tr>
<tr>
<td>Persistence in cold weather</td>
<td>Days</td>
<td>Days</td>
<td>Days</td>
<td>Days</td>
</tr>
<tr>
<td>Persistence in warm weather</td>
<td>Hours</td>
<td>Hours</td>
<td>Hours</td>
<td>Weeks</td>
</tr>
<tr>
<td>Vapour pressure at 25°C (mmHg)</td>
<td>0.07</td>
<td>2.9</td>
<td>0.4</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

LC50, the product of the concentration of NA in air and the time that is needed until it kills 50% of an unprotected population inhaling the agent; LD50, dosage that would kill half of an unprotected population through subcutaneous exposure.

The ‘ageing’ process, which occurs most significantly in soman poisoning, prevents AChE from being reactivated by the oximes. This process barely exists following exposure to organophosphate pesticides, demonstrating their relatively low toxicity compared with NAs.
NA activity. AChE, which is found at the receptor sites of tissues innervated by the cholinergic nervous system, hydrolyses ACh very rapidly (Fig. 4). A similar enzyme (butyrylcholinesterase) is found in red blood cells (RBCs) and plasma. Figure 3 shows the chemical formulae of both the reversible and the irreversible anticholinesterases. The difference between these two compounds when reacting with AChE is the basis for the lethality of NA. Carbamates attach to both the anionic and the ester site of the AChE enzyme. When this occurs, a moiety of the carbamate is immediately split off, leaving the enzyme carbamylated at the ester site. In this case, hydrolysis of ACh does not occur for a period ranging from minutes to hours. Most of the organophosphate compounds combine with the AChE only at the ester sites and the stability of the bond depends on the structure of the compound attached. For example, hydrolysis recurs within a few hours if the alkyl group of the organophosphate, which is attached to the AChE active site, is a methyl or ethyl moiety. Organophosphate compounds containing larger alkyl groups may hinder cleavage, leaving the phosphorylated AChE inactivated almost indefinitely so that normal activity recurs only upon the synthesis of a new enzyme. Nevertheless, since most AChE inhibitors attach to the ester site of the enzyme, a second ligand cannot bind to the same site, leaving the enzyme protected from a second attack. This is the biochemical explanation for the partial protection given by carbamates, such as pyridostigmine (PYR), for period of 6–8 h (Fig. 2).6

NAs bind covalently to AChE resulting in irreversible inhibition and consequently unlimited accumulation of ACh at the neuro-effector junctions, thus disrupting normal synaptic transmission in both the peripheral and
Anticholinesterase poisoning

the central cholinergic system (Fig. 2). Although AChE is present in many types of tissue, including plasma, its inactivation in the nicotinic or muscarinic synaptic cleft produces the main toxic damage. The covalent bond between the NA and AChE can undergo a rapid chemical process of stabilization due to an increase in its thermodynamic stabilization. This may occur as a result of the formation of additional hydrogen bridges between the PO₄ groups and the other organic groups within the NA molecule (Fig. 3). In addition, part of the NA is cleaved and the other part of the compound remains irreversibly attached to the AChE molecule, thus inactivating it permanently. This process is known as ‘ageing’ and its time course varies depending on the NA (Table 1).

Although the classic explanation for the toxic potential of NAs is their ability to inhibit AChE, resulting in excess of Ach, this may not be their only effect. Research suggests that NA might inhibit additional non-AChE enzymes by the same mechanism of action. Reversible AChE inhibitors, such as PYR or physostigmine, in concentrations that are 7-fold higher than those of the lethal anticholinesterases can also produce direct effects on nicotinic receptor sites by blocking neural conductance through the nicotinic receptor–ionic channel complex or by acting as agonists at the channel complex itself.

Neurobiochemical physiology and clinical manifestations of NA–AChE binding (Table 2)

AChE is the transmitter of the cholinergic nervous system, which innervates the neurons of the skeletal muscles, the pre-ganglionic autonomic nerves

<table>
<thead>
<tr>
<th>End target</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscarinic receptors</td>
<td>Smooth muscle contractions (intestinal, bladder, bronchial) lead to nausea, vomiting, abdominal cramps, diarrhoea, urinary and faecal incontinence, bronchoconstriction, wheezing, and dyspnoea</td>
</tr>
<tr>
<td></td>
<td>Secretory gland hyperstimulation: excessive bronchorrhoea, lacrimation, salivation, rhinorrhoea, sweating</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: bradycardia, arrhythmias, hypotension, prolonged Q-Tc</td>
</tr>
<tr>
<td></td>
<td>Ocular: blurred vision, miosis</td>
</tr>
<tr>
<td></td>
<td>Central nervous system: depressed activity up to coma</td>
</tr>
<tr>
<td>Nicotinic receptors</td>
<td>Skeletal muscles: fasciculation, flaccid paralysis</td>
</tr>
<tr>
<td></td>
<td>Sympathetic ganglia: pallor, tachycardia, hypertension</td>
</tr>
</tbody>
</table>

Table 2  Clinical signs and symptoms of NA poisoning

The acute symptomatology of NA poisoning depends on the delicate balance between muscarinic and nicotinic receptor activity. Therefore, soon after intoxication, overstimulation of the sympathetic receptors prevails, leading to tachycardia or elevated blood pressure. Subsequently, the dominant muscarinic effect prevails, causing severe cardiovascular depression. Miosis, together with excessive secretion, is the most consistent sign of NA poisoning.
and the post-ganglionic parasympathetic nerves (Fig. 4). The cholinergic system can be divided into the muscarinic and nicotinic systems based on the fact that the structures that are innervated have receptors with specific affinity to muscarine alkaloids and nicotine alkaloids, respectively. The muscarinic sites are innervated by post-ganglionic parasympathetic fibres. These sites control glandular activity, the smooth muscle of the respiratory and gastrointestinal systems, and the efferent innervation to the heart. Nicotinic sites are autonomic ganglia and are responsible for skeletal muscle contractions.

Accumulation of the common potent muscarinic and nicotinic cholinergic neurotransmitter causes intense, protracted and generalized post-synaptic stimulation, both peripherally and centrally. The constantly activated nicotinic cholinergic receptors generate involuntary skeletal muscle contractions, followed by complete depolarization block, the clinical manifestation of which is flaccid paralysis. In a manner similar to the events in the peripheral nervous system, the accumulation of ACh in the central nervous system (CNS) nerve endings causes anxiety, disorientation and general convulsions, followed by loss of consciousness and respiratory arrest. Haemodynamic collapse accompanied by bradycardia (a muscarinic effect) precedes death.5,6 NA-induced ACh accumulation at the muscarinic sites also enhances the activity of various secretory glands, leading to excessive salivation, lacrimation, bronchorhoea, diarrhoea, micturition and sweating. The enhanced smooth muscle activity results in increased peristalsis, bronchial constriction and miosis.9 The severity of poisoning by NA can vary from mild cases (mild dyspnoea, blurred vision and glandular hypersecretion) to more severe poisoning, which is characterized by severe dyspnoea, skeletal muscle fasciculation, loss of sphincter control, convulsions and unconsciousness, which occurs soon after an intense exposure of only a few minutes. This is followed by a significant fall in blood pressure and bradycardia, leading to death because of cardiorespiratory arrest or prolonged seizures. Interestingly, delayed muscle weakness can appear 3–4 days after a prolonged subacute or low-intensity NA exposure; this late manifestation does not respond to the common antidotal treatment (see below).10

**Diagnostic approach to NA poisoning**

The diagnosis of acute NA poisoning is primarily based on the history of exposure and findings of characteristic signs and symptoms; confirmatory laboratory evidence could expedite initial therapeutic intervention. When the diagnosis is equivocal (e.g. mild intoxication or chronic exposure), measurements of AChE levels in RBCs (‘true’ AchE) or plasma (pseudo-AchE) will also prove useful.11 These measurements approximate
the activity of AChE in the CNS and relate to the degree of toxicity, since current clinical laboratory tests cannot directly measure serum or urine concentrations of NA or their metabolites. Although AchE values may vary within the population, they will be low after true NA poisoning has occurred.\textsuperscript{11}

Based on their experience with 173 adult patients, Senanayake \textit{et al.}\textsuperscript{12} developed a simple objective scale to assess the severity of organophosphate poisoning. Their scale relies on five common clinical parameters which are assessed when the patient is admitted to hospital. Each parameter is assessed on a 3-point scale, ranging from 0 to 2 points.

- Miosis: >2 mm (0); <2 mm (1); pinpoint (2)
- Fasciculation: none (0); present but either generalized or continuous (1); generalized and continuous (2)
- Ventilatory frequency: <20 bpm (0); >20 bpm (1), >20 bpm with central cyanosis (2)
- Heart rate: >60 beats/min (0); 41–60 beats/min (1); <40 beats/min (2).
- Level of consciousness: conscious and rational (0); impaired response to verbal commands (1); no response to verbal commands (2).

The total scores can be used to differentiate between mild, moderate and severe intoxication (scores 0–3, 4–7 or 8–11, respectively). Good correlation was found between these scores and the need for mechanical ventilation or total dose of atropine administered in the first 24 h after admission, enabling the differentiation of the severely intoxicated patients from the remainder.\textsuperscript{12} It is noteworthy that, although this scale was originally based on data retrieved from organophosphate-poisoned adults, its use to evaluate NA intoxication, especially in children, may be particularly beneficial as no cooperation from the patient is needed. In addition, the presence of miosis is emphasized as being a pathognomonic sign for NA intoxication based on experience gained after the sarin terrorist attack in Tokyo in 1995.\textsuperscript{13}

**Pharmacological antagonization of NA poisoning**

In the immediate (pre-hospital) phase, casualties should be adequately decontaminated in order to stop the continuous absorption of the gas and to prevent secondary contamination of medical teams. Use of copious amounts of water on exposed body areas has proved to be as effective a method as chemical neutralization by oxidative chlorination using freshly prepared alkaline hypochloride solution (0.5%).\textsuperscript{14,15} Skin decontamination is less important after exposure to vapour alone, but clothing
should be removed because it may contain trapped vapour. Indeed, in the UK and many other countries casualties would still be formally decontaminated. All medical and paramedical personnel participating in acute care of the victims must wear full protective gear consisting of a suitable gas mask and butyl rubber gloves.\textsuperscript{15}

Although non-pharmacological measures following a poison threat are beyond the scope of this article (see Weinbroum \textit{et al}.\textsuperscript{16} for a more detailed discussion), airway management deserves brief comment. Briefly, the severe irritation of the intoxicating vapour and the neurogenic effect of NA on the bronchi tonus frequently lead to pulmonary oedema (originally non-cardiogenic) and bronchospasm, which may require increasingly high ventilatory pressure for adequate oxygenation; barotrauma may subsequently ensue. Sedatives and analgesics are also essential in such conditions. Maintenance of a patent unobstructed airway, i.e. endotracheal intubation or, less safely, insertion of a laryngeal mask (LMA),\textsuperscript{17} would require awake or rapid sequence induction associated with Sellick’s manoeuvre and delivery of 100\% oxygen. Prolonged respiratory support using mechanical ventilation will be needed in many cases; repeated endobronchial aspiration will be mandatory in almost all patients. It is noteworthy that, since there may be many vapour-intoxicated patients and few caregivers, intubation may not be available to all intoxicated individuals.\textsuperscript{17} This may result in an unspecified number of individuals whose airways are not secured (such as those ventilated with an LMA)\textsuperscript{17} or with no ventilatory support (as occurred in Tokyo in 1995). The outcome for these patients is unpredictable.

Systematic pharmacological antagonization of acute NA poisoning is based on specific antidotal therapy. Delaying such treatment will certainly lead to a poor outcome for the victims. The treatment should be titrated according to the clinical severity of the intoxication, which is defined as follows.\textsuperscript{18}

- Mild intoxication: the patient can walk but suffers from miosis, blurred vision, lacrimation, salivation, chest discomfort, nausea and vomiting, and/or abdominal pain.
- Moderate: the patient is unable to walk, breathing is laborious with marked wheezing and bronchospasm; in addition, there is muscle fasciculation and urinary and faecal incontinence.
- Severe cases: in addition to the above manifestations, the patient is brady- or apnoeic.

In moderate or severe cases, antidotal treatment should be given intravenously and titrated according to the clinical response.\textsuperscript{19} The administration of cholinolytics as well as oximes and anticonvulsant should aim at minimizing toxic manifestations; in reality, this will probably only
Atropine blocks the overstimulation of the muscarinic receptor, thus affecting cardiac manifestations of toxicity and glandular hypersecretion. Symptoms like bronchoconstriction, nausea and vomiting, abdominal cramps and diarrhoea may also diminish. Atropine will also reduce the parasympathetic overstimulation and the consequent risk of bradyarrhythmias induced by ACh accumulation. Atropine must be given in large amounts that may reach up to 50 mg/70 kg in a 24 h period before signs of full atropinization appear. The limited experience with NA casualties indicates that only cumulative doses of atropine as high as 10–20 mg in the first 2–3 h after intoxication will provide adequate control of the symptoms. The initial dose (2 mg for adults and 0.02 mg/kg for children) should be administered intravenously; the full atropinization effect (flushed dry skin, pupillary dilatation, increased heart rate and attenuation of bronchorrhoea) is achieved only with large doses. Maintenance treatment for 2–3 days is necessary to abort the intoxication completely. It should be noted that, since miosis can persist after NA exposure and skeletal muscle paralysis is not affected by atropine, these two parameters are not suitable for monitoring the degree of atropinization. Rather the flushed dry skin, pupillary dilatation and increased heart rate mentioned above should be used for this purpose.

The normal activity of the nicotinic neuromuscular synapse can be restored by drugs belonging to the oxime group such as pralidoxime chloride (Fig. 5). Phosphorylated AChE, when bound to NA, undergoes hydrolytic regeneration at a slow or negligible rate. Oximes, which are nucleophilic agents, act as chemical ‘reactivators’ of AChE via a nucleophilic attack at the phosphorylated enzyme, enabling the release of NA from AChE which is thus reactivated. Pralidoxime chloride reactivates AChE a million times more rapidly than the spontaneous release of the bound organophosphate compound. The speed of the AChE reactivation by oximes depends on their accessibility to the AChE active centre, which

Table 3  Antidotal treatment for acute NA poisoning

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine: anticholinergic alkaloid;</td>
<td>IM/IV; 2 mg every 20 min until full effects of atropinization occur; children, 0.02 mg/kg</td>
<td>Dry mucus membranes, intense thirst, dry hot red skin, tachycardia, fever, confusional state</td>
</tr>
<tr>
<td>blocks the effects of parasympathetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>muscarinic hyperstimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pralidoxime chloride: oxime; disrupts the bond</td>
<td>IM/IV; 1–2 g (single dose), slow administration; children, 15–25 mg/kg</td>
<td>Elevated blood pressure, dizziness and blurred vision after rapid administration</td>
</tr>
<tr>
<td>between NA and AChE, restoring normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>synaptic transmission; especially effective at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the neuromuscular junction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine: central anticholinergic effect</td>
<td>IV/IM; scopolamine 0.25mg;</td>
<td>Drowsiness, sleepiness, loss of consciousness</td>
</tr>
<tr>
<td>Benzodiazepines: abort seizures</td>
<td>diazepam 0.2 mg/kg; midazolam0.1 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>
depends on their molecular structure.\textsuperscript{22} Many types of oximes have been synthesized for this biopharmacological antagonization, and the bis-quaternary compounds, i.e. HI6, HI7 and pralidoxime chloride (Fig. 5), have been shown to be the most potent AChE reactivators.\textsuperscript{19} Administration of the oximes as soon as possible after intoxication is essential because the chemical bond between the NA and AChE becomes resistant to deactivators when ageing occurs. In the case of soman ageing occurs a few minutes after exposure.\textsuperscript{18} If this occurs, the bound AChE cannot be reactivated and physiological activity at that specific site can be restored only by synthesis of a new enzyme 12–24 h later.\textsuperscript{23} The recommended regimen for pralidoxime chloride is a single i.v. dose of 1–2 g for adults and 15–25 mg/kg for children. Administration should take place over a period of 30 min to prevent side effects such as headache, blurred vision, epigastric discomfort and vomiting. Finally, the autonomic effector sites are minimally affected by the oximes, and atropine in ample doses must be administered for abortion of their NA-induced poisoning.

Prolonged seizure activity, resulting from the effect of NA on the CNS cholinergic receptors, must be stopped with high doses of anticonvulsive agents. Scopolamine has a sedative effect in addition to a central anticholinergic effect, while benzodiazepines halt and prevent convulsions and reduce stress response associated with panic and severe dyspnoea, while facilitating mechanical ventilatory support. Intramuscular injection of scopolamine 0.25 mg is recommended for mild poisoning and should be repeated after 4–6 h. In more severe cases, intravenous administration must be used. Diazepam should be administered in repeated i.m. or i.v. doses (10–15 mg or 0.2 mg/kg for children). Midazolam, which is a water-soluble benzodiazepine, can also be administered intramuscularly or intranasally (0.05–0.1 mg/kg). Both drugs must be titrated until complete control of convulsive activity is gained.
Preventive pharmacological measures for NA poisoning

PYR (Fig. 2) is an effective preventive measure against NA intoxication which is distributed to military and civilian populations at risk.\textsuperscript{22,24} In 1946 Koster\textsuperscript{25} first reported that pretreatment with PYR could protect against the lethal effects of diisopropyl-phosphorofluoridate. Since then, a great deal of research has centred on the utility of carbamate pretreatments as adjunct therapy after exposure to organophosphate compounds. Gordon \textit{et al.}\textsuperscript{23} reported the suitability of PYR as a measure against soman poisoning in 1978, and this was followed in 1981 by its incorporation as a pretreatment drug against organophosphate compounds.\textsuperscript{26} The recommended dosage is one 30 mg tablet every 8 h. From a pharmacological standpoint, PYR is a dimethyl carbamate containing a quaternary amine site. Therefore, it does not readily penetrate the blood–brain barrier. In the given doses, its actions are peripheral and only high doses may cross the blood–brain barrier and have central effects. The protective effects of PYR stem from its ability to create a reversible, rather than an irreversible, chemical bond at the AChE active site. The resultant carbamylated complex is resistant to subsequent NA attack. If exposure to a lethal dose of NA occurs soon after PYR administration, the active site of AChE is largely shielded since it is already bound to PYR. While the remaining free (unprotected) AChE will be irreversibly bound by the NA resulting in excess ACh in the synaptic cleft, the carbamylated (i. e. protected) portion of the AChE spontaneously breaks, releasing free enzyme which is available for effective action in the synaptic cleft of the post-junctional membranes. This enables the re-establishment of neuromuscular transmission based on the available quantity of AChE.\textsuperscript{6}

If given as a single drug, PYR affords only partial protection against potential NA lethality so that, in cases of a later exposure, the full post-intoxication antidotal drug protocol described above should be implemented as rapidly as possible.

Like other carbamates, because of the partial and reversible enzymatic blockade induced at the synaptic cleft, the administration of PYR carries with it some degree of accumulation of ACh, resulting in transient cholinomimetic nicotinic and muscarinic overstimulation. This clinical entity is called Gulf syndrome, and is characterized by weakness, diarrhoea, nausea, vomiting, hyperperistalsis, excessive salivation, difficulty in breathing and development of CNS signs such as restlessness, dizziness and hallucination. This PYR-induced AChE inhibition is reversible ~12 h after the last dose and the clinical symptoms should subside when most AChE activity returns to normal.\textsuperscript{27}
Conclusion

Nerve agents are toxic compounds which may be used in armed conflict, resulting in death of the exposed victims within seconds. The main biological effect of NAs stems from their ability to inhibit the AChE enzyme irreversibly with resultant excessive accumulation of ACh in the synaptic clefts. Therapy with atropine and oximes must be administered as rapidly as possible, together with supportive measures, including anti-convulsants, sedatives and mechanical ventilation, for the severely intoxicated victims. Pre-emption of the majority of the symptoms can be obtained by treatment with oximes.

References