

Chemical Warfare: Nerve Agents

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Nerve agents, sometimes also called nerve gases, are a class of chemical weapons that disrupt the transmission of nerve signals in the brain and from the brain to the muscles and organs. The repeated documented use of these agents on civilians implies that a threshold has now been crossed and it is likely that this threat will continue into the foreseeable future. Hence, a review of the medical effects and treatment of nerve-agent exposure is warranted, most particularly for the highly classified Russian Novichok nerve agents.

Historical Background

The first nerve agents were accidentally discovered in Germany in 1936 as a byproduct of research into new insecticides. The first actual agent was an organophosphate compound named tabun. A year later, a team of German scientists created an organophosphate that was 10 times more lethal than they called sarin (named after the team of scientists: Schrader, Ambros, Ritter, and von der Linde). During World War II, another new organophosphate called soman (derived from the Greek “to sleep”) was developed.¹ Although nerve agents were manufactured and stockpiled, these were never used on the battlefield. After the war the G-series naming system for these compounds designated tabun as GA (German Agent A), sarin as GB, and soman as GD. The newly discovered ethyl sarin was tagged as GE, and a chemical called cyclosarin was designated GF.

In 1955, British scientists discovered a new organophosphate insecticide that they named Amiton. Using this as a starting point, further British research discovered several analogue compounds that were designated the V (or venomous) agents. In 1958, the U.S. started manufacturing VX for use as a front-line nerve-agent weapon.²

The VX compound is 10 times more potent than other nerve agents, and fatalities occur with milligram exposures through skin (Figure 1). Another danger of VX results from the fact that it is a persistent liquid with a very slow evaporation rate. Consequently, while this diminishes its inhalation threat, the liquid can remain dermally active in the environment for weeks unless decontaminated. Its extreme dermal toxicity forced the U.S. to develop VX into a binary weapon for safety. In a binary weapon, two relatively less hazardous compounds are mixed together at the time of use to form a final product containing active VX liquid. This makes the binary chemical munitions much safer to transport, and it facilitates their long-term storage. In 1993, VX was categorized as a weapon of mass destruction and banned by the Chemical Weapons Convention (CWC) of 1993.



Figure 1. The Lethal Amount of VX (Small White Drop) on a 1-Cent Coin

Photo modified from the U.S. Soldier Biological / Chemical Command, Domestic Preparedness Program, Hospital Provider Section

The Novichok Nerve Agents

Russia made significant advances in new nerve-agent development throughout the Cold War. They manufactured soman, sarin, and their own version of VX (called VR) in a binary form. Under the classified Foliant program they developed several new nerve agents that they named the Novichok (or Newcomer) series. These included substance A-230 which is five to eight times more lethal than VX, followed by the synthesis of substance A-232 and its ethyl-analog substance A-234, which can be produced in a binary form. Both Novichok-5 and Novichok-7 can rapidly penetrate through human skin and the respiratory tract. The Novichoks were specifically designed to defeat NATO countermeasures against chemical weapons. This development continued in spite of the CWC.³

Some of the Novichok agents are eight to 10 times more toxic than VX. While these chemicals are designed for exposure by skin contact, they can also be absorbed through the mucous membranes, or by inhalation or ingestion. Exposure management requires more aggressive supportive care, greater amounts of medication, and a longer duration of treatment than with the classical nerve agents. Some of these compounds are difficult to detect using standard 1970s and 1980s NATO chemical detection equipment, and low-dose exposures may have delayed onset of symptoms for up to three days post-exposure.

Some of the Novichoks are highly soluble in water with the potential to contaminate large areas. Their vapors are heavier than air, and active Novichok agent can remain on environmental surfaces for days or even many months if it is

not decontaminated. Some of the Novichoks are resistant to degeneration in water, and unlike with the classical G-series agents, all decontamination water runoff must be controlled, as it is hazardous. This complicates clean-up and site-remediation efforts.⁴

Civilian Incidents Involving the Use of Classical Nerve Agents

On Jun 27, 1994, the Aum Shinrikyo cult carried out a nerve-agent attack against Japanese civilians by releasing sarin (GB) in the central Japanese city of Matsumoto. Using a converted refrigerator truck and their own personal protective equipment (PPE), members of the cult released a cloud of sarin from a hot plate inside the open truck. The vapor cloud floated over the homes of some judges who were overseeing a lawsuit against the cult. This incident in Matsumoto killed eight individuals and harmed 500 more. It was not recognized until months later that this was a nerve-agent attack.⁵

The world was shocked when on Mar 20, 1995, this cult used a crude preparation of sarin, which lacked the vacuum distillation step, to perform a coordinated attack on five trains in the Tokyo subway system. This act killed 13 commuters and seriously injured 54. Some estimates suggest as many as 6,000 people received a mild exposure to this crude sarin preparation.

Recent Disturbing Events

On Feb 13, 2017, a VX-type nerve agent (possibly VR) was used in the assassination of Kim Jong-nam, the half-brother of the North Korean president Kim Jong-un, at the Kuala Lumpur International Airport in Malaysia. While he was at the airport, a woman splashed a liquid in his face. Then, at the check-in at the Level-3 departure hall, another woman wiped a liquid on a cloth across his face. He started feeling unwell and was taken to the airport clinic where he collapsed and then died while being transported to hospital. Forensic toxicology confirmed he was exposed to a VX-type nerve agent.⁶

A year later, on Mar 4, 2018, a former Russian double agent living in the United Kingdom underwent an attempted assassination. Sergei Skripal and his daughter were both poisoned by a nerve agent together with a Wiltshire Police officer. In addition, 21 members of the public suffered a minor exposure. Following an analysis, British Prime Minister Theresa May stated that the substance used was a Novichok nerve agent.⁷

Three months later, on Jun 30, 2018, a similar poisoning of two British citizens occurred in Amesbury, seven miles from the site of where Skripal and his daughter were attacked. In this incident, a man found a perfume bottle in a trash can. He gave it to his girlfriend, who sprayed it on her wrist. The woman fell ill within 15 minutes and died on Jul 8; the man survived. This incident was a result of the way the nerve agent was disposed of after the attack in Salisbury.

The Novichok agents are highly classified, and their use on civilians implies that a threshold has now been crossed.

In addition, a small but sophisticated ISIS (Islamic State in Iraq and Syria) chemical weapon production facility has been discovered in Iraq, and this group has already carried out 76 chemical attacks over 3 years.⁸ While the use of nerve agents by ISIS has not been reported, it is likely that this threat will continue into the foreseeable future.

Signs, Symptoms, and Pathophysiology of Nerve-agent Exposure

Normally, when a motor neuron is stimulated, it releases the neurotransmitter acetylcholine (ACh) into the space between the neuron motor end plate and an adjacent muscle cell. When ACh is taken up by the muscle cell, it stimulates muscle contraction. To control muscle contraction, the ACh is then enzymatically hydrolyzed into acetic acid and choline by the acetylcholinesterase (AChE) enzyme, and muscle stimulation is stopped.⁹

Nerve agents can enter the body in the form of a vapor, small particle aerosol, or liquid, through inhalation, skin contact, or consumption. As these compounds enter the body, they bind and inhibit the AChE enzyme that is responsible for breaking down ACh. This AChE inhibition causes an accumulation of ACh, and the overstimulation of the nicotinic receptors at the neuromuscular junctions (Figure 2).

This causes a spectrum of muscle activity ranging from bronchospasm, skeletal muscle fasciculations, tetany, and eventual complete fatigue and skeletal muscle paralysis, depending on the dose of nerve agent absorbed. The systemic accumulation of ACh in the central nervous system causes neuronal excitotoxicity due to the activation of nicotinic receptors in the brain and glutamate release, with CNS damage. Sustained paralysis of the diaphragm leads to death by asphyxiation.

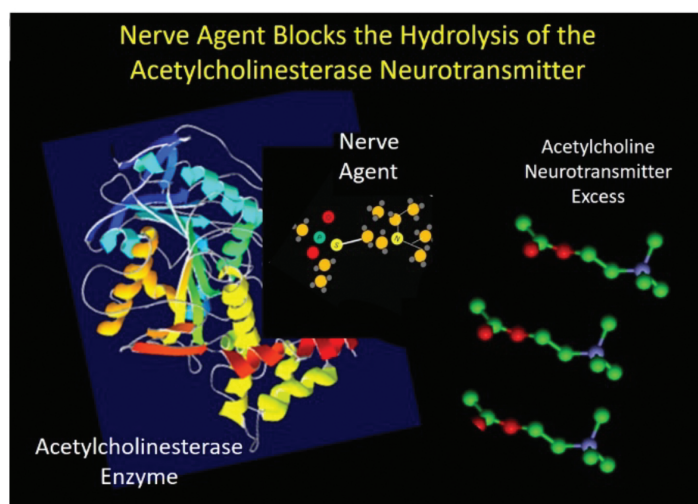


Figure 2. Nerve Agents Bind to Acetylcholinesterase (AChE)

Simultaneously, an ongoing overstimulation of the parasympathetic muscarinic receptors causes the onset of excessive apocrine secretions with rhinorrhea, increased lacrimation, and

bronchorrhea. Excess parasympathetic effects on the heart result in bradycardia.

In contrast to the organophosphate insecticides, nerve agents tend to produce more nicotinic than muscarinic effects. Overstimulation of the parasympathetic axons that innervate the iris sphincter muscle initiates painful miosis, even with mild nerve-agent vapor exposures. Defecation and urinary incontinence may also occur.

Clinical Presentation and Diagnosis

The clinical presentation of nerve-agent exposure is extremely variable. It depends on the agent involved, the route of exposure, and the concentration/purity of the toxicant. With the classical nerve agents, mild, low-dose dermal exposure victims may only become symptomatic eight-to-24 hours later.

The diagnosis of nerve-agent exposure is clinical, and early recognition is key to preventing death. The onset of symptoms is most rapid with vapor inhalation, and slowest with transdermal absorption. Signs and symptoms of accumulation of ACh in the body are summarized with the mnemonic DUMBBELS (Table 1). These may progress to a cholinergic crisis.¹⁰ High-dose nerve-agent exposures tend to present with rapid cardiovascular collapse and respiratory failure.

Table 1. Signs and Symptoms of Acetylcholine (ACh) Accumulation

DUMBBELS

- Defecation
- Urination
- Miosis/Muscle weakness
- Bronchospasm/Bronchorrhea
- Bradycardia
- Emesis
- Lacrimation
- Salivation/Sweating

The sudden onset of a runny nose, tightness in the chest, constriction of the pupils (miosis, Figure 3), and muscle fasciculations are reliable early signs of an exposure to a nerve agent.

Soon after, the victim will have difficulty breathing and will experience nausea, salivation, eye pain and lacrimation, followed by urination, defecation, gastrointestinal pain, nausea, and possible vomiting. In high-dose exposures, this phase is followed by initial myoclonic jerks, then a period of almost status epilepticus-type seizures with tetany, and finally flaccid skeletal muscle paralysis. Seizures may continue, but after the onset of paralysis they may not be easy to detect. Death occurs from respiratory muscle paralysis and asphyxiation.

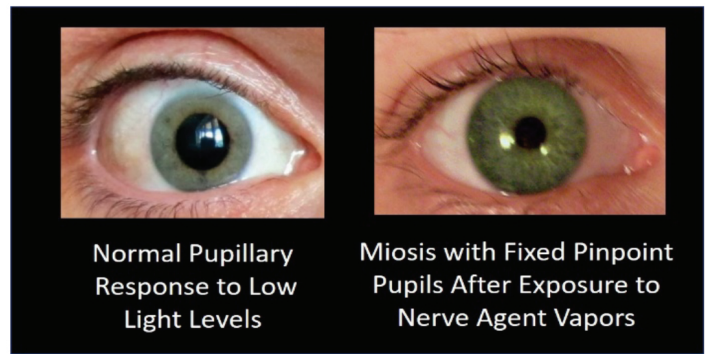


Figure 3. Pupillary Findings with Nerve-Agent Exposure

Initial Medical Management of Nerve-agent Exposures

First responders and medical workers must ensure their own protection. Protective suiting and respiratory protection are the key for managing patients with a liquid or vapor nerve-agent exposure. Decontamination should take place outside the hospital; many hospitals have a dedicated outside decontamination facility for self-triaged patients. Responding HAZMAT personnel must establish a decontamination site for both ambulatory and stretcher cases. Victims that are confirmed fatalities are temporarily left on site. All area hospitals are informed that a HAZMAT incident has occurred.¹⁰

If catastrophic hemorrhage is occurring as a result of blast or ballistic injury, tourniquets are used to control the bleeding on site. Airway and respiration management will be difficult if not physiologically impossible until antidotes to the nerve agent have been administered.

Three different antidotes must be administered rapidly, of which atropine is the most important.¹⁰ The dose for Atropine can range from 2 mg to 6 mg at a time, depending on the severity of symptoms. The victim should be reassessed every five minutes and the atropine dose doubled if there is no improvement. In severe exposures, atropine must be given to restore airway and lung compliance to permit successful ventilation. Atropine is continued until lung auscultation reveals clear breath sounds. Concomitantly, the patient should be monitored for any signs of excess atropine exposure.

While atropine has anticholinergic properties that are very effective at the peripheral muscarinic sites, the drug is less effective at the muscular nicotinic sites. Therefore, a second drug must be administered at the same time as the atropine. Pralidoxime chloride (2-PAM chloride) is administered to reverse the nicotinic effects. It cleaves the nerve agent from the AChE by scavenging the phosphoryl group attached on the functional hydroxyl group of the enzyme. This restores the enzyme's activity and functionality. The muscarinic effects of nerve agents are not observably altered by 2-PAM chloride. Therefore, repeated administration of both atropine and 2-PAM chloride is needed. Although 2-PAM chloride takes longer to act than atropine, it is safer to use.

Benzodiazepine can be used to control the seizures from severe exposures, and phentolamine may be needed to treat 2-PAM chloride-induced hypertension. For resistant

seizure activity observed on EEG in a paralyzed patient, some synthetic anticholinergics, such as biperiden,¹¹ may be useful because of its better blood-brain barrier penetration. While diazepam is recommended for field use by first responders in the treatment of seizures, there is poor absorption from intramuscular (IM) injection if not administered by pressurized autoinjector. Midazolam is absorbed from muscle much more rapidly than diazepam if an autoinjector is not used. Consider rectal dosing for infants. Ventilation may be needed after repeated doses of benzodiazepines or barbiturates.

Both atropine and 2-PAM chloride are available to medical professionals as spring-loaded auto-injector pressurized syringes for IM administration (see Figure 4). The doses provided by the Mark I kits are designed for adults not children.

Typically, U.S. servicemembers are issued three Mark-1 kits in areas where nerve agents are considered a potential hazard. Along with these three kits they are issued one CANA (Convulsive Antidote, Nerve Agent) for simultaneous use. (CANA is diazepam). A newer model, the ATNAA (Antidote Treatment Nerve Agent Auto-Injector),¹ has both the atropine and the 2-PAM chloride in one syringe, allowing for simplified administration.



Figure 4. The Mark-1 Nerve Agent Antidote Kit
The kit contains a 2-mg atropine autoinjector and a 600-mg 2-PAM chloride autoinjector. The atropine is administered first. Photo courtesy of United States Army Medical Research Institute of Chemical Defense

Patients who are contaminated with nerve agent can expose others by direct contact or through evaporation of vapor (“off-gassing”) from their body or clothing. Therefore, after the stopgap antidote and airway measures, the next step is full victim decontamination and definitive respiratory support. Victims are removed from the source of the exposure and taken to a rapid decontamination station. Their contaminated clothing is removed, their eyes flushed with water and their skin washed with copious amounts of soap and water. For the first generation of nerve agents, a 0.5% sodium hypochlorite solution (one part household bleach plus nine parts water) was used for the hair and skin. For the newer Novichok agents, bleach should be avoided, and all removed clothing should be double-bagged and labeled as a biohazard after removal. The used decontamination water is

hazardous and must be controlled.

Bleeding control should be reassessed, and definitive airway management and ventilation undertaken if required. Antidote efficacy must be continuously reassessed, and an evacuation priority is assigned. At no time will any ambulance ever enter the actual contaminated area.

Special Problems Caused by the Novichok Nerve Agents

After binding to AChE, nerve agents will undergo a time-dependent loss of an alkyl group. This is called “aging,” and when it is complete, it causes a covalent binding of the nerve agent to AChE, irreversibly inactivating the enzyme. Consequently 2-PAM chloride becomes ineffective as an antidote. The time that this takes depends on the particular agent.

For sarin (GB), aging develops within three to five hours after exposure. This allows time for first responders to administer the 2-PAM antidote to a victim. Unfortunately, with the Novichok agents and with soman (GD), a complete enzyme/nerve agent “aging” occurs within the space of just a few minutes. This negates the use of 2-PAM chloride as an antidote. However, for reasons that are unclear, the 2-PAM chloride seems helpful in maintaining blood pressure and renal perfusion in Novichok poisoning.⁴

The Novichok agents are not readily degraded by water, and there are concerns that they can persist in body fluids, posing a potential long-term hazard to personnel. Human exposures seem to be accompanied by a deposition of the Novichok agent in the skin. Decontamination of skin and hair is crucial and may provide clinical benefit even when performed hours to days after exposure to liquid agent. In addition, repeated decontamination of the skin and hair over a course of several days post-exposure may be both beneficial and required.

For these reasons, once lifesaving efforts are under control, the incident command should develop a comprehensive waste management plan along with a site-specific health and safety plans. These should address the fact that the Novichok agents can persist for extremely long periods of time on materials and in effluent liquids such as water (e.g., from patient and responder decontamination processes). Any personnel handling these materials and liquids must be made aware of the potential hazard and provided with appropriate PPE.

Main Points in Managing Novichok Exposures

- Exposure victims will need medications and intensive care for an extended duration.
- Because of rapid AChE aging, 2-PAM chloride is ineffective in restoring enzyme activity.
- Novichok victims require significantly higher doses and longer repeated dosing of atropine.
- Anticholinergics should be given until secretions diminish and airway resistance resolves.
- Victims cannot be properly ventilated until atropine has taken effect.
- If diazepam is not administered by pressurized autoinjector, there is poor IM absorption.

- Bronchoconstriction, if it occurs, may be difficult to manage clinically.
- Patients may develop severe metabolic acidosis with markedly elevated serum lactate.
- Avoid using products containing alcohol for skin decontamination because they may enhance absorption.
- Unlike with sarin exposures, do not use bleach to decontaminate the skin.
- Novichok agents persist in body fluids. Basic PPE is still required after decontamination.
- Tests that measure AChE activity exist, but the results are of limited clinical value.

Patients Refractory to Treatment

For bronchospasm refractory to standard atropine therapy consider that inhaled or nebulized ipratropium (or another antimuscarinic medication) can be combined with adjunct beta-agonists such as albuterol, terbutaline, formoterol, or salmeterol. Critically ill patients not responding to antimuscarinic and bronchodilator therapies should be treated to the standard of care for impending respiratory failure.⁴ Systemic corticosteroid dosing similar to the treatment of refractory reactive airway disease (1-2 mg/kg methylprednisone) may be considered. Magnesium sulfate 2 g IV may be given as an adjunct.

Even if a neuromuscular blockade has been given for intubation/ventilation, anticholinergic therapy must still be titrated to respiratory secretions and EEG monitoring used to detect any continuing seizure activity in the brain. Novichok-induced seizures may not be responsive to some anticonvulsants, and sedation with general anesthesia or medically induced coma may be required.

Long-Term Health Effects of Nerve-agent Exposure

Survivors of nerve-agent poisoning almost invariably suffer some degree of permanent neurological damage. Shorter term sequelae include blurred vision, tiredness, memory loss, cardiac arrhythmias, and insomnia, which can last for at least 2–3 years in survivors.¹¹

The Novichok agents are particularly likely to cause this. In May 1987, a Russian scientist was exposed to a small amount of A-232 while conducting precursor research. He was rapidly given atropine and 2-PAM but required 10 days to recover consciousness. He lost the ability to walk, exhibited a chronic weakness in his arms, and developed a toxic hepatitis with cirrhosis of the liver. He also suffered from epilepsy, spells of severe depression, and an inability to read or concentrate. He died as a chronic invalid 5-years later.³

Summary and Continuing Research

Recognizing that the world is likely to see an increasing number of nerve-agent attacks on civilian populations, the U.S. Army has funded a continuing search for more effective antidotes. One of these involves the use of galantamine as a reversible AChE inhibitor to prevent irreversible enzyme/

nerve agent aging. Early studies have shown a synergistic interaction in which galantamine given 30 minutes after exposure decreased the dose of atropine needed to protect experimental animals from the toxicity of soman in dosages 1.5 times the LD₅₀. In addition, galantamine has anticonvulsant properties.¹²

In other work, the enzyme butyrylcholinesterase is being tested as a universal prophylactic countermeasure effective against the entire spectrum of organophosphate compounds by binding to nerve agents in the bloodstream before they can exert effects in the nervous system.¹³

Irrespective of whatever countermeasures are developed, it is the civilian authorities who will have to quickly realize that a nerve-agent attack has taken place and formulate an effective initial stopgap response until federal resources can arrive.

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