A primer on nerve agents: what the emergency responder, anesthesiologist, and intensivist needs to know

Une mise à jour sur les agents neurotoxiques: ce que le premier répondant, l'anesthésiologiste et l'intensiviste doivent savoir

Keith Candiotti, MD

Received: 26 March 2017 / Revised: 3 June 2017 / Accepted: 19 June 2017 / Published online: 1 August 2017
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Abstract

Purpose The purpose of this review article is to familiarize first responders, anesthesiologists, and intensivists with the medical management of patients exposed to nerve agents.

Source This review is based on the current medical literature available to the general medical community.

Principal findings Nerve agents are some of the deadliest substances known to humanity. Though they kill primarily via muscle paralysis, which leads to respiratory arrest, these agents affect virtually every organ system in the body. Their primary mechanism of action is the body-wide inhibition of cholinesterases. This inhibition leads to the accumulation of acetylcholine, stimulating both nicotinic and muscarinic receptors. After decontamination, the primary treatment is with atropine to control muscarinic symptoms and with oximes to reactivate the cholinesterases and treat the nicotinic symptoms. Atropine doses can be much higher than conventionally used. Seizures are generally best treated with benzodiazepines. Patients with substantial exposure may require ventilatory and intensive care unit support for prolonged periods of time.

Conclusion While it is unlikely that most medical practitioners will ever encounter nerve agent poisoning, it is critical to be aware of the presenting symptoms and how best to treat patients exposed to these deadly agents. History has shown that rapid medical treatment can easily mean the difference between life and death for a patient in this situation.

Résumé

Objectif L'objectif de cet article de synthèse est de familiariser les premiers répondants, les anesthésiologistes et les intensivistes à la prise en charge médicale des patients exposés à des agents neurotoxiques.

Source Cette synthèse est fondée sur la littérature médicale actuellement disponible pour la communauté médicale générale.

Constatactions principales Les agents neurotoxiques sont parmi les substances les plus létales connues. Bien qu'ils tuent principalement par la paralysie musculaire provoquant un arrêt respiratoire, ces agents peuvent affecter tous les organes du corps. Leur mécanisme d'action principal est l'inhibition des cholinestérases dans tout le corps. Cette inhibition entraîne l'accumulation d'acétylcholine, qui stimule à la fois les récepteurs nicotiniques et muscariniques. Après la décontamination, le traitement principal se fait avec de l'atropine afin de contrôler les symptômes muscariniques, les oximes étant utilisées pour réactiver les cholinestérases et traiter les symptômes nicotiniques. Les doses d'atropine peuvent être beaucoup plus élevées que celles utilisées traditionnellement. Les convulsions sont en général traitées le plus efficacement par des benzodiazépines. Les patients ayant subi une exposition substantielle à ces agents pourraient nécessiter une assistance ventilatoire et un séjour prolongé à l'unité de soins intensifs.

K. Candiotti, MD
University of Miami, Miller School of Medicine, Miami, FL,
USA

K. Candiotti, MD (✉)
Department of Anesthesiology, Perioperative Medicine and Pain
Management, Jackson Memorial Hospital, (C-302), University
of Miami, 1611 NW 12th Ave, Miami, FL 33136, USA
e-mail: kcandiotti@miami.edu

Conclusion *Bien que la plupart des praticiens ne seront probablement jamais confrontés à un empoisonnement aux agents neurotoxiques, il est crucial qu'ils soient conscients de la présentation clinique et de la meilleure façon de traiter les patients exposés à ces substances mortelles. L'histoire démontre qu'un traitement médical rapide peut facilement faire la différence entre la vie et la mort d'un patient dans une telle situation.*

Poisons have been known to humankind since the earliest days, and modern science has given further rise to poisons of unimaginable toxicity. Of the agents developed over the years, few substances can match modern nerve agents (NAs) in terms of lethality and effectiveness as poisons. First developed prior to World War II as pesticides, organophosphate (OP)-based NAs have inflicted casualties during times of both war and peace.¹

Recent use of NAs in warfare was noted during the Iran-Iraq War in the 1980s,² the 1988 Iraqi attack on the Kurds,³ the August 2013 mass killing in the Syrian civil war⁴ (when 1,400 deaths occurred, reportedly due to NA attacks),⁵ and, most recently, again in Northern Syria in April 2017.⁶ During these conflicts, NAs were used against both military targets and civilian populations. Outside of organized state warfare, terrorists have also used NAs on civilian populations. In Japan in 1994, the Aum Shinrikyo (Supreme Truth) sect released the NA sarin in the town of Matsumoto, Japan killing seven and poisoning 600 residents and rescue staff.⁷ Later in 1995, the sect struck again, on a larger scale, releasing sarin on the Tokyo subway system. While a dozen people were killed in that incident, more than 5,500 sought medical help, 1,050 of whom appeared to have suffered some level of NA exposure.^{8,9} More recently, Malaysian authorities reported that Kim Jong-nam, the elder brother of North Korea's leader, Kim Jong-un, was assassinated on February 13, 2017 when VX liquid was wiped on his face in a public place at the Kuala Lumpur International Airport.¹⁰ This was not the first time VX was used with murderous intent. Members of the Aum Shinrikyo sect also confessed to three attempted murders using VX liquid in isolated attacks,¹ with at least one attack possibly resulting in death.¹¹

Because significant exposure to these agents often results in respiratory and cardiac arrest and depression of the central nervous system (CNS), anesthesiology and critical care staff should be acutely aware of these agents and understand their mechanisms of action and how best to treat exposed patients. Furthermore, first responders and medical staff involved in early resuscitation may find themselves exposed to these agents and should be

knowledgeable about the methods of decontamination and the proper use of protective gear.

History

In 1936, the German scientist Dr. Gerhard Schrader was attempting to develop a new pesticide while working for the chemical complex IG Farben. In doing so, he produced a phosphorus containing OP of the highest toxicity. This agent named tabun was the first NA manufactured. In 1938, this was followed by the development of *sarin*, which is ten times more toxic than *tabun*. In 1944, a third NA, *soman*, was produced, followed by *cyclosarin* in 1949.² All of the known NAs are OPs. The American military designated these original nerve chemicals as “G” agents—i.e., tabun (GA), sarin (GB), soman (GD) and cyclosarin (GF). The designation “GC” was skipped to avoid confusion with an infection by the bacteria *Neisseria gonorrhoeae*.¹² Other agents subsequent to these originals were even more lethal and were designated as “V” agents (VE, VG, VM, VX, and VR). The most familiar of these is VX (200-fold more toxic than soman [GD] and 300-fold more toxic than sarin [GB]),¹³ which was developed in England by another chemist attempting to develop an insecticide. The chemical VR is a form of VX developed by the Russian military.¹⁴ A notable feature of these newer V-agents is that they are more persistent—i.e., they do not wash away or degrade easily and can remain active on surfaces for weeks or even months. In contrast, G-agents are considered non-persistent. While V-agents primarily work by contact, they are also highly effective when inhaled as a gas or aerosol. In the second half of the 20th century, the Russians also developed a series of novel OP agents under the grouping of Novichok (Russian for “newcomer”) agents. These agents were designed to be even more lethal and harder to treat and protect against.¹⁵ Finally, there is a group of NAs designated as “GV” agents, which appear to combine the elements of both G and V agents.¹

The agents discussed above are typically described as unitary agents—i.e., they are ready to use in their final form. Nevertheless, due to the highly hazardous nature of these agents, they are sometimes handled in a binary form, consisting of two relatively safer agents that can be combined to become active. As an example, VX-2 consists of O-ethyl O-2-diisopropylaminoethyl methylphosphonite and sulfur, and when they are combined, active VX is formed.¹⁶

Properties

In their basic form, all NAs are generally colourless and odourless, though some agents are reported to have a slightly

fruity odour and VX may have a slightly amber coloration.¹ At room temperature, all NAs are in liquid form but can be aerosolized, vaporized (explosives), or dispersed by evaporation. These aerosols or vapours are denser than air.¹² Sarin has a volatility similar to water (boiling point 147°C), and primary exposure is typically inhalation when aerosolized. In contrast, VX is often described as appearing to be an oil-like substance (with a boiling point of 300°C), and its main route of exposure is by direct contact. Also, VX is stable enough that it can persist in the environment for several weeks or months. The other agents fall between these two extremes¹⁷ (Table 1).

Mechanism of action

All NAs work by similar mechanisms and are related to many pesticides, specifically, they are a subgroup of OP. They function by irreversibly inhibiting the action of cholinesterases throughout the body, primarily the acetylcholinesterase (AChE) in tissues. Nevertheless, they also affect pseudocholinesterase in plasma and cholinesterase in erythrocytes, effectively shutting down both enzymes. Nerve agents form a covalent bond with these cholinesterases, which inhibits them and leads to the accumulation of acetylcholine. These agents also bind to nicotinic, cardiac muscarinic, and glutamate N-methyl-D-aspartate receptors and are able to antagonize GABA (γ -aminobutyric acid)-mediated neurotransmission.¹⁸⁻²¹ The onset and severity of symptoms depend on the characteristics of absorption and distribution as well as the route and dose of the agent.²² Nerve agents may enter the body through the skin and mucous membranes, or they may be ingested or inhaled (the primary route for G agents). In dermal exposure, the onset of symptoms may be delayed, with early signs resulting from nicotinic stimulation which manifests as localized sweating, weakness, and muscle fasciculations. It has been demonstrated that VX is absorbed more quickly through the skin in warmer environments.²³ Sufficient exposure by inhalation or dermal contact will result in general weakness

that can progress to complete muscle paralysis, similar to a complete depolarization block (i.e., type II block).²⁴ This then leads to generalized muscle weakness, cardiac and respiratory collapse, and depression of the CNS, all of which can lead to death.²⁵ Exposure to NA vapour may result in a rapid onset of symptoms (in seconds), and high vapour levels can be lethal within one to two minutes.²⁶ There is no real mechanism for the body to “store” inhaled NA for release over time, and if a patient survives the initial exposure for more than 20-30 min without respiratory failure, they have a good chance of survival.^{7,27,28} In cases of very low dermal exposure, symptoms may not occur for up to 18 hr.^{1,26,29} The slow onset of symptoms may lead to the “clearing” of a patient who might still suffer from the effects of an NA as time progresses. Fortunately, the longer the delay of the onset of symptoms, the lesser the severity of symptoms. Dermal exposure from persistent agents is probably the greatest hazard to healthcare providers and rescue workers.

As NA exposure affects the entire body, the clinical manifestations are a combination of the effects of excessive acetylcholine at the nicotinic and muscarinic receptors, both peripherally and centrally. These two types of receptors were originally defined by their ability to bind nicotine and muscarine, respectively. Specifically, nicotinic receptors reside in multiple places in the body, including the CNS, the sympathetic and parasympathetic ganglia, and the neuromuscular junction. Muscarinic receptors also reside in the CNS, postganglionic parasympathetic nerve endings, and the postganglionic sympathetic receptors that activate sweat glands.¹ Nerve agents appear to produce more nicotinic symptoms than OP pesticides, which usually present with more notable muscarinic symptoms.⁸

Effects by system

Central nervous system

These agents can induce headache, confusion, seizures, irritability, lethargy, ataxia, coma, and permanent brain damage.² The effects of NAs on the CNS are quite complex

Table 1 Toxic exposure levels for nerve agents (NAs)

Agent	LC ₅₀ (mg·min ⁻¹ ·m ⁻³)	LD ₅₀ (mg)	T _{1/2} Aging (min)	Persistence T _{1/2}
Tabun	400	1,000	420	24-36 hr
Sarin	100	1,700	150	2-24 hr
Soman	50	100	2-5	Relatively persistent
VX	10	10	Prolonged	2-6 days

LC₅₀ = the concentration of agent in the air and the time that it will take to kill 50% of an unprotected population that inhales it (median lethal concentration/time); LD₅₀ = amount of NA that will kill 50% of unprotected patients by a subcutaneous dose; Aging = the property of nerve agents where they form irreversible bonds to cholinesterases and can no longer be reversed; Persistence = the amount of time a nerve agent can remain active in the environment

and appear to go beyond simple cholinergic stimulation. It appears that seizures, which are actually relatively uncommon in NA exposure, involve interactions with the GABAergic, glutamatergic, noradrenergic, dopaminergic, and serotonergic systems in the CNS. There is also some evidence which suggests that seizures may also be the result of overstimulation of central muscarinic acetylcholine receptors.¹

Ocular

Reduced vision and pupillary constriction (miosis) occur—a characteristic sign of exposure from a direct muscarinic effect.³⁰ Indeed, the pupillary response was used to follow the progress of sarin-exposed survivors in Japan. A majority of the patients exposed to sarin in the Tokyo subway attack had significant miosis. Miosis may persist for prolonged periods of time, even in the presence of adequate treatment. In low-dose skin exposure, miosis may not occur.

Cardiovascular system

Nerve agents can cause potentially lethal cardiac disturbances in rate, rhythm, and conduction.³¹ Nicotinic effects are usually dominant, initially with tachycardia and hypertension. Muscarinic stimulation follows and leads to bradycardia, heart block, prolonged QT, arrhythmias, and hypotension, all of which may be severe in the face of hypovolemia and last for hours.³² Sarin has also been reported to cause coronary artery vasospasm.³³ In animal models, both sarin and soman demonstrated myocardial injury and necrosis, with one study implying that, if a CNS effect was seen, cardiac damage would likely be noted.³⁴

In a case report of VX poisoning, bradycardia was a dominant feature, which differs from victims of sarin poisoning who present with tachycardia. The mechanism of this difference is unclear.³⁵

Respiratory

Inhalation of NAs or sufficient dermal exposure typically results in a rapid onset of respiratory symptoms. Early respiratory symptoms include shortness of breath, wheezing, pulmonary edema, and profound bronchorrhea. This is a result of both nicotinic and muscarinic receptors being affected. Respiratory collapse appears to be related to both muscle weakness and a direct effect of inhalation on respiratory centres in the CNS.¹ Respiratory and ocular symptoms are often the first signs of NA exposure.

Gastrointestinal

The muscarinic effects of NAs predominate, causing nausea, vomiting, abdominal cramping, and diarrhea.

Genitourinary

Urinary incontinence is the predominant symptom.

Musculoskeletal

Initial exposure, especially dermal, may result in localized fasciculations. As exposure increases, symptoms progress to profound muscle weakness and eventually flaccid paralysis. This is a direct result of excessive acetylcholine at the neuromuscular junctions, resulting in a depolarizing-like (type II) blockade.

Other systems

Profound salivation, lacrimation, perspiration, and rhinorrhea—possibly one of the first signs of exposure as a result of muscarinic stimulation—will occur.

In summary, stimulation of muscarinic receptors causes defecation, urination, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, and salivation (made easier to remember by the mnemonic DUMBBBELS).³⁶ Nicotinic receptor stimulation leads to *mydriasis*, tachycardia, weakness, hypertension, and fasciculations (remembered with the mnemonic, *Monday-Tuesday-Wednesday-Thursday-Friday*).³⁶ Presentation of other drug overdoses, such as opioids, which can show pinpoint pupils and respiratory depression, can be differentiated by the lack of associated symptoms described above for NA exposure (see Table 2).

Treatment

Decontamination

Treatment of exposed victims involves several steps. Initially, the continuation of NA exposure should be limited if possible. Contaminated clothing should be removed as soon as possible. Clothing should still be removed and placed in a plastic bag, even if the sole exposure was vapour due to the possibility of residual agent. The skin should be flushed with copious amounts of soap and water or other decontaminating agents such as reactive skin decontamination lotion,³⁷ if available. Although plain water will hydrolyze NAs to relatively non-toxic substances,¹² dilute hypochlorite solution 0.5% (i.e., 5% household bleach diluted 9:1) has also been shown to inactivate these agents by enhancing hydrolysis.

Table 2 Clinical effects of nerve agents by receptor type

Organ System	Nicotinic Effects	Muscarinic Effects
Central Nervous	Seizures, Coma	Seizures, Coma (?), Decrease in respiratory rate, Central Respiratory Depression
Eyes	Mydriasis	Miosis
Cardiac	Tachycardia, Hypertension	Bradycardia, Hypotension, Heart Block, Prolonged QT, Arrhythmias
Respiratory	Respiratory muscle paralysis	Bronchorrhea, Bronchospasm
Gastrointestinal		Nausea, Vomiting, Diarrhea
Musculoskeletal	Fasciculations, Weakness, Paralysis	
Other	Perspiration	Salivation, Lacrimation, Urination

Nevertheless, these solutions should be used only on intact skin.²⁶ If eye exposure occurred, they should be flushed with water or saline for five to ten minutes.³⁸ If NA was ingested, emesis is not recommended. The patient should be treated with oral activated charcoal 25–50 g.³⁹ The urgency of decontamination should not be underestimated, and any delay may worsen outcomes. Decontamination is particularly important in cases of contact exposure. There is an increased risk to healthcare providers if contact occurred with a persistent agent, such as VX, vs exposure to a G agent, and additional caution should be taken to prevent exposure during decontamination.

There are no readily available assays for the clinician to use to gauge NA exposure levels. Measuring erythrocyte AChE levels best indicates the severity of an acute exposure. This test may not be available in all hospitals or laboratories. A 15–25% depression in cholinesterase levels indicates slight poisoning. A 25–35% decrease in activity suggests moderate poisoning, while a 35–50% decline in cholinesterase activity is supportive of severe poisoning.⁴⁰ An erythrocyte AChE inhibition of $\geq 70\%$ is often seen in subjects with severe systemic effects. The function of the enzyme returns at a rate of approximately 1% per day. During recovery, plasma cholinesterase (i.e., pseudocholinesterase) may be a better indicator of returning tissue activity.²⁶ There is a low correlation between enzyme inhibition and the local severity of symptoms from mild to moderate vapour exposure.

Personal protective equipment

Protection of first responders and other healthcare workers is essential when faced with a situation of NA exposure. Indeed, approximately 25% of the hospital workers directly involved in the sarin Tokyo subway attack developed symptoms of acute poisoning. Of those who were working in areas of poor ventilation, 46% complained of symptoms, the most common being eye symptoms and headache.⁸ Protective gear should consist of impermeable suits, chemical gloves and boots made of

butyl rubber, and if vapour exposure is possible, protective face masks with charcoal filters. The use of powered air purifying respirators may prove to be more comfortable and allow the staff to wear eyeglasses while performing critical procedures such as intubation.⁴¹ The correct gear, worn and sealed properly, should provide full protection from NAs.²⁶ Once a patient is fully decontaminated, there is limited risk of exposure for hospital personnel. If a patient is still contaminated with an NA, standard surgical gowns, gloves, and masks may provide some very limited protection; however, the provider could still be easily exposed to agent if any is present. Full details on personal protective equipment are described on the United States Government website, “Occupational Safety and Health Administration Best Practices for Hospital-Based First Receivers of Victims from Mass Casualty Incidents Involving the Release of Hazardous Substances”.⁴²

Drug management

Patients with significant NA exposure may require intubation, ventilation, and other advanced resuscitation (i.e., advanced cardiovascular life support [ACLS]) and supportive efforts. As in any scenario, establishing an airway and maintaining breathing and respiration should be top priority; however, in this case, only after decontamination. Due to bronchoconstriction and severe bronchorrhea, ventilation may prove difficult and higher ventilator pressures may be required. Antidotal treatment with atropine should aid in improving the ventilation of affected patients. Inhaled ipratropium bromide has also been suggested as an adjunct treatment for pulmonary symptoms.^{5,43} In some patients who had severe exposure to an NA, ventilation was required for hours despite aggressive atropine management.^{2,44}

Overall, the pharmacologic treatment for NA exposure involves three classes of drugs: anticholinergics, oximes, and anticonvulsants (i.e., benzodiazepines) (Table 3).

Table 3 Antidotal treatment of nerve agent-exposed patients (adapted from reference)³¹

Drug	Dosage	Additional information
Atropine	-Mild case: 2 mg <i>iv</i> repeated every 20 min until full atropinization. Children: 0.02 mg·kg ⁻¹ -Moderate/Severe exposure: 2 mg <i>iv</i> repeated every 5-10 min until full atropinization. Children: 2 mg or 0.02-0.08 mg·kg ⁻¹	-In elderly patients, after initial 2-mg dose, consider decreased repeat doses of 1 mg. -MARK 1 autoinjector is a 2-mg <i>im</i> dose. -In severe intoxication, 6 mg may be needed in first hour, 10-20 mg in the first 2-3 hr, and 50-100 mg over 24 hr in severe cases. -Glycopyrrolate may be useful to treat peripheral symptoms. It does not cross to the CNS. -Do not use in children
Scopolamine	-Mild cases: 0.25 mg <i>im</i> every 4-6 hr. -Moderate/Severe exposure: 0.25 mg <i>iv</i> repeated every 30 min for 2 doses. Then <i>q4-6 hr</i> as needed.	-Do not use in children
Pralidoxime/ Obidoxime/ HI-6	Pralidoxime-Mild cases: 1-2 mg <i>iv</i> , over 5-10 min or <i>im</i> . Children: 15-25 mg·kg ⁻¹ <i>iv</i> or <i>im</i> . Infants: 15 mg·kg ⁻¹ <i>iv</i> -Moderate/Severe cases: Same dose but intravenously preferred Obidoxime-Mild cases: 250 mg <i>im</i> every 2 hr to a maximum of 3 doses. -Children < 2 yr: 62.5 mg <i>im</i> every 2 hr to a maximum of 3 doses. 2-10 yr: 125 mg every 2 hr to a maximum of 3 doses. Over 10 yr as an adult. -Moderate/Severe exposure: 250 mg <i>iv</i> over 30 min, maximum 3 doses typically but up to 2 g if clinically effective -Children: 250 mg every 2 hr (maximum of 3 doses but an additional 5 doses may be given if proving effective) HI-6: Autoinjector dose is 500 mg, typically a single dose may prove efficacious in mild poisoning. Higher dosing may be required in more significant exposure. (3 doses)	-MARK 1 autoinjector is a 600-mg <i>im</i> dose. -Individual doses should not exceed 2 mg. -If given intravenously should be given slowly.
Benzodiazepines	-Diazepam: 0.2 mg·kg ⁻¹ or 2-10 mg <i>iv</i> in adults Children 0.2-0.4 mg·kg ⁻¹ -Midazolam 0.1-0.2 mg·kg ⁻¹ <i>im</i> or <i>iv</i>	-Diazepam autoinjector is a 10-mg <i>im</i> dose. -Individual diazepam doses should not exceed 10 mg -Total doses of diazepam to suppress seizures in adults may be as high as 30-40 mg.

All drug doses are estimates. In cases of severe intoxication, especially with organophosphate pesticides, additional doses may be required above the stated maximum doses. CNS = central nervous system

Anticholinergics

Atropine is the main treatment for NA-exposed patients. It is effective in blocking the muscarinic effects of NA by competitive antagonism of acetylcholine at the muscarinic receptors, both peripherally and centrally. Nevertheless, it has little effect on muscle weakness or paralysis as atropine has little effect on nicotinic receptors. Any patient with NA symptoms other than ocular findings should receive a dose of atropine. Ideally, atropine should be given intravenously with an initial dose of 2 mg in exposed adults. If necessary, doses may also be administered intramuscularly as with the MARK I autoinjectors (Meridian Medical Technologies, Columbia, MD, USA), which are often carried by the military or first responders (Figure). MARK I atropine doses are 2 mg *im* and show similar efficacy to

intravenous atropine.⁴⁵ A combined autoinjector that sequentially delivers atropine 2.1 mg followed by pralidoxime 636 mg through a single 23G needle (Antidote Treatment-Nerve Agent, Auto-Injector) has also been developed and is available to the United States military (Meridian Medical Technologies, Columbia, MD, USA). Additionally, the intraosseous route may be a viable option, if necessary.

If a patient does not respond to the initial 2-mg dose of atropine with an increase in heart rate, drying of secretions, and mydriasis, this can be considered pathognomonic for a cholinergic crisis from OP poisoning.⁴⁶ Initial atropine doses of ≥ 6 mg may be required in patients who are exposed to high levels of NA. Doses of 10-20 mg in the first two to three hours after exposure may be needed to control symptoms,⁴⁷ with total doses up to 50-100 mg in the first 24 hr. Pediatric atropine doses range from 0.02-

Figure MARK 1 Autoinjector. The MARK 1 Autoinjector is designed to deliver intramuscular doses of 2 medications, atropine (2 mg) and pralidoxime (600 mg). When removed from the base and pressed against the outer thigh, a dose is delivered via a spring-loaded needle. In the setting of significant nerve agent exposure, more than one autoinjector may be required for initial treatment

0.08 mg·kg⁻¹.² The goal is “atropinization” of the patient, which may require 2-mg doses of atropine every five to ten minutes until control of symptoms is achieved. In older patients, 1-mg doses may be used after the initial 2-mg dose.

The main objective of treatment is to halt symptoms, specifically to dry secretions and to reverse the effects of the NA and allow the resumption of normal cardiopulmonary function.¹ Pupillary response and heart rate are not useful measures for assessing the degree of atropinization.⁴⁷ Scopolamine crosses the blood brain barrier more readily and may be used to help treat CNS-related cholinergic symptoms such as seizures. Specifically, scopolamine has been shown to stop soman-induced seizures in animals.⁴⁸ The scopolamine dose is 0.25 mg *im* q4-6hr in mild exposure cases and 0.25 mg *iv* in moderate to severe exposures, repeated within 30 min and then given q4-6hr as needed. Scopolamine treatment is not recommended in children.³¹ There is limited evidence, based on the treatment of OP poisoning, that glycopyrrolate 0.2 mg *iv/im* (repeated) or 7.5 mg in 200 mL (titrated to effect) may be an effective substitute for atropine or used in addition to it, especially if supplies of atropine are running low. Importantly, glycopyrrolate does not cross the blood brain barrier and therefore does not cause CNS anticholinergic toxicity as with atropine.⁴⁹ Based on OP studies, glycopyrrolate can also be combined with atropine as a combination treatment.⁵⁰ Once again, based on indications from non-NA OP poisoning, the drug ipratropium bromide may be useful for inhalation in cases where bronchorrhea and bronchoconstriction are the primary signs of toxicity.^{5,43} Other options to address NA-induced bronchospasm include traditional β -agonists (i.e., albuterol).⁵¹

Oximes

A class of agents known as oximes has been shown to be effective in reactivating inhibited cholinesterases and is part of the current recommended treatment for OP poisoning and NA exposure. While there is some controversy in the dosing of these agents and their overall utility for OP poisoning and certain NAs, they are recommended by the United States Army Medical Research Institute of Chemical Defense for victims of NA exposure.²⁶ As a group, oximes are more effective in reversing nicotinic effects, muscle weakness, and paralysis, while atropine has better efficacy against muscarinic receptors and related symptoms. Pralidoxime chloride (Protopam Chloride, 2-PAM) is an oxime that reactivates cholinesterases by breaking the covalent bond between the enzyme and the NA, thus displacing the NA from the esteratic binding site of the enzyme. Pralidoxime chloride is the only oxime currently approved by the United States Food and Drug Administration (FDA). The intravenous route is preferred for 2-PAM; however, intramuscular injections may be given. The MARK I autoinjector kit contains a 600-mg dose of 2-PAM that is given intramuscularly.

There is some debate over the exact dose of 2-PAM. Some recommendations indicate an initial dose of 1–2 g *iv* over five to ten minutes, with a continued intravenous infusion of 500 mg·hr⁻¹ or 1 g every six to 12 hr after significant exposure.^{1,5} Recommendations from the World Health Organization are for higher doses (30 mg·kg⁻¹ bolus, then 8 mg·kg⁻¹·hr⁻¹ or 30 mg·kg⁻¹ every four hours). Pralidoxime chloride doses of ≥ 8 g may be required to treat symptoms. A maximum dose of 12 g·day⁻¹ is recommended, since 2-PAM, in high doses, can itself contribute to the inhibition of AChE.^{8,12} The pediatric dose of 2-PAM is 15–25 mg·kg⁻¹ for children (not to exceed 2 g per dose) and 15 mg·kg⁻¹ for infants, intravenously.⁵²

For those countries with obidoxime approved for use, the recommended dosing regimen is 4 mg·kg⁻¹, then 0.5 mg·kg⁻¹·hr⁻¹ or 2 mg·kg⁻¹ every four hours to a maximum dose of 750 mg·day⁻¹; however, higher doses have been used in cases of severe OP poisoning.^{5,12,53,54} Alternative dosing for obidoxime in adults with mild exposure is 250 mg *im* every two hours to a maximum of three doses·day⁻¹. In moderate or severe exposure, a 30-min intravenous infusion of 250 mg repeated every two hours (maximum of three doses; however, up to 2 g can be given if clinically effective) is recommended.³¹

The overall efficacy of 2-PAM and obidoxime has been called into question, especially in the treatment of soman, cyclosarin, and Russian VX exposure.⁵⁵ Some countries have adopted the use of the newer oxime, asoxime chloride

or HI-6 dichloride (Canada, Sweden, and the Czech Republic), which is reported to have superior efficacy against the more resistant NA compared with 2-PAM and obidoxime. At this time, HI-6 is not commercially available and is available only to government agencies. The dosing of HI-6 in autoinjectors has been reported to be 500 mg although newer injectors have been reported to contain 636 mg of HI-6.⁵⁶ In most cases of NA exposure, one autoinjector should prove sufficient; however, up to three may be needed for maximal dosing.⁵⁴ Studies looking at HI-6 administration and safety have shown that single doses up to the level of 500 mg·kg⁻¹ have been well tolerated.⁵⁴ In reports of using HI-6 for patients poisoned with OP, a dose of 500 mg *im* given four times a day to a cumulative dose of 14 g showed no undesirable side effects attributed to HI-6.⁵⁷ While HI-6 appears to be more efficacious against many NAs compared with 2-PAM and obidoxime, it is not effective against some OP pesticides. In general, the dosing of oximes should be adjusted to levels of exposure and symptoms. Administering oximes at a slow rate helps reduce the side effects of hypertension, laryngospasm, muscle rigidity, and tachycardia.^{2,22,58} Oxime-induced hypertension can be treated with phentolamine 5 mg *iv*.¹² Oxime therapy should be started as early as possible and continued as long as free NA is present in the patient.⁵⁴

Aging

Over a period of time the bond between the NA and enzyme will become permanent. This is known as “aging”. Aging occurs when the NA loses an alkyl side chain, making the agent-enzyme bond more stable. Under this situation, reversal agents have little or no efficacy. Recovery is then dependent on replacing the enzyme, which takes weeks (i.e., approximately 1% per day). Different agents age at different rates. Aging is fastest for soman (about two minutes) and can take days for VX. Sarin aging falls in between, occurring in three to four hours.¹ In most NA events, it is likely that the specific agent will initially be unknown, and the administration of 2-PAM should not be delayed (administered within two to three minutes of exposure) once an NA is suspected. While aged bonds cannot be repaired, there is some evidence that 2-PAM may be able to provide some benefits at high doses.^{59,60}

Benzodiazepines

Diazepam is a benzodiazepine used in the setting of NA exposure primarily to inhibit seizures. If the use of atropine and an oxime are instituted for significant NA exposure, then diazepam should also be given, even if no seizure

activity is readily present.²⁶ The diazepam autoinjector used by the United States military (labelled CANA) administers a 10-mg dose intramuscularly. Intravenous doses of 2-10 mg can also be used and repeated every 10-20 min as needed (if seizures are occurring).^{5,12,22} Higher doses of diazepam overall (30-40 mg) may be required to stop seizures.⁶¹ In children, doses of 0.2-0.4 mg·kg⁻¹ given over two to three minutes, repeated every 15-30 min, and up to 10 mg can be utilized.² Diazepam has a long half-life (43 hr), but free plasma levels may drop in half due to tissue sequestration.¹² If diazepam is not available, based on limited data, including animal models, other benzodiazepines can be substituted, such as lorazepam, 2-4 mg given slowly at 2 mg·min⁻¹ and repeated after five to ten minutes if seizures persist. Midazolam can be dosed by loading 0.1-0.2 mg·kg⁻¹ *iv* with a continuous infusion of 0.1-0.4 mg·kg⁻¹·hr⁻¹ in adults and a similar loading dose in children followed by a maintenance dose of 1 µg·kg⁻¹·min⁻¹.^{12,52} If no intravenous line catheter is present, these drugs may be given intramuscularly, and some formulations of midazolam can be given intranasally or buccally. Other anticonvulsants, which are traditionally used to control seizures, may not be effective in the case of NA-induced seizures.⁶²

If seizures are not controlled by benzodiazepines, then barbiturates may be an option.

Other

Ocular pain may result from severe miosis. This can be treated with 0.5% tropicamide and anticholinergic agents (anti-muscarinic). While atropine or homatropine ophthalmic solutions are suggested, they may worsen vision for longer periods of time than tropicamide, which has a shorter half-life.^{1,22}

Pyridostigmine

Pyridostigmine bromide, 30 mg *q8hr*, a carbamate reversible AChE inhibitor, has been approved by the FDA as a prophylaxis against the effects of soman. By binding to the active AChE site, it blocks the binding of NAs. Over time, the pyridostigmine-enzyme bond degrades leaving the active enzyme. When pyridostigmine is used as a pretreatment prior to exposure and combined with rescue medications, the LD₅₀ (lethal dose to kill 50% of those exposed) dose of soman appears to increase several fold. Pyridostigmine does not appear to alter the outcomes from exposure to sarin or VX. There are insufficient data on whether outcomes are improved against tabun or cyclosarin. Pyridostigmine is useful only as a prophylaxis, and even in its presence, rescue with oximes and atropine is still required. Pyridostigmine should not be

given to patients after NA exposure since it may worsen their condition.²⁶

Anesthetic management

If an NA-exposed patient requires surgery, due to either related trauma or another surgical condition, numerous factors need to be considered. Prior to surgical intervention, patients should undergo full decontamination and antidote treatment. Patients with higher levels of exposure may be given ventilatory support and often require high levels of pressure and positive end-expiratory pressure.²⁵ The question of triage often presents a challenge. Patients with very high levels of NA exposure in the field may not be viable surgical candidates due to their expected high mortality. This concept has to be considered in mass casualty situations where resources may be limited. Nevertheless, if an NA-exposed patient can reach a medical facility while still breathing and with a pulse, they have a good chance of survival.^{12,27}

Sedation of preoperatively exposed patients can best be accomplished with benzodiazepines. Additionally, atropine, glycopyrrolate, and scopolamine are useful for drying secretions and are considered primary treatments for NA-exposed patients.³¹ Aside from the standard preoperative history, if possible, it should be clarified if the patient had been taking pyridostigmine. This may be more relevant in first responders and military personnel. Pyridostigmine-treated patients often have increased secretions and a reduced heart rate and may require more aggressive anticholinergic premedication as a result.⁶³ Due to the primary effects of the NA, namely, extreme diaphoresis, urination, lacrimation, defecation, and overall loss of fluids, it is highly likely that exposed patients will be hypovolemic.

Induction

Depending on the level and degree of concomitant injury, general anesthesia may be required for the treatment of patients who have suffered NA exposure. Though ketamine is a desirable agent for induction of general anesthesia in patients who are hemodynamically unstable, it does, however, increase upper airway secretions. This is often solved by using agents such as glycopyrrolate and atropine. Additionally, the sympathomimetic activity of ketamine is desirable against the predominantly parasympathetic cardiac effects of NAs.³¹ Etomidate also has a good safety profile and minimal cardiac effects, making it a highly desirable drug for induction. Propofol, the most commonly used induction agent, may not be suitable for NA-exposed patients due to its tendency to cause some

degree of myocardial depression and vasodilation. This effect may also be exaggerated due to hypovolemia.

Intraoperative management

Inhaled agents have desirable characteristics that support their use in NA-exposed patients. Volatile agents induce bronchodilation and relax skeletal muscles through mechanisms outside of the AChE-ACh mechanism aiding in ventilation.³¹ Chemical agent monitors are frequently used by the military and emergency response teams to detect vesicant sulfur mustard (military designation HD) and G series NAs. It has been noted that volatile anesthetics may give a false positive reading on some chemical agent detection systems. Isoflurane, desflurane, sevoflurane, and halothane can produce signals consistent with vesicant sulfur mustard (HD).⁶⁴

Opioids may be required as part of general anesthesia and to treat pain. They do not interact with the cholinergic receptors or AChEs. Morphine may present issues due to its characteristics of histamine release and potential to decrease blood pressure in hypovolemic patients. Additionally, morphine, fentanyl, and sufentanil are vagotonic and may worsen bradycardia. Remifentanyl has the same issues and may also have a prolonged half-life due to inhibition of plasma cholinesterase by the NA. If a patient is hemodynamically stable, fentanyl or sufentanil may be options but should be used cautiously. A better option may be meperidine ($0.25 \text{ mg} \cdot \text{kg}^{-1}$), which can increase heart rate due to its vagolytic properties and has no histamine release associated with its administration.³¹

Succinylcholine should be used with caution. Its mechanism of action has similarities to that of NAs—i.e., increasing acetylcholine at the neuromuscular junction. Additionally, NAs impair the functioning of plasma cholinesterases, which may further prolong the action of succinylcholine by decreasing metabolism. If succinylcholine is utilized, it should be administered in reduced doses and used with caution. Gulf War soldiers who were prophylactically treated with pyridostigmine and received succinylcholine did not experience prolonged paralysis.⁶⁵ For patients requiring a longer operation or prolonged tracheal intubation, pancuronium is desirable due to its positive chronotropic effects. Probably the best choice for neuromuscular blockade would be rocuronium due to its speed of onset, lack of metabolic issues (such as with succinylcholine), and the fact that it can be fully reversed by sugammadex, even with a dense block, thus avoiding neostigmine altogether.⁶⁶ Pancuronium has some reversibility with sugammadex,⁶⁷ however, less so than rocuronium or vecuronium. Sugammadex also has the benefit of having no interaction with AChEs.⁶⁷ The use of neostigmine is controversial in NA-exposed patients. Its

primary action is to inhibit AChE, which is similar to NA, but in a far more reduced fashion. If used, dosing should be reduced, and the minimal amount of drug required for reversal should be used. Close titration of muscle relaxants with monitoring may reduce the level of reversal required.

Pain control

If local anesthetics are used for wound infiltration or nerve blocks, amide local anesthetics (lidocaine, bupivacaine, ropivacaine, etc.) are preferred over esters, which are metabolized by cholinesterases which are inhibited by NAs.⁶⁸

Post-exposure considerations

Prolonged muscle weakness may complicate the postoperative course of patients surviving OP and NA exposure. Upper airway obstruction has been reported as well as bilateral recurrent laryngeal nerve paralysis.^{69,70} Direct myonecrosis has also been reported with OP poisoning, which would be indicated by elevations in myoglobin and creatine kinase. Creatinine levels and potassium should be monitored in post-exposure patients. Cardiac instability, arrhythmias, including “torsades de pointes” have been reported in OP-exposed patients.^{25,71} QT prolongation may also be a problem, even up to two weeks after exposure. Minor electroencephalography changes have been noted, even after a year in subjects exposed to NAs. These changes were noted on average in a large patient group and were not predictive for the individual patient.²⁶ The exact mechanism of these effects remains unclear. Minor coagulation disorders have been reported, with elevations in thrombin time and prothrombin time values.²⁵

Nerve agent victims who survive often have residual neurologic damage, including psychological damage that can persist for years.⁴⁴ They have also reported experiencing forgetfulness, inability to concentrate, insomnia, nightmares, emotional instability, and depression. These symptoms may persist for weeks or longer post-exposure.

Other treatments

The antihistamine cyproheptadine has been shown to be effective in controlling seizures in experimental models (rat), including reducing the duration of seizures and the number of dying cells in the brain following soman exposure, thus improving overall survival.⁷²

Human butyrylcholinesterase is a stoichiometric bioscavenger which is being studied as a possible treatment for NA poisoning. It inhibits the NA in the

bloodstream and prevents the NA from attacking other enzymes. In one study, human butyrylcholinesterase was effective as both a pretreatment and as a post-exposure therapy.⁷³ There is additional work being performed on the development of improved oximes, such as HI-6, for use in the United States and other countries.

Conclusions

The deployment of NA weapons of mass destruction against civilian targets is a cold reality. To date, these events have occurred on a limited scope; however, fatalities have still been numerous. To hope, even for a second, that we will not see another event is naïve at best. Medical centres and first responders must be prepared to recognize and deal with NA-exposed patients both in the field and at medical facilities. If patients receive rapid treatment, fatalities can be limited. While no single facility can maintain a permanent ready status for a large-scale event, by preparing entire regions and districts, there is a better chance of dealing with the injuries resulting from this type of weapon.

Attestation Dr. Keith Candiotti is solely responsible for the content of this entire article.

Conflicts of interest None declared.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia*.

Funding source University of Miami, Department of Anesthesiology, Perioperative Medicine and Pain Management.

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