Clinical Manifestations of Sarin Nerve Gas Exposure

Ernest C. Lee, MD, MPH

CHEMICAL WARFARE HAS EXisted for millennia. As far back as 1000 BC, the Chinese used arsenical smoke as a weapon.[1] In the last century, chemical agents have been used in warfare on numerous occasions, from World War I to the Iran-Iraq conflict.[2] The world remains vulnerable to the deliberate use of chemical agents as weapons of mass destruction. Chemical attacks can be delivered with almost any type of conventional ballistic weapon, spray device, or by nontraditional means, such as that used by the Aum Shinrikyo religious cult to launch 2 attacks in public places in Japan by using sarin gas. The first attack occurred in Matsumoto, Japan, in June 1994.[3] The second attack occurred in a Tokyo subway in March 1995.[4] Terrorists involved in this attack carried diluted sarin solution in plastic bags into subway trains and punctured the bags with sharpened umbrella tips. This released diluted sarin vapor into 3 convergent lines of the Tokyo subway system.[5] This attack is the largest disaster caused by nerve gas in peacetime history.[4] These attacks illustrated how an ill-prepared disaster management system can become overwhelmed.

Sarin is a highly toxic nerve agent that can be fatal within minutes to hours.[6] It was first synthesized in Germany in 1937 as an insecticide, although its battlefield potential was soon recognized.[7] During World War II, Germany prepared thousands of tons of the potent nerve agents tabun and sarin but refrained from using them. Sarin was first used in wartime during the Iran-Iraq conflict in the 1980s.[8]

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Sarin Toxicology

Sarin (*o*-isopropyl methylphosphonofluoridate) is a high-potency organophosphate ester. It is a clear, colorless liquid with a vapor pressure of 2.1 mm Hg. Sarin is more volatile than other nerve agents, such as soman, tabun, and VX.[9] Thus, sarin presents both a liquid and vapor hazard. In the liquid state, it can rapidly penetrate skin and clothing. As a vapor, it can rapidly penetrate the mucous membranes of the eye or be inhaled into the lungs, where it is rapidly absorbed.[6]

Mechanisms of Acute Toxicity

Sarin exposure causes inhibition of acetylcholinesterase (AChE) and a consequent rise in acetylcholine, leading to hyperstimulation at cholinergic synapses.[10,11] These effects are dose related.[12]

Sarin inhibits AChE by phosphorylating the serine hydroxyl on the ester portion of the enzyme's active site. Normally, AChE hydrolyzes acetylcholine to produce choline, acetic acid, and the reactivated enzyme very rapidly. Once reactivated, AChE is available to bind to another acetylcholine molecule. However, once phosphorylated, the enzyme's reactivation half-life can extend to hours or even days.[13] Additionally, the phosphorylated enzyme can undergo a second process known as aging through dealkylation. After sarin exposure, the half-life for aging is about 5 hours.[14] Several compounds can remove sarin from AChE if administered before aging. The most important group of compounds is the oximes.[15] After aging has occurred, the phosphorylated enzyme is resistant to hydrolysis and can be considered irreversibly inhibited. This results in excess stimulation of nicotinic and muscarinic receptors, leading to an acute cholinergic syndrome.[16]

New research also suggests that sarin may act as a muscarinic-receptor antagonist inhibiting the release of γ-aminobutyric acid.[17,18] Reductions in levels of γ-aminobutyric acid, an inhibitory neurotransmitter, may contribute to the convulsive properties of sarin.

Exposure Variables and Toxicokinetics

The potential number of casualties during an attack is determined by whether it occurs in an indoor or outdoor setting and by environmental conditions such as wind, humidity, rainfall, and temperature.[15] Specifically, the dispersal of sarin vapor can be significantly diminished by the absence of wind or in an indoor setting. The liquid form of sarin can be diluted by rainfall. Sunlight may cause evaporation of liquid sarin.[15]

Sarin may be absorbed through inhalation, ingestion, or dermal contact. Percutaneous absorption of liquid sarin typically results in localized sweating, followed by muscular fasciculations and weakness as the agent penetrates deeper and affects the underlying muscle.[19] Following dermal contact, symptoms can be delayed up to 18 hours; however, inhalation symptoms can occur within seconds.[2,20]

Author Affiliation: Harvard Medical School, Boston, Mass.
Corresponding Author and Reprints: Ernest C. Lee, MD, MPH, Major, Medical Corps, US Air Force, Occupational and Environmental Medicine Fellow, Harvard Medical School, 401 Park Dr, Landmark Center, 3-111-3 East, Boston, MA 02215 (e-mail: elee@hsph.harvard.edu).
Contempo Updates Section Editor: Sarah Pressman Lovinger, MD, Fishbein Fellow.

Box 1. Signs and Symptoms of Nerve Agent Exposure Based on Type of Cholinergic Receptor Stimulated

Muscarinic
Pinpoint pupils
Blurred or dimmed vision
Rhinorrhea
Headache
Hypersecretion by salivary, lacrimal, sweat, and bronchial glands
Nausea, vomiting, or diarrhea
Bradycardia
Crampy abdominal pain
Bowel and bladder incontinence
Dyspnea

Nicotinic
Skeletal muscle twitching and cramping, followed by weakness and flaccid paralysis
Tachycardia
Hypertension

Central Nervous System
Irritability
Ataxia
Seizures
Respiratory depression

Sarin can produce local and systemic effects. Local effects, such as miosis and rhinorrhea, are the product of sarin vapors directly interacting with AChE at the nerve endings near body surfaces.[14] Systemic effects occur as a result of absorption of sarin into the circulation from the respiratory tract, gastrointestinal tract, or the skin.[21]

Detection, Acute Clinical Manifestations, and Diagnosis

Exposure to high doses of sarin produces an acute cholinergic syndrome featuring a variety of signs and symptoms affecting the peripheral and central nervous systems (BOX 1).[19-22] The signs and symptoms of nerve agent exposure depend on the type of cholinergic receptor stimulated. Muscarinic signs and symptoms include pinpoint pupils (one of the earliest signs of sarin exposure[22]); blurred or dimmed vision, rhinorrhea, headache, hypersecretion by salivary, lacrimal, sweat, and bronchial glands; nausea; vomiting; diarrhea; crampy abdominal pain; bowel and bladder incontinence; and dyspnea.[22] Nicotinic signs and symptoms include skeletal muscle twitching and cramping, followed by weakness and flaccid paralysis, tachycardia, and hypertension.[22] Central nervous system signs and symptoms include irritability, ataxia, seizures, and respiratory depression.[19] If the dose is sufficient, death results after convulsions and respiratory failure.[21]

Because the actual doses affecting humans under terrorist or battlefield events are difficult to reconstruct, they can be inferred on the basis of acute clinical effects. A high level of exposure may be presumed to have occurred if an acute cholinergic syndrome is present. Signs and symptoms limited to miosis, rhinorrhea, and depressed blood cholinesterase levels suggest the occurrence of an intermediate-level exposure. Low-level exposure may have occurred even in the absence of cholinergic signs and symptoms if a well-documented history of exposure exists.[8] The TABLE summarizes the signs and symptoms of nerve agent exposure as determined by exposure level and elapsed time.[4,9,15,19]

Patients who survive exposure to nerve agents may experience long-term deficits. Approximately 2 years after the day of the Tokyo subway sarin attack, the hospital that treated individuals involved in the attack mailed a questionnaire to the 606 individuals who came to the hospital for treatment. Of the 303 respondents, 46% still complained of either physical or psychological symptoms: 19% complained of eye symptoms, 12% had easy fatigability, and 9% complained of headaches. For psychological symptoms, 13% complained of fear of subways, 12% indicated fears concerning their escape from the attack, 11% reported flashbacks, 8% had feelings of depression, and 8% reported lack of concentration.[4]

Sarin can inhibit AChE in red blood cells, butyrylcholinesterase in plasma, and AChE at cholinergic receptor sites in tissue.[2] The most reliable parameter for monitoring the biological effects of acute exposure to sarin is the erythrocyte AChE activity.[23] Acetylcholinesterase activity is an indirect measure that reflects the degree of cholinesterase inhibition at tissue sites and at neuromuscular junctions.

Prehospital Management, Triage, and Treatment

Because first responders can absorb sarin and other nerve agents by touching or inhaling vapors from contaminated clothing, they should be trained and appropriately attired before entering a contaminated zone. If rescuers have not been trained, they should telephone for assistance in accordance with local emergency operational guides (or US Soldier and Biological Chemical Command, telephone number 410-671-4411 from 7:00 AM to 4:30 PM eastern standard time and 410-278-5201 from 4:30 PM to 7:00 AM eastern standard time).

For response situations that involve exposure to any nerve agent vapor or liquid, pressure-demand self-contained breathing apparatus is recommended. When skin contact may occur, chemical-protective clothing and butyl rubber gloves and boots are recommended.[2,9] Decontaminable gurneys made of monofilament polypropylene fabric that does not absorb chemical agents and nonpermeable fiberglass backboards specifically developed for use in such situations should be used, if possible.

Exposed individuals should be separated from the source of exposure and decontaminated. Contaminated clothing and personal belongings should be removed and sealed in nonpermeable double bags. The eyes should be flushed with water for 10 minutes. The skin should be washed with soap and water or 0.5% sodium hypochlorite solution (bleach and isotonic sodium chloride solution).[2,15,20,22,24,25] Extreme care should be taken not to use hypochlorite solution in or near the eyes. All exposed individuals must be decontaminated before transport to the receiving medical facility.[9] Although skin decontamination is not necessary after exposure to vapor alone, clothing should be

removed to release possible trapped vapor.[2] Because symptoms occur within seconds to minutes after exposure, patients with a history of possible exposure to vapor only who have no signs of exposure by the time they reach the medical facility have not been exposed and can be discharged.[9]

Treatment for nerve agent toxicity begins with assessment of airway, breathing, and circulation. Respiratory failure is the principal cause of death in nerve agent exposure.[15,19] Early endotracheal intubation and ventilatory support are critical in treating patients with manifestations of severe toxic reactions. Suction is important because copious amounts of airway secretions may occur.[19] To ventilate patients in a contaminated environment, rescuers can use a bag-valve mask equipped with a chemical agent canister such as the Chemical Resuscitation Device.[9] If rapid sequence intubation is used, succinylcholine should be avoided because it is metabolized by plasma cholinesterase.[19]

Antidotes for nerve agent poisoning include atropine, pralidoxime chloride, diazepam, and tropicamide (Box 2).[19] The initial adult dose of atropine should be continued until the patient is breathing comfortably.[2,19] In a severe exposure, atropine should be given until secretions are dry (or nearly dry) and until ventilation can be accomplished with ease.[2] Administration of atropine before treatment of possible hypoxemia may cause ventricular fibrillation.[19] Pralidoxime chloride is an oxime that acts as an AChE reactivator that binds the nerve agent and removes it from the enzyme. Although intravenous administration is preferred, both atropine and pralidoxime chloride may be given by intramuscular injection.[19] Diazepam is indicated for the treatment of seizures associated with nerve agent toxicity. Prolonged seizures may lead to brain injury. Patients with flaccid paralysis should have electroencephalogram monitoring, because health care workers can fail to suspect seizure activity in such patients. To reverse miosis and relieve occular pain caused by nerve agent toxicity, tropicamide may be used.[19]

Table. Signs and Symptoms of Nerve Agent Exposure as Determined by Exposure Level and Elapsed Time*

Exposure	Immediate Effects Primarily via Inhalation Exposure (Seconds to Minutes)†	Delayed Effects Primarily via Dermal Exposure (From 10 Minutes to 18 Hours Postexposure)‡	Long-term Effects (Several Weeks to 1 Year Postexposure)
Low	Miosis Ocular pain Tearing Rhinorrhea Bronchospasm Slight dyspnea Respiratory secretions Salivation Diaphoresis	Localized sweating at site of contact Muscular fasciculations and weakness deep to site of contact	
Intermediate	Moderate dyspnea Nausea Vomiting Diarrhea	Weakness Nausea Vomiting Diarrhea	Visual symptoms Easy fatigability Nervousness Irritability Headache Palpitation Depression Poor concentration Memory impairment
High	Loss of consciousness Convulsions Muscle fasciculations Flaccid paralysis Copious secretions Apnea Death	Loss of consciousness Convulsions Muscle fasciculations Flaccid paralysis Copious secretions Apnea Death	

*Data from references 4, 9, 15, and 19.
†The full effects of nerve agent vapor usually occur by the time the exposed person presents to the emergency department.
‡With dermal exposure, delayed symptoms may occur despite decontamination if the nerve agent was absorbed before decontamination.

Box 2. Treatment for Nerve Agents (Tabun, Sarin, Soman, and VX)*

Atropine

Adult dose: 2 mg intravenously every 2-5 min, titrated to effect; although intravenous is preferred, also may be administered by intramuscular/endotracheal tube in similar doses

Pediatric dose: 0.02 mg/kg intravenously every 2-5 min, titrated to effect; 0.1 mg minimum dose

Pralidoxime Chloride

Adult dose: administration of 1-2 g intravenously over 30-40 min minimizes adverse effects (eg, hypertension, headache, blurred vision, epigastric pain, nausea, and vomiting), may be followed by an infusion of 200-500 mg/h; also may administer by intramuscular injection

Pediatric dose: 15-25 mg/kg intravenously

Diazepam

Adult dose: 5-10 mg intravenously every 10-20 min, titrated to effect until seizures resolve (not to exceed 30 mg per 8 h); may repeat in 2-4 h, as occasion requires

Pediatric dose: 0.05-0.3 mg intravenously over 2-3 min every 15-30 min, titrated to effect until seizures resolve (not to exceed 10 mg); may repeat in 2-4 h, as occasion requires

Tropicamide

Adult dose: 1-2 drops of 0.5% solution to eye; may repeat in 5 min

Pediatric dose: not established

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Historical and Public Health Perspective

The Tokyo subway sarin attack alerted countries around the globe to the possibility of a terrorist attack involving nerve gas. A US team that went to Japan shortly after the attack found that less than 1000 passengers were injured. Twelve passengers died as a consequence of the attack.[26] Sidell[27] of the US Army Medical Research Institute for Chemical Defense stated, "About 4000 casualties reported to medical facilities who seemingly had nothing wrong with them. . . . Four thousand nine hundred and seventy-three patients were seen on day 1 and not hospitalized. They had no signs of agent effects." In the panic that followed the subway attack, the number of people who sought medical attention was probably substantially higher than the number of people actually exposed.

Several problems with disaster management and hospital plans were revealed in the aftermath of the Tokyo sarin attack. The hospital involved had 3 entrances but had not set up a definite plan for the guidance of mass casualties. Casualties, their families, television crews, and onlookers streamed into the hospital from all 3 entrances creating a chaotic situation inside the hospital. As a result, many medical records were lost.[4]

Many hospital staff were secondarily exposed to sarin for several reasons. The cause of the illnesses was not known until about 3 hours after the sarin had been released. Although the hospital staff wore gloves and masks, they had no access to chemical-resistant personal protective equipment. Ventilation was poor in some patient treatment areas and hospitals lacked decontamination facilities.[4]

Antidote availability was crucial for the treatment of exposed casualties. The hospital alone used 700 ampules of pralidoxime chloride and 2800 ampules of atropine sulfate. With its original stockpile of antidote depleted, the hospital had to airlift in additional supplies.[4]

After reviewing the disaster management problems, the administrators formulated these conclusions: each hospital should have a decontamination area and have chemical personal protective equipment available, ventilation in the emergency department and main treatment areas should be well designed, and hospital disaster planning should include an efficient emergency medical chart system and an emergency staff call-up system.[4] The development of a legal basis for the concentration of authority during major disasters was also recommended.[28]

Conclusion

The ease of production, transport, and use of sarin and other chemical agents enhances their potential use as terrorist weapons. Physicians and emergency response personnel must be prepared to deal with the clinical signs and symptoms of nerve agent poisoning and familiarize themselves with decontamination procedures and treatment. Hospitals must provide personal protective equipment, ventilation, and decontamination facilities to prevent secondary exposure to medical staff. Hospital and community organizations must coordinate disaster drills and disaster management planning.

Disclaimer: The views expressed in this article are those of the author and do not reflect the official policy or position of the US Air Force, Department of Defense, or the US government.

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