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14 ATROPINE AND OTHER ANTICHOLINERGIC DRUGS

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The opinions expressed herein are solely of the authors and not necessarily those of the Department of Defense, the Department of the Army or the Army Medical Research and Materiel Command.

The nerve agents are highly toxic organophosphorous (OP) compounds. The agents of greatest concern, along with their chemical names and two-letter military designations, are tabun (*o*-ethyl *N*,*N*-dimethyl phosphoramidocyanidate; GA), sarin (isopropyl methylphosphonofluoridate; GB), soman (pinacolyl methylphosphonofluoridate; GD), cyclosarin (cyclohexyl methylphosphonofluoridate, GF), VX (*o*-ethyl *S*-2-*N*,*N*-diisopropylaminoethyl methyl phosphonofluoridate) and a Russian V-type agent designated VR (*o*-isobutyl *S*-(2-diethylamino)ethyl methylphosphonothioate). The nerve agents inhibit the cholinesterase (ChE) family of enzymes that includes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). It is the inhibition of AChE, the enzyme that hydrolyzes the cholinergic neurotransmitter acetylcholine (ACh), that produces the toxic action of nerve agents. Inhibition of BChE activity by itself is not known to produce any toxic effect. Nerve agents bind to the active site of the AChE enzyme, thus preventing it from hydrolyzing ACh. The enzyme is inhibited irreversibly, and the return of esterase activity depends on the synthesis of new enzyme molecules ($\sim$ 1% per day in humans). All nerve agents penetrate the central nervous system (CNS), with the G-type agents acting more rapidly centrally than the V-type.

ACh is the neurotransmitter at the neuromuscular junction of skeletal and smooth muscle, the preganglionic nerves of the autonomic nervous system, the postganglionic parasympathetic nerves and muscarinic and nicotinic cholinergic synapses within the CNS. Following nerve agent exposure and subsequent inhibition of the AChE enzyme, levels of ACh rapidly increase at the various effector sites, resulting in continuous stimulation. It is this hyperstimulation of the cholinergic system at central and peripheral sites that leads to the toxic signs of poisoning with these compounds, resulting in a syndrome referred to as a *cholinergic crisis*. These signs include miosis (constriction of the pupils), increased tracheobronchial secretions, bronchial constriction, laryngospasm, increased sweating, urinary and fecal incontinence, muscle fasciculations, tremor, convulsions, electrical seizures and loss of respiratory drive from the CNS. The relative prominence and severity of a given toxic sign depend highly on the route and degree of exposure. Ocular and respiratory effects occur rapidly and are most prominent following vapor exposure, while localized sweating, muscle fasciculations and gastrointestinal disturbances are the initial signs following percutaneous exposures and usually develop more gradually. The acute lethal effects of the nerve agents are generally attributed to respiratory failure caused by a combination of effects at both central (loss of respiratory drive) and peripheral (weakness at diaphragm and intercostal muscles) levels. These effects are

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exacerbated by copious secretions, bronchoconstriction, bronchospasm, muscle fasciculations and convulsions, which also contribute to the compromise of respiratory status. Several excellent reference sources provide more detailed discussions of the history, chemistry, physiochemical properties, pharmacology and toxicology of the nerve agents (Koelle, 1963; Sidell, 1997; Taylor, 2001).

PRINCIPLES OF TREATMENT OF NERVE AGENT EXPOSURE

Physical protective measures (e.g. gas masks, gloves and overgarments) and strict decontamination procedures are the most effective means of protection against the toxic action of nerve agents. The USA and North Atlantic Treaty Organization (NATO) also advocate the use of carbamate prophylaxis with pyridostigmine bromide as a way to enhance the therapeutic efficacy of antidote treatments in the case of poisoning with rapidly aging nerve agents, such as soman. Discussion of the use of carbamate pretreatment is covered in more detail in another chapter in this volume.

If intoxication does occur, treatment of nerve agent poisoning is focused along several lines. Prevention or reduction of the toxic signs is accomplished primarily via (a) administration of anticholinergic drugs, atropine sulfate being almost universally used for this purpose, (b) reactivation of agent-inhibited enzyme with oxime reactivators such as pralidoxime chloride (2-PAM Cl), and, when indicated, in cases of more severe poisoning, (c) treatment of convulsions and seizures with the benzodiazepine class of drugs (Army FM 8-285: Treatment of Chemical Agent Casualties, 1995; *Medical Management of Chemical Casualties Handbook*, 2000; Sidell, 1997). It should be noted that different countries have different complements of drugs for treating nerve agent casualties, but the differences are more in the specific drug used rather than in the general treatment approach (anticholinergic, oxime reactivator, anticonvulsant) itself (Moore *et al.*, 1995). Virtually all countries use atropine as an anticholinergic treatment compound and some use other synthetic anticholinergic drugs to supplement the effects of atropine. Diazepam, or a water-soluble prodrug form of diazepam (avizafone), is typically used as the benzodiazepine for field treatment. The greatest difference among the countries involves the choice of oxime treatment. The USA uses the chloride salt of the monopyridinium oxime, pralidoxime (2-PAM Cl); the UK uses the methanesulfonate salt, referred to as P2S or pralidoxime mesilate; France uses pralidoxime methylsulfate, known as Contrathion; Japan uses the iodide salt. Other countries favor more potent bispyridinium oximes, such as obidoxime (Toxogonin), trimedoxime (TMB-4) or HI-6.

An anticholinergic drug such as atropine blocks the effects of ACh overstimulation at central and peripheral muscarinic sites. Since it is the muscarinically mediated effects of nerve agent poisoning that are the most life-threatening, atropine or another anticholinergic is the most important life-saving treatment. It provides symptomatic relief of the excessive secretory responses (nose – rhinorrhea, salivary, pulmonary and gastrointestinal), laryngospasm, and bronchoconstriction. Atropine also increases the heart rate and, to a lesser extent, antagonizes the loss of central respiratory drive (Brown and Taylor, 2001). Atropine at high doses and other centrally active anticholinergic drugs are also effective treatments of nerve agent-induced seizures/convulsions (Capacio and Shih, 1991; McDonough and Shih, 1993; McDonough *et al.*, 2000; Shih *et al*, 2003). Atropine and other muscarinic anticholinergic drugs are unable to counteract the nicotinic signs of intoxication (e.g. muscle fasciculations, muscle fatigue, weakness). Reversal of the nicotinic signs of intoxication is therapeutically accomplished via oxime reactivation of inhibited AChE (Dawson, 1994; Kassa, 2002). This topic is dealt with in detail in Chapter 15 in this volume. Treatment of nerve agent-induced seizures/convulsions is essential for overall casualty management and prevention of neurological damage (Lemercier *et al.*, 1983; Lallement *et al.*, 1998; McDonough and Shih, 1997; Shih *et al.*, 2003). While there is a major cholinergic component to the initiation and early maintenance of these seizures, benzodiazepine drugs such as diazepam are most commonly used to antagonize this feature of nerve

agent poisoning. The use of benzodiazepines for the treatment of nerve agent-induced seizures is discussed in greater detail in Chapter 16.

Since nerve agents can produce rapid lethal effects, military personnel are issued several different automatic injector devices to deliver drugs intramuscularly (IM) for immediate emergency treatment of exposure. In the US military, individuals are issued three MARK I treatment drug kits; each kit contains two autoinjectors, one with 2 mg of atropine and the other with 600 mg of the oxime 2-PAM Cl. The MARK I kits are currently in the process of being replaced by a multichambered autoinjector (drugs in separate chambers) known as Antidote Treatment – Nerve Agent Autoinjector (ATNAA), that delivers atropine (2.1 mg) and 2-PAM Cl (600 mg) as a single injection. Individuals are also issued a single autoinjector (known as CANA – Convulsive Antidote Nerve Agent) containing 10 mg of diazepam. Thus, each soldier carries 6 mg of atropine, 1800 mg of 2-PAM Cl, and 10 mg of diazepam. The armed forces of many other countries provide their service members with autoinjector devices similar to the types described above. The guidelines and training for the use of these treatment drugs are based upon the medical treatment recommendations and doctrines established by the medical services of each country (e.g. Army FM 8-285: Chemical Casualty Care, 1995; Medical *Management of Chemical Casualties Handbook*, 2000). In the USA, the Food and Drug Administration has just recently approved autoinjectors with 0.5 and 1.0 mg atropine pediatric dosage forms for homeland defense use. Guidelines for atropine dosages to use in children poisoned with nerve agent have been recently published (Rotenberg and Newmark, 2003).

The treatment of nerve agent exposure in a military setting poses a unique medical problem. Individuals who have limited emergency medical training must accurately recognize and diagnose the signs and symptoms of a potentially lethal toxic exposure and then promptly administer to themselves or a fellow soldier the necessary treatment drugs in the proper order and the proper dosage. In addition to self-protection, protection of the casualty from further exposure, as well as decontamination and evacuation needs to be considered. This poses a set of tasks that requires constant and realistic training if they are to be accomplished smoothly in the case of a real nerve agent attack.

ANTICHOLINERGIC DRUGS

Atropine and similar anticholinergic drugs are pharmacologically classified as muscarinic receptor antagonists (Brown and Taylor, 2001). Muscarinic receptor antagonists compete with ACh for a common binding site on the muscarinic receptor. This binding prevents ACh from binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, heart muscle, glands, peripheral ganglia and in the CNS. In the context of nerve-agent intoxication, this means that muscarinic receptor antagonists can block the hyperstimulation that is produced by the repeated binding of high levels of ACh at peripheral and central muscarinic cholinergic synapses. Five subtypes of the muscarinic receptor have been identified, designated M_1, M_2, M_3, M_4 and M_5 (Caulfield and Birdsall, 1998). Each receptor subtype couples to a second messenger system through an intervening G-protein. M_1, M_3 and M_5 receptors stimulate phosphoinositide metabolism, while M_2, and M_4 receptors inhibit adenylate cyclase. The relative tissue distribution also differs for each subtype. M_1 receptors are enriched in the forebrain, especially in the hippocampus and cerebral cortex. M_2 receptors are found in the heart and brainstem, while M_3 receptors are found in smooth muscle, exocrine glands and the cerebral cortex. M_4 receptors are most abundant in the striatum; M_5 receptors are most concentrated in the substantia nigra. Studies with muscarinic receptor subtype knockout mice have revealed that specific receptor subtypes are involved in agonist-induced hypothermia (M_2, M_3), tremor (M_2), salivation (M_3, and to a lesser extent, M_1 and M_4), pupil diameter (M_3), dilation of cerebral blood vessels (M_5) and seizures (M_1) (Hamilton *et al.*, 1997; Gomeza *et al.*, 1999; Yamada *et al.*, 2001; Bymaster *et al.*, 2003). Because all of these responses are involved to varying extents in the toxic effects of nerve-agent intoxication, nonspecific anticholinergic drugs, such as atropine or scopolamine, that act at all

receptor subtypes, produce the most effective antidotal effects.

The antagonism of ACh by atropine at muscarinic receptor sites is competitive; this means the antagonism produced by a certain level of atropine can be overcome if the concentration of ACh is sufficiently high. ACh levels have been reported to increase from 150 to 300% in various brain regions following nerve-agent exposure in experimental animals (Shih, 1982; Fosbraey *et al.*, 1990; Lallement *et al.*, 1992). Since the increases in ACh are directly at the cholinergic synaptic nerve terminals, this leads to very high ACh concentrations close to the receptors. It is for this reason that atropine, or any other antimuscarinic drug, has to be given at relatively high doses to antagonize the effects of this increased ACh in cases of severe poisoning. This is also why a rapid administration of sufficient atropine or an anticholinergic drug like atropine is essential to quickly blockade the receptors and reverse the toxic muscarinic effects of poisoning.

A second feature that determines the speed of atropine action is the route of administration. The action of 2 mg of atropine sulfate on the human heart rate begins 1, 8 or 20 min after intravenous (IV), intramuscular (IM) or oral administration, and maximal rate increases occur in 6, 35 or 50 min by these routes, respectively (Grob, 1956; Ketchum *et al.*, 1973). The use of autoinjectors to administer atropine IM speeds up uptake of the drug over conventional IM injections when using a needle and syringe. This is due to a spraying effect as the needle plunges into the muscle, resulting in the distribution of drug within a larger muscle area, allowing for more rapid drug uptake (Sidell *et al.*, 1974). A conventional IM injection, using a needle and syringe, results in a depot disposition of drug, leading to slower uptake. Nevertheless, even with autoinjectors, it should be remembered that IM drug administration has an inherent lag-time between drug delivery, onset of effects and peak drug effect. Even though these times may only be minutes, such a delay may be clinically significant in a severely poisoned casualty with compromised respiration and cardiovascular status.

Atropine and other natural (e.g. scopolamine) or synthetic (e.g. benactyzine, biperiden, caramiphen, trihexyphenidyl) antimuscarinic compounds all cause the same constellation of effects, with the greatest difference between the drugs being their abilities to penetrate the CNS and their durations of action (Brown and Taylor, 2001). Atropine has more prominent peripheral effects at low doses than does scopolamine or other synthetic anticholinergics (Ketchum *et al.*, 1973). In contrast, scopolamine and other synthetic anticholinergics produce marked CNS effects at low doses with minimal concominent peripheral effects. Low doses of atropine (2 mg) depress salivation, bronchial secretions and sweating, increase heart rate, produce pupilary dilation and inhibition of lens accommodation for near vision (Headley, 1982; Penetar, 1990; McDonough, 2002). The one side-effect of atropine with the greatest operational impact on military performance is inhibition of sweating and the potential for inducing heat casualties due to the inability to regulate core temperature. This can occur even after a 2 mg dose of atropine, especially with heavy work, a hot environment or the use of chemical protective suits. Larger doses (5 mg) of atropine have more pronounced effects on salivation, bronchial secretions, sweating, heart rate and pupilary dilation, as well as inhibiting parasympathetic control of the urinary bladder and gastrointestinal tract. Still higher doses ($\geq$ 8 mg) inhibit gastric secretion and motility and produce a constellation of CNS effects (restlessness, disorientation, amnesia, hallucinations) best characterized as delirium (Ketchum *et al.*, 1973). At these doses, the EEG is shifted to slower activity, there is a reduction in the voltage and frequency of the alpha-rhythm and rapid eye movement (REM) sleep is depressed (Longo, 1966; Pickworth *et al.*, 1990). One feature of practical significance in using atropine as an immediate antidote for nerve-agent poisoning is that increasing the dose of atropine, or any of the other anticholinergics, beyond a certain maximum dosage will not produce any greater response. The onset of effects will just be more rapid after IM administration and the duration of effects will be longer.

Atropine has been the antidote of choice for treatment of nerve agent intoxication since nerve agents were first discovered and produced during World War II. It was included in the German nerve agent first-aid kits (Comstock and

Krop, 1948) and was determined to be an effective antidote by British scientists at Porton Down who first analyzed the pharmacology and toxicology of tabun obtained from captured German artillery shells (Wilson, personal communication; Sidell, 1997). Since the 1940s, atropine has been adopted as the first-line antidote to counteract nerve-agent poisoning by the armed forces of most countries. It is also almost universally used as the antidote to treat anticholinesterase poisoning by organophosphate or carbamate pesticides (Eddleston *et al.*, 2004a,b). The use of 2 mg as the 'unit dose' of atropine in the MARK I or ATNAA autoinjectors was established because this amount of atropine can reverse the effects of low or moderate exposures to nerve agent. The associated side-effects of this dose are well-tolerated, change in mental status is very unlikely and reasonable military performance can be maintained as long as care is taken to prevent heat injuries (McDonough, 2002). Thus, if exposure were suspected, this dose could be self-administered without significant performance compromise even if it was given inadvertently in the absence of agent exposure (Sidell, 1997).

Several countries use, or have proposed to use, other anticholinergic drugs as adjuncts to atropine for the treatment of nerve-agent poisoning. The common feature of all of these products is that these anticholinergics have much more potent and rapid effects on the CNS than does atropine. Israel uses a mixture of drugs, known as TAB, as their immediate nerve-agent treatment; this mixture contains the oxime TMB-4, atropine and the synthetic anticholinergic benactyzine. From 1975 to 1980, the US military also used TAB. The atropine and benactyzine combination in the TAB mixture is similar in composition to atropine, benactyzine and 2-PAM-combination antidote mixtures investigated by Yugoslov researchers in the early 1970s (Vojvodic and Maksimovic, 1972; Vojvodic *et al.*, 1972). Animal studies have shown that benactyzine is much more potent and rapidly acting in reversing the CNS effects of nerve-agent intoxication than atropine (Jovic and Milosevic, 1970; McDonough *et al.*, 2000). In addition, benactyzine is significantly less potent in inhibiting sweating or producing mydriasis than atropine, and therefore less likely to induce heat casualties in a warm environment or compromise near-vision in the case of accidental use. Military researchers in the Czech Republic have advocated the use of the synthetic anticholinergics benactyzine and trihexyphenidyl, along with the carbamate pyridostigmine, in a prophylactic mixture they have designated as PANPAL (Bajgar *et al.*, 1994). In addition, the Czechs utilize benactyzine and biperiden, as well as atropine, as post-exposure antidotal treatments (Bajgar *et al.*, 1994; Kassa and Bajgar, 1996). For several years, researchers in Israel, the UK and the Netherlands have demonstrated the effectiveness of scopolamine or hyoscine as part of a pretreatment combination with the centrally active carbamate physostigmine against soman poisoning (Meshulam *et al.*, 2001; Philippens *et al.*, 2000; Wetherell, 1994; Wetherell *et al.*, 2002). Most recently, Russian scientists have discussed the use of a synthetic anticholinergic, pentifin, as a potential post-exposure treatment (Petrov *et al.*, 2004). This compound is reported to possess central muscarinic and nicotinic antagonistic activity and is a strong M_1 muscarinic cholinoreceptor blocker. Exact details of how this compound may possibly be used (dose, frequency of administration) were not discussed. While many countries have other anticholinergic drugs to use as adjuncts to atropine for the treatment of nerve-agent poisoning, none of these compounds have been tested or used in human clinical cases of poisoning either with nerve agents or other organophosphate or carbamate pesticides.

Animal studies

Since the 1940s, animal studies have been critical for understanding the biochemical and physiological mechanisms by which nerve agents produce their toxic effects and for evaluation of various drugs to provide effective medical countermeasures. Over those years, there have been numerous studies to determine whether atropine is the most effective anticholinergic drug to treat nerve-agent poisoning. Initial studies by US researchers evaluated the effects of different anticholinergics alone to protect against increasing challenge doses of nerve agents (Wills, 1963). In the 1960s, Canadian researchers (Coleman

et al., 1962,1968) performed an extensive series of studies of both tertiary and quaternary anticholinergic drugs, in conjunction with the oxime P2S, to antagonize the lethal effects of sarin in mice and rats. They were trying to identify the specific cholinolytic mechanisms of action that were associated with enhanced protective activity against sarin toxicity. None of the pharmacological tests of peripheral anticholinergic action (mydriatic action, inhibition of ACh-induced spasm in ileum and lung, inhibition of gut motility) predicted protection against sarin-induced toxicity, a finding also confirmed by Brimblecombe *et al.* (1970). Further tests of using the compounds as adjuncts with a standard dose of atropine showed that caramiphen (called Parpanit in the papers) and the glycolate compound G-3063 (4′-*N*-methylpiperidyl 1-phenylcyclopentanecarboxylate HCl) demonstrated significantly enhanced protective activity against sarin lethality. A study by Jovic and Milosevic (1970) examined the protective effects of twelve anticholinergic compounds alone or in conjunction with 2-PAM against poisoning by soman, sarin and tabun, as well as a number of other highly toxic OP compounds in mice. They concluded that anticholinergics with pronounced central effects, specifically caramiphen or benactyzine in their study, could enhance the protective action of atropine, especially against the nerve agents, which they believed have more pronounced central toxic effects than the other OP compounds tested.

Nerve agents are potent convulsant compounds (McDonough and Shih, 1993,1997). The contribution of these seizures to the overall toxicity of these agents and the need to control them as part of total poisoning treatment were just being fully appreciated in the 1970s (Lipp, 1972,1973; Rump *et al.*, 1972,1973). It was Green *et al.* (1977) who first recognized that some anticholinergics have anticonvulsant activity and that this property was related to their enhanced antidotal activity against nerve agents. Subsequent studies by many other groups expanded on this observation, showing that potent centrally acting anticholinergics can (a) antagonize nerve agent-induced seizures (Pazdernik *et al.*, 1983; Samson *et al.*, 1985; Capacio and Shih, 1991; McDonough and Shih, 1993), (b) protect against the development of seizure-related brain damage (Samson *et al.*, 1985; McDonough *et al.*, 1989,1995), and (c) reverse the physical incapacitation associated with nerve-agent intoxication (Leadbeater *et al.*, 1985; Anderson *et al.*, 1994). All of these anticholinergic actions enhance the ability to protect against the lethal effects of nerve agents (Shih *et al.*, 2003). Atropine also displays anticonvulsant action against nerve agent-induced seizures in animal studies, but much higher doses are required compared to the anticholinergics with strong central activity (e.g., scopolamine, benactyzine, trihexyphenidyl) (McDonough *et al.*, 2000; Shih and McDonough, 2000; Shih *et al.*, 2003). It should be noted that, except in this context, anticholinergics are not routinely thought of as anticonvulsants and none is clinically licensed for such an indication.

In studies with rodents (rats, guinea pigs), there is a pronounced time-dependency to the anticonvulsant effects of these anticholinergic compounds. Relatively low doses of these compounds can rapidly terminate seizures when they are administered shortly (5 min) after seizure onset. As the delay between seizure onset and anticholinergic treatment is increased (40 min), some animals become totally refractory to the anticonvulsant effects, whereas others require significantly greater amounts of drug (1-2 log units), and the delay between drug administration and seizure termination is also greatly delayed (McDonough and Shih, 1993; McDonough *et al.*, 2000). It is not known if this same time-dependency is seen in higher species, including non-human primates and man. The reason for such a pronounced shift in anticonvulsant effectiveness of these anticholinergics is thought to be due to the early trigger of seizure activity by the high ACh levels and the later recruitment of non-cholinergic excitatory neurotransmitter systems (i.e. glutamatergic) by the excessive neural activity of the seizure itself (McDonough and Shih, 1997). In that regard, many of these synthetic anticholinergic drugs (e.g. benactyzine, biperiden, procyclidine, trihexyphenidyl) have been shown to have *N*-methyl-D-aspartate (NMDA) antagonistic properties (Olney *et al.*, 1987; McDonough and Shih, 1995), an additional pharmacological feature

that has been demonstrated to be beneficial in the treatment of nerve agent-induced seizures (Sparenborg *et al.*, 1992; Carpentier *et al.*, 1994; Lallement *et al.*, 1994,1998).

USE OF ATROPINE IN THE TREATMENT OF NERVE AGENT POISONING IN HUMANS

There are three major sets of clinical reports on the use of atropine in the treatment of humans suffering from severe nerve-agent poisoning. Sidell (1974,1997) described the treatment of a small number of workers at Edgewood Arsenal accidentally exposed to either soman or sarin. There are several clinical reports on the treatment of the victims of the terrorist attacks with sarin in Matsumoto and Tokyo (Masuda *et al.*, 1995; Morita *et al.*, 1995; Nozaki and Aikawa, 1995; Ohbu *et al.*, 1997; Okumura *et al.*, 1996; Sekijima *et al.*, 1995) as well as one individual poisoned with VX (Nozaki *et al.*, 1995). Finally, Newmark (2004) has summarized a series of articles originally published in the Kowsar Medical Journal by Dr Syed Abbas Foroutan that describes his experiences and protocols for treating nerve-agent casualties in a chemical aid station during the 1981–1987 Iran–Iraq war. The Sidell and Japanese reports describe the treatment of either single or limited numbers of severely poisoned casualties in fully equipped clinical emergency room settings. This is in contrast to the chemical-aid-station environment of Dr Syed Abbas Foroutan, where multiple nerve agent and other chemical casualties were treated following attacks, stabilized, and then evacuated further behind the front lines for recovery.

Sidell (1974,1997) described treating two severely poisoned individuals. The first received a vapor exposure to sarin and was seen in the treatment facility 5–10 min after the first symptom. He was cyanotic and convulsing, with labored breathing, fasciculations and copious secretions. He was immediately given 2 mg of atropine IV and 2 mg IM and an additional 2 mg IV several minutes later; 2-PAM and oxygen were also given, and another 2 mg IV of atropine was administered about 20 min after admission to control the return of secretions. Over the next 30 min, the patient deteriorated despite another 2 mg IM of atropine. By 60 min after admission, the patient became apneic, required assisted ventilation and received an additional 3 mg of atropine IV. Respiratory assistance was required for ~ 2 h during which another 1 mg of atropine was given IV to counteract bronchoconstriction. About 2.5 h after admission, the patient began to regain consciousness, began to breathe spontaneously and slowly recovered. In all, the casualty received 14 mg of atropine over ~ 2.25 h after admission, 10 mg of which was given IV. The second patient seen by Sidell was accidentally exposed to a small amount of soman solution orally. He immediately flushed his mouth with water and arrived at the treatment facility within 10 min of the accident. There, he immediately developed signs of intoxication and collapsed. Within a minute of developing symptoms, he was administered 2 mg of atropine IV and received a total of 4 mg IV and 8 mg IM of additional atropine over the next 15 min, along with 2-PAM, as well as oxygen and frequent nasopharyngeal suction. Bronchoconstriction and a decreased respiratory rate and amplitude were noted and the patient developed cyanosis. These signs began to diminish following the atropine therapy; heart rate and blood pressure remained stable, and about 30 min after admission the patient began to regain consciousness. He received additional atropine, 4 mg IV and 4 mg IM, at 14 h and 22 h post-exposure, respectively, to control nausea, vomiting and abdominal pain. This casualty received a total of 14 mg of atropine (6 mg IV) within ~ 20 min after admission, and a total of 22 mg of atropine in the first 24 h.

Treatment of the victims exposed to sarin and VX in the Japanese terrorist incidents is similar in many ways to the descriptions of the 'Sidell casualties'. All victims were seen in hospital emergency rooms where treatment was initiated. In cases of severe poisoning, atropine therapy was given IV, which insures maximum therapeutic effect within minutes. Nozaki and Aikawa (1995) described the treatment of one severely poisoned patient of the Tokyo subway exposures at Keio University Hospital. The patient arrived at the hospital in a coma ~ 1 h after exposure (Glasgow coma scale: E1M1V1), displaying profuse sweating and oral secretions, convulsions,

cyanosis and respiratory arrest. Over the next 10 min, the patient was intubated, mechanically ventilated and administered 0.5 mg IV of atropine, 5 mg IV of diazepam and 1000 mg IV of pralidoxime iodide; over the next 25 min, he received an additional 4 mg IV of atropine and 20 mg IV of diazepam. The patient gradually recovered consciousness and was extubated ~ 4.5 h after admission. He was treated with a total dose of 15 mg IV of atropine for two days in addition to the atropine administered as initial treatment. Treatment of five severely exposed patients at St. Luke's International Hospital (Okumura *et al.*, 1996; Ohbu *et al.*, 1997) followed a similar protocol. These patients either presented in a coma and respiratory arrest or were 'drowsy' and then developed generalized convulsions and lapsed into respiratory arrest. Two of these patients were in total cardiopulmonary arrest: one did not respond to cardiopulmonary resuscitation and died, while the other was successfully resuscitated but suffered severe brain damage and died 28 days later. All of the severely poisoned patients required intubation and ventilatory support; IV atropine was given up to total doses of 2–5 mg, along with IV pralidoxime iodide (1000 mg initially, followed by 500 mg h^{-1} for total doses up to 8500 mg); IV diazepam (5–20 mg total dose) was used to control convulsions. St. Luke's International Hospital also treated 105 moderately exposed patients. Miosis and other ocular signs of exposure were present in all patients; dyspnea, nausea, vomiting, muscle weakness, fasciculations and agitation were the other most common signs. These patients received 2 mg IV of atropine, 2000 mg IV of pralidoxime iodide and IV diazepam (dose not noted) for those with fasciculations. The authors note that miosis was severe and persistent (continuing > 1 week) in these patients and was unresponsive to systemic atropine treatment, but did respond to locally applied mydriatic agents.

Nozaki *et al.* (1995) also reported on the treatment of a patient exposed to VX in an attempted murder by the same *Aum Shinrikyo* cult that released sarin in Matsumoto and the Tokyo subway terrorist attacks. Reportedly, VX was sprayed on the victim's back; the man noted impaired vision and then experienced seizures and loss of consciousness. He arrived at the emergency room about 2 h after exposure semi-comatose (Glasgow scale E2M4V2) with profuse oral secretions, sweating, cyanosis, muscle fasciculations and convulsions, and was intubated. Organophosphate poisoning was not suspected at first, and he was treated with dopamine and isoprenaline to increase blood pressure and heart rate and with phenytoin to control the convulsions, but all of these treatments were without effect. At 3.5 h after exposure, he was treated with 2 mg IV of atropine, which immediately increased both heart rate and blood pressure, and 10 mg IV of diazepam, which controlled the convulsions. He was maintained on continuous IV atropine (3 mg day^{-1}) and mechanical ventilation, and 9 days after exposure he became alert and was extubated. The authors stressed the importance of systemic atropine for treating the bradycardia produced by the VX.

Battlefield experience contrasts strongly with the treatment environments of 'Sidell's patients' and with those of the Japanese terrorist attacks. Dr Syed Abbas Foroutan is an Iranian physician who set up and ran a chemical casualty-aid station during the 1981–1987 Iran–Iraq War. As such, he saw sometimes hundreds of nerve-agent casualties following a single Iraqi attack. Several years after the war, he published a series of articles in Farsi in the *Kowsar Medical Journal* describing his experiences and treatment protocols. These articles have been reviewed and summarized by Newmark (2004); he compares Dr Foroutran's experiences and treatment protocols for nerve-agent casualties with both US and NATO nerve-agent care doctrine. Dr Foroutan categorized the conditions of his nerve agent casualties as either 'mild', 'moderate' or 'poor'. Patients in the 'mild' classification consisted mostly of those with ocular symptoms, rhinorrhea and mild dyspnea. Patients in the 'moderate' classification presented with miosis, rhinorrhea, dyspnea, nausea, muscle weakness and fasciculations, but were conscious. The 'poor' classification would correspond in clinical presentation to the severely poisoned patients described by Sidell or those in the Japanese terrorist incidents.

The hallmark of Iranian nerve-agent-casualty treatment doctrine was 'to administer the highest required dosage of atropine in the shortest possible period of time'. This almost total

reliance on atropine may have been due to limited availability of oximes (see discussion in Newmark, 2004). Each Iranian soldier carried three 2 mg autoinjectors of atropine for immediate treatment of exposure. However, Dr Foroutan stated that this amount of atropine 'is effective on mild to moderate poisoning and has no effect on severely poisoned patients'. For those severely poisoned or for those who did not receive atropine, he states 'it is imperative that the patient be administered atropine under any and all circumstances' before evacuation back to the emergency unit. In the emergency unit, his atropine treatment protocol for severe exposures was a tradeoff between the need for rapid atropinization and over-atropinization. The patient would be given a test dose of 4 mg of atropine IV, and if in 1 to 2 min there was no sign of atropinization, then the patient would be given 5 mg of atropine IV over the next 5 min while checking pulse rate. An increase in pulse rate of 20–30 beats per min (BPM) was taken as evidence of initial atropinization. The rate at which atropine was given was tied to the pulse rate; if pulse rate decreased below 60–70 BPM, the rate at which atropine was given was increased, and the rate of atropine administration was slowed if the pulse rate was > 110 BPM. The total amount and rate at which atropine was given, according to Dr Foroutan's recommendations, was considerably higher than that recommended by the US or NATO treatment doctrine. He stated that if atropinization was not achieved following the first 4 and 5 mg IV atropine doses, that doses of 25 to 50 mg atropine be given IV every 5 min using the pulse rate guidelines outlined above, up to a total dose of 150 mg. In several very severe cases, he reported administering up to 200 mg IV of atropine in a 10–15 min period in an effort to achieve atropinization. Ease of breathing and drying of respiratory secretions were the end-points he recommended to consider atropine therapy adequate.

The rate and total amounts of atropine administered by Dr Foroutan to severely poisoned nerve-agent casualties differ considerably from the doses and treatment protocols used by Sidell and the physicians treating the Japanese terrorist victims. Dr Foroutan states that using more conservative treatment approaches wastes time and risks lives. In mass casualty situations such as those he faced, with limited oxime available and probably limited available means of mechanical respiration, this is probably a reasonable approach. He also stated that the faster atropinization is achieved, then the lower the chance of cardiopulmonary arrest. While offering no proof of this last statement, animal studies show that the more rapidly normal respiration and cardiac status are restored, then the less likely is the development of cyanosis, hypoxia, lowered cardiac rate and blood pressure, all factors that increase the risk of cardiopulmonary collapse (Lipp, 1976; Lipp and Dola, 1978; personal observation). Several of these factors (lowered cardiac rate, low blood pressure) also work against rapid uptake and distribution of IM administered treatment drugs.

Once atropinization had been accomplished in Dr Foroutan's Chemical Emergency Unit, casualties were evacuated to a recovery unit 100 km behind the front lines. There, he recommended that the atropine dose be reduced to a few milligrams per day, and that atropine 1 to 2 mg every 4 to 6 h be given for up to two days after the resolution of all clinical symptoms, with the dose only to be increased if bradycardia developed.

FIELD TREATMENT OF NERVE AGENT EXPOSURE WITH ANTICHOLINERGICS

It must be remembered that for immediate field treatment most soldiers are equipped with only three 2 mg autoinjectors of atropine (as well as oxime, and possibly anticonvulsant injectors) for administration by themselves or a 'buddy'. Most medical treatment doctrines call for oxime administration only with the first three autoinjectors of atropine. Additional oxime beyond this initial treatment will be administered under direction of a physician at a medical treatment facility. Additional atropine and anticonvulsant treatment is carried by the medic/corpsman in most Western/NATO forces and will be absolutely required in cases of severe poisoning. US medical treatment guidelines call for the administration of the first CANA anticonvulsant (10 mg of diazepam)

whenever all three atropine autoinjectors are administered, regardless of the apparent presence or absence of convulsions/seizures. Other countries have slightly different treatment regimens for anticonvulsant use. General guidelines for the treatment of nerve-agent exposure are based on the speed and intensity with which signs and symptoms of poisoning develop, as well as consideration of the probable route of exposure. Therapy should be titrated to relieve distress, minimize the casualty's discomfort and stop or reverse the toxic process. For anticholinergic drugs, this will mean primarily the control of excessive secretions, relief of bronchoconstriction, reversal of dyspnea and the maintenance of adequate oxygenation. Atropine and/or other anticholinergic drugs administered IM as immediate antidotes under most conditions will not counteract miosis or eye pain produced by vapor exposure, nor do they affect muscle fasciculations (Sidell, 1997). As a general rule, consciousness, spontaneous and clear respiration and lack of seizure activity are three indicators of successful therapy and a good clinical outcome for treatment in severe cases.

Knowledge of the suspected route of nerve-agent exposure is crucial in determining treatment guidelines. As a general rule, then the greater the exposure the more rapid the onset of signs, while the longer the time between exposure and onset of effects, then the less severe the effects will eventually be. Signs and symptoms develop relatively rapidly following vapor exposure, and both ocular and respiratory symptoms dominate the clinical picture in the case of adults. In contrast, signs and symptoms develop in a more gradual fashion following dermal exposure to liquid nerve agent, with localized sweating and muscle fasciculations being the first signs, followed by gastrointestinal distress and nausea. With dermal exposures, the development of signs and symptoms may be quite delayed, up to 18 h. Toxic effects can begin hours later, even after thorough decontamination since absorbed dose is determined by how much agent was on the skin and the duration of contact before decontamination. As can be seen from the clinical descriptions of poisoning cited above, rapid onset of miosis, excessive respiratory secretions, difficulty in breathing and, especially, the development of muscle fasciculations are good indications of a moderate to severe vapor exposure that needs to be aggressively treated. Likewise, gastrointestinal signs, accompanied by localized sweating, fasciculations, and dyspnea, are indications of a moderate to severe dermal exposure. Exposure through an open wound is expected to follow a time-course intermediate between the vapor and dermal routes. With either vapor or dermal exposure, diminished cognitive status or loss of consciousness should be taken as a sign of moderate to severe exposure. The general guidelines for atropine treatment following different categories of nerve agent exposure are shown in Table 1. It has been adapted from recommendations found in the Army Field Manual 8-285: Treatment of Chemical Agent Casualties (1995), the *Medical Management of Chemical Agent Casualties Handbook* (2000), and Sidell (1997). A more detailed discussion of these treatment guidelines for vapor and dermal exposures is provided below.

Vapor exposures

The effects of nerve agents occur very quickly following vapor exposure and can reach maximum intensity within minutes, even after the casualty is protected or removed from the vapor. Because toxic effects occur so rapidly, antidotal therapy should be more aggressive for a casualty seen during or immediately after an exposure than for one seen 15 to 30 min after exposure has ended. The effects from an absorbed vapor exposure may continue to progress to a maximum over several minutes, even after the exposure is terminated. Thus, the more aggressive therapy given immediately after onset of effects is due to anticipation of more severe effects in the ensuing minutes. In contrast, a casualty seen 15 to 30 min after vapor exposure is terminated will most probably be displaying maximum signs and not progress further. If the patient is displaying only mild signs at this time (e.g. miosis, rhinorrhea), these signs may resolve without any or with minimal atropine therapy.

For a casualty seen immediately after a vapor exposure, 2 mg of atropine should be given if the only toxic sign is miosis. If any dyspnea is also present, a second 2 mg of atropine

Table 1. General guidelines for immediate atropine treatment of a nerve agent casualty based upon the suspected route and severity of clinical signs of exposure

Route of exposure	Severity of exposure	Signs and symptoms	atropine dose[a.b.c]
Inhalation – vapor	Mild	Miosis; rhinorrhea; mild dyspnea; nausea/vomiting	> 5–10 min since exposure: observation or 1 × 2 mg atropine autoinjector, depending upon severity of dyspnea < 5 min of exposure: 2 × 2 mg atropine autoinjectors
	Moderate	Miosis; rhinorrhea; moderate to severe dyspnea; nausea/vomiting	> 5–10 min since exposure: 1 or 2 × 2 mg atropine autoinjectors < 5 min of exposure: 3 × 2 mg atropine autoinjectors
	Moderately severe	Miosis; rhinorrhea; severe dyspnea; nausea/vomiting; fasciculations	3 × 2 mg atropine autoinjectors; additional atropine (2 mg every 5 min) and ventilatory support may be required
	Severe	Loss of consciousness; convulsions; severe dyspnea/apnea	5 × 2 mg atropine autoinjectors; additional atropine (2 mg every 5 min) and ventilatory support probably required
Dermal	Mild	Localized sweating; fasciculations	1 × 2 mg atropine autoinjector
	Moderate	Localized sweating; fasciculations; nausea/vomiting	1 or 2 × 2 mg atropine autoinjectors
	Moderately severe	Localized sweating; nausea/vomiting; generalized fasciculations; dyspnea	3 × 2 mg atropine autoinjectors; additional atropine (2 mg every 5 min) and ventilatory support may be required
	Severe	Loss of consciousness; convulsions; severe dyspnea/apnea	5 × 2 mg atropine autoinjectors; additional atropine (2 mg every 5 min) and ventilatory support probably required

Notes:
[a] For each of the first three 2 mg autoinjectors of atropine administered, there should also be corresponding autoinjectors of oxime that is delivered in conjunction with the atropine dosing; no further oxime is to be given in the field after the delivery of these first three doses.
[b] If the severity of toxic signs requires that all three 2 mg autoinjectors of atropine need to be administered, then for US forces, anticonvulsant treatment is also given.
[c] Injections administered IM.

(total dose = 4 mg of atropine) should be given. If dyspnea is severe or if any other sign of severe intoxication is present (e.g. fasciculations, collapse/loss of consciousness) then all three 2 mg atropine injectors (total dose = 6 mg of atropine) should be administered and the medic/corpsman alerted to the possibility of the need for additional atropine. For casualties seen 15–30 min after vapor exposures have been terminated, no atropine is required if miosis is the only sign. If mild or moderate dyspnea is present, 2 mg of atropine should be given; if dyspnea is more severe (obvious gasping for breath), then two 2 mg of atropine (total dose = 4 mg of atropine) should be given. Improvement should be noted within 5 to 10 min following such treatment. If dyspnea is severe and more serious signs of intoxication are also present (e.g. fasciculations, collapse/loss of consciousness, convulsions), then all three 2 mg atropine injectors (total dose = 6 mg of atropine) should be administered and the medic/corpsman alerted to the need for additional atropine.

Dermal exposures

Because of the time-lag between exposure and the onset of toxic effects, the treatment of dermal exposure to nerve agent is more problematic. As stated above, toxic effects may develop hours after a dermal exposure, even though thorough decontamination may have been performed, since a toxic dose may have already been absorbed through the skin. Nerve agents penetrate skin at different rates based on moisture, temperature, location on the body and even age and gender of the patient. An asymptomatic person who has had dermal contact with a nerve agent should be kept under medical observation for up to 24 h and be regularly re-evaluated for changes in their condition. This is especially so for contact with agents such as VX or VR, which have greater skin penetrating capabilities than the G-agents. Localized sweating and muscle fasciculations are the first signs of dermal exposure to nerve agents and indicate that the nerve agent has already penetrated the skin. Observation of these signs calls for the administration of 2 mg of atropine. Nausea and vomiting are the other early signs of exposure to liquid nerve agent. If these signs occur soon after a suspected dermal exposure, it is an indication of a severe exposure and the need for more aggressive treatment. If these signs occur within 1 h of a suspected dermal exposure, then two 2 mg of atropine (total dose = 4 mg of atropine) should be administered and the need for further therapy anticipated. If nausea and vomiting occur several hours after suspected exposure, they may be successfully treated with a single 2-mg atropine dose if symptoms do not grow worse, but the casualty needs to be closely monitored. When dyspnea and/or more generalized muscle fasciculations are present in addition to the nausea and vomiting, this requires administration of all three 2 mg atropine autoinjectors (total dose = 6 mg of atropine) and the medic/corpsman alerted to the possibility of the need for additional atropine. The presence of more severe signs, e.g. loss of consciousness convulsions/seizures, requires administration of all three 2 mg atropine autoinjectors (total dose = 6 mg of atropine) and immediate notification of the medic/corpsman for additional atropine.

The severe casualty

A casualty that has been severely exposed by either the vapor or dermal route will probably have altered mental status or be unconscious, have severe dyspnea or apnea, cyanosis, copious secretions, generalized fasciculations and/or periodic convulsions/seizures. Not all signs need be present, but two of the above signs, along with altered mental status, indicate a potentially life-threatening exposure. In addition to therapeutic drugs, such a casualty requires ventilatory support, since the success of therapy under such circumstances depends upon the status of the cardiovascular system. Studies have also shown that rapid IV administration of atropine to animals rendered hypoxic by OP agents can trigger ventricular fibrillation, a potentially fatal cardiac arrhythmia (Kunkel *et al.*, 1973; Wills *et al.*, 1950). Because of this, it has always been recommended that ventilatory support be provided to counteract the hypoxia before or in conjunction with administration of large amounts of atropine (Sidell, 1997). In field treatment, a cricothyroidotomy may be the most practical way to provide an airway for assisted ventilation, while in a medical treatment facility endotracheal intubation should be attempted. Supplemental oxygen is helpful if available, as well as suction to clear secretions from the airway. Resistance to ventilation will decrease and secretions dry up as atropinization is achieved. Ventilatory assistance may be required for only a short time (20–30 min), but in cases of severe poisoning it may be required for hours before the return of spontaneous respiration (Sidell, 1974). Ohbu *et al.* (1997) describe several patients from the Tokyo subway incident in cardiopulmonary or respiratory arrest at time of admission that were successfully resuscitated, provided cardiovascular and respiratory support, and then successfully treated with atropine, oxime and diazepam.

Additional atropine beyond the initial 6 mg carried by the service member will most assuredly be needed promptly in a severely poisoned casualty. Sidell (1997) recommends that an additional 4 mg of atropine be given immediately, for a total initial dose of 10 mg. If the patient is in a medical treatment facility, the atropine should be given IV if that is possible and

if the casualty is not hypoxic. If the casualty is in the field, the medic/corpsman should give two additional 2 mg atropine autoinjectors. Under either circumstance, the caregiver should then wait for several minutes to assess the response to this initial 10 mg dose. Additional 2 mg autoinjector doses of atropine should then be given at 3 to 5 min intervals until atropinization is achieved. Signs of successful atropinization include decreased bronchospasm, reduced airway resistance, the drying up of respiratory and salivary secretions and a heart rate $\geq$ 90 beats per minute. All of these effects result in ease of respiration and adequate oxygenation, the keys to successful therapy.

Guidelines for the treatment of pediatric casualties in a potential homeland defense type of situation have been recently published (Rotenberg and Newmark, 2003). They recommend atropine doses scaled to the weight of the child, with 0.05 mg kg^{-1} per dose being the rough unit dose: 2 mg for 40 kg+; 1 mg for 20 kg+; 0.5 for 10 kg+. They recommend that these doses be given every 5–10 min to a moderate or severe pediatric casualty until atropinization is accomplished.

There has recently been increased discussion about the end-points of atropinization and the most efficient means to achieve it. Eddleston *et al.* (2004a) assessed variations in textbook recommendations for early atropinization using model data of atropine dose requirements in patients severely poisoned with OP pesticides. They concluded that a 'dose-doubling strategy', continued 'doubling' of successive doses, would be the most rapid and efficient way to achieve atropinization. Likewise, the treatment regimen used by Dr Foroutan also would result in a rapid atropinization. However, it must be remembered that the guidelines discussed above are for field treatment of a casualty, where a medic/corpsman is the caregiver and respiratory support is limited, while those of Eddleston *et al.* (2004a) and Dr Foroutan refer to treatment at a medical facility by a physician. The end-points of atropinization recommended by Army Field Manual 8-285: Treatment of Chemical Agent Casualties (1995), the *Medical Management of Chemical Agent Casualties Handbook* (2000), Sidell (1997), Dr Foroutan and Eddleston *et al.* (2004a) are very similar: lack of bronchoconstriction, ease of respiration, drying of respiratory secretions and a heart rate > 90 beats per minute. Eddleston *et al.* (2004a) recommended a target heart rate of > 80 beats per minute). Pupil size is not recommended as a therapeutic end-point to judge adequacy of atropinization in nerve-agent casualties since miosis produced by exposure to nerve agent vapor is resistant to systemic atropine treatment (Sidell, 1997).

Once atropinization has been achieved, the casualty needs to be closely monitored and additional atropine provided to maintain atropinization if toxic signs begin to reappear. Although very large amounts of atropine may be required to achieve initial atropinization (15 mg or more in Sidell's cases; up to 200 mg in Foroutan's experience), the need for such large doses has not extended beyond 2–3 h with nerve agents. This statement applies primarily to clinical experiences with vapor exposures to the G-type agents. There is limited clinical experience treating severe percutaneous exposures with V-type agents, where poisoning may very well be more protracted.

Additional atropine may be required beyond the initial atropinization to control reappearance of secretions and continuing nausea and vomiting for the next 6 to 36 h after severe poisoning. This has been typically administered as 1 or 2 mg doses IM (Sidell, 1974) or given by slow IV infusion of 1 to 2 mg h^{-1}. The point at which to discontinue atropine administration is a clinical judgment. With severe intoxication by nerve agents, continuing atropine administration beyond 36 h has not been needed. This is not the case with severe OP or carbamate pesticide poisoning where pesticides may be sequestered in fat tissue and cause continued acute cholinergic crisis for days or even weeks (LeBlanc *et al.*, 1986; Vale *et al.*, 1990).

Atropine, or other anticholinergic drugs, will not reverse all toxic signs of exposure. Muscle fasciculations may persist for hours after the other signs of intoxication have been controlled with atropine. The casualty may feel weak or easily fatigued for days. Some of the sarin-exposed victims of the Matsumoto terrorist attack still complained of fatigue, asthenopia (weakness or easy fatigue of the visual organs), dimness of vision and a general loss in strength up to one year

following that incident (Nakajima *et al.*, 1997). Sidell (1974) was the first to call attention to the protracted CNS effects that can linger for several weeks following exposure. A patient may become depressed, withdrawn, have poor sleep accompanied by vivid dreams and have moderate to mild cognitive impairment. These effects are virtually identical to the behavioral changes that are seen in volunteers exposed to moderate doses of DFP, sarin or VX (Grob *et al.*, 1947; Grob and Harvey, 1953,1958; Bowers *et al.*, 1964). These CNS changes noted by Sidell (1974) could be counteracted with moderate doses of scopolamine, and this treatment seemed to assist with recovery, especially achieving restful sleep. This is the only report in the literature that describes the use of anticholinergics to treat the behavioral sequela of a severe nerve-agent exposure.

SUMMARY

Atropine is an anticholinergic drug that binds to muscarinic cholinergic receptors and blocks the stimulating effects of the neurotransmitter ACh. As such, atropine or other antimuscarinic anticholinergic drugs provide life-saving immediate therapy to individuals exposed to nerve agents, OP pesticides or overdoses of other ChE inhibitors. Atropine decreases secretions and reverses the spasm or contraction of smooth muscle. It relieves bronchoconstriction and allows for better air exchange and maintenance of cardiovascular function. Rapid administration of what may seem as very large doses of atropine is required to control the toxic signs of nerve-agent poisoning in severely exposed individuals. Caregivers must be trained to be aggressive in the use of atropine for successful management of nerve agent casualties. Other centrally active anticholinergic drugs show significant promise as either replacements for, or as adjuncts to, atropine therapy based on extensive laboratory tests in animals, but have not, as of yet, been used clinically for this purpose.

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