Terrorism and Disaster

WHAT CLINICIANS NEED TO KNOW




Sarin

RUSH UNIVERSITY MEDICAL CENTER

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Sarin

CASE AUTHOR: James M. Madsen, MD, MPH, COL, MC-FS, USA

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INSTRUCTIONS

The questions that appear throughout this case are intended as a self-assessment tool. For each question, select or provide the answer that you think is most appropriate and compare your answers to the key at the back of this booklet. The correct answer and a discussion of the answer choices are included in the answer key.

Note: These self-assessment questions are not intended for CME credit. To apply for CME credit, you must complete the CME Test at the back of this booklet and submit it according to the directions provided.

In addition, a sign is provided in the back of this booklet for posting in your office or clinic. Complete the sign by adding your local health department's phone number.

Sarin

CASE AUTHOR: James M. Madsen, MD, MPH, COL, MC-FS, USA

INTENDED AUDIENCE

Internal medicine, family medicine, and emergency medicine physicians, and other clinicians who will provide evaluation and care in the aftermath of a terrorist attack or other public health disaster

LEARNING OBJECTIVES

Upon completion of this case, participants will be able to:

- Explain the pathophysiology of nerve agents in terms of their effects on cholinergic neurotransmission.
- Describe the end-organ clinical effects of nerve agent poisoning.
- Compare the clinical presentation of victims exposed to sarin vapor to those exposed to sarin liquid.
- Explain the use of decontamination and nerve-agent antidotes in the treatment of sarin exposure and poisoning.

CASE PRESENTATION

On a cold Saturday evening in winter, a pregnant woman wearing an overcoat buys a ticket at a large metropolitan multiplex for the second night of a highly anticipated movie featuring the newly introduced OlfacTree™ technology for allowing moviegoers "the ultimate scents of realism" by experiencing odors relating to the film. The film has also generated enormous controversy (and corresponding ticket sales) by its moments of sudden and graphic terror, and in fact two moviegoers in separate cities collapsed from apparent myocardial infarctions during a particularly gruesome and unexpected scene on the opening night.

The woman enters the large theater in plenty of time to take a seat in the middle of the room. She takes off her overcoat and places it underneath her seat. Eventually, the theater is packed. Near the middle of the showing, a few minutes before a scary scene set in a dim herbal shop, she excuses herself and walks to a women's rest room, leaving her overcoat underneath her seat. In the rest room, she pulls a canister from a package under her bulky sweater, forming the bulge that had made her look pregnant, and hides it just inside an inconspicuous but crucial ventilation duct that she had investigated on previous visits to the multiplex. After exiting the building through the crowded lobby, she walks out to her van and sends a radio signal to the canister in the vent and to a second canister hidden under her overcoat in the packed theater but connected to a hose and a nozzle slightly protruding from a buttonhole in the overcoat. She then drives away without attracting attention.

Liquid flowing slowly from the canister in the theater ends up drenching the overcoat and eventually flowing down the floor to other rows of the theater. A few annoyed moviegoers look behind them to see who spilled soda. Meanwhile, the canister in the ventilation duct quietly releases a spray into the ventilation system supplying four large theaters in the multiplex.

In the theater where the woman had been watching the movie, a few moviegoers near the hidden canister quietly lose consciousness in their seats and attract no particular attention. Some people nearby feel tightness in their chests and some nausea, but at this point in the movie these reactions are not unexpected. When one person stands up, clutches his chest, and then falls over onto another moviegoer in the row in front of him, nearby people try to aid him but also slump over. Other people in that area try to run out of the theater but are in the middle of their rows and panic as their egress is inhibited by others who are still seated, and, in some cases, unresponsive. A general panic ensues, with people screaming and heading toward the exits. Popcorn and drinks are spilled throughout the theater, and some people slip on the spilled liquid. The lights come on in the room, and an announcement is made for an orderly exit, but the screaming and fighting for the exits continue. Some collapse in the rows and in the aisles, and several are trampled by other patrons.

By the time people spill into the main area of the multiplex, people from other theaters are also starting to pour out of those rooms. Many are coughing and complaining of difficulty breathing. Many feel very weak and are crying and rubbing their eyes, which feel on fire. Many patrons are still sprawled across seats and on the floors of several theaters in the building, and several are dead. The multiplex is evacuated, but it is very cold outside and many moviegoers have left their coats inside the building. When questioned, many report having smelled a faint fruity odor that would not have been out of place in the herbal shop portrayed in the scene that had been playing in the movie.

Upon their arrival, emergency personnel notify the receiving hospital to be prepared for casualties. The hospital activates its mass casualty plan, calling for additional staff to be on-hand in the emergency department, wards, and intensive care units.

COMMENT: The reported odor, irritation, weakness, salivation, collapse, and deaths suggest a chemical agent. However, the presence of a chemical agent does not exclude the simultaneous presence of a biological or radiological agent. In addition, these effects can all be psychological (including collapse and even death from vasovagal dysrhythmias or myocardial infarction) following exposure to a relatively nontoxic substance or to a psychologically stressful situation.

Chemical warfare agents include four types of toxic agents[1]:

- Respiratory tract irritants (pulmonary agents)
- Asphyxiants (cyanides)
- Vesicants (blister agents)
- Cholinesterase inhibitors (nerve agents)

The reported effects, including sudden collapse and death, can occur with extremely high concentrations of any of these agents but would be most likely with either a nerve agent or a cyanide compound and would be the least likely with a blister agent. The nature of odors is often used to try to identify a chemical agent, but olfaction is very subjective and often misleading. For a review of factors that differentiate nerve agent and other chemical agent effects, refer to Table 1.

Table 1. Features of Selected Major Chemical Exposures*

Feature	Asphyxiants	Cholinesterase Inhibitors	Respiratory Tract Irritants	Vesicants
Most likely agent in accidental release	Carbon monoxide	Organic phosphorus pesticides	Chlorine and its derivatives, ammonia	_
Most likely agent in act of terrorism	Cyanide	Sarin and VX	Chlorine, phosgene	Sulfur mustard
Hallmark	Tissue hypoxia in cardiovascular system and central nervous system; usually, absence of respiratory tract irritation; no increase in secretions	Cholinergic syndrome with pupil constriction (miosis) and increased exocrine secretions, with or without fasciculations; increasing effects on central nervous system with increasing exposure	Respiratory tract irritation and symptoms, usually more prominent than irritation of eyes and skin	Eye injuries and skin burns with vesicle formation, followed by respiratory irritation and, in the case of exposure to high concentration, systemic effects
Typical presentations				
Mild symptoms	Headache, fatigue, anxiety, irritability, dizziness, nausea	Miosis, dim vision, eye pain, rhinorrhea, irritability, headache, chest tightness, sweating	Nose and throat irritation, sore throat, cough, chest tightness, eye irritation	Conjunctivitis, limited erythema, epistaxis, sore throat, cough
Moderate–to–servere symptoms	Dyspnea, altered mental status, cardiac ischemia, syncope, coma, seizure	Salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis, wheezing, muscle weakness, fasciculations, cognitive impairment, incontinence, coma, seizure	Laryngitis, wheezing, stridor, laryngeal edema, acute lung injury	Corneal damage, vesicles and bullae, nausea, wheezing, stridor, laryngeal edema, acute lung injury
Hyperacute onset – sudden collapse	High concentrations of cyanide or hydrogen sulfide and oxygen deficiency within a confined space	Exposures to VX or high-vapor concentrations of other nerve agents	—	—
Acute onset– typically within minutes to hours after exposure	Most exposures to asphyxiant gases (carbon monoxide, cyanide) or oxygen deficiency	Vapor exposure, ingestion of liquid form, or moderate –to-large dermal exposure	Riot-control agents, irritants highly and intermediately water soluble (ammonia, hydrochloric acid, chlorine)	Lewisite, phosgene oxime, high concentrations of sulfur mustard
Delayed onset– typically 4 to 6 hrs after exposure	Low-to-moderate concentrations of substances that metabolize to primary asphyxiant- methylene chloride (carbon monoxide), acrylonitrile, and propionitrile (cyanide)	Limited exposure of skin to droplets but not vapor	Poorly soluble gases (phosgene, nitrogen dioxide)	Sulfur mustard

*Reprinted with permission from *N Engl J Med*.[1]

QUESTION 1

Which of the following signs and symptoms suggest a nerve agent rather than a cyanide or pulmonary agent?

a. Increased secretions

b. Cough

c. Headache

d. Sore throat

Reminder: You can find the Answer Key & Discussion on page 11.

COMMENT: The agent released from the canisters was sarin (o-isopropyl methylphosphonofluoridate), also known as GB. Sarin is a man-made chemical warfare agent classified as a nerve agent, the most toxic and rapidly acting of the known chemical warfare agents.[2] Nerve agents are chemicals that inhibit the enzyme acetylcholinesterase, preventing the breakdown of acetylcholine. Other nerve agents include tabun (GA), soman (GD), cyclosarin (CF), and VX.

Sarin is a colorless, nonirritating, nearly odorless liquid with a faint perfume-like, floral, or fruity odor. It can exist as a liquid and a vapor, with potential for direct contact with the eyes and mucous membranes, absorption into the eyes and skin, and inhalation.[3] Eye irritation and coughing or choking may be secondary to physiologic reactions to sarin (eg, miosis and bronchoconstriction) or may result from a caustic carrier chemical mixed with the sarin.

In the theater lobby and in the street, several moviegoers have difficulty finding their way around, bumping into one another or into walls. Also, several complain of chest tightness and difficulty breathing.

QUESTION 2

Which of the following statements is TRUE about the mechanism of action that produces stumbling, chest tightness, and difficulty breathing after sarin exposure?

a. Stumbling is probably secondary to excess cholinergic stimulation of the constrictor muscles of the irises, leading to miosis.

b. Chest tightness is probably a pre-cursor of sarin-induced damage to alveolar-capillary membranes and incipient pulmonary edema.

c. Because sarin causes weakness and then paralysis of the diaphragm, tightness of the chest would not be expected and would imply the mixture of sarin with a pulmonary agent.

d. Stumbling is probably an early manifestation of damage to cerebellar pathways involving balance from direct effects of sarin on the central nervous system.

COMMENT: Sarin and other nerve agents are anticholinesterases, chemicals that inhibit the enzyme acetylcholinesterase (AChE). AChE is responsible for the breakdown of the cholinergic neurotransmitter acetylcholine (ACh) following its release from neurons in the body. This enzyme, AChE, resides on the postsynaptic membranes of neurons, the post-junctional membranes of striated-muscle and smooth-muscle cells, and on the post-junctional membranes of cells in exocrine glands stimulated by ACh. Normally, AChE acts to break down ACh into choline and acetate, thereby terminating the effect of ACh on the end-organ.

When nerve agents are introduced into the body, they bind to and inhibit AChE. When nerve agent binds to cholinesterase, this enzyme can no longer hydrolyze ACh. ACh then accumulates at postsynaptic and post-junctional cholinergic receptors in cholinergic end-organs. Two major types of receptors for ACh exist:

1) Nicotinic receptors – present postsynaptically on the dendrites and cell bodies of neurons in autonomic ganglia and post-junctionally in myocytes of voluntary, or skeletal, muscle.
2) Muscarinic receptors – found postsynaptically in certain populations of neurons in the brain and post-junctionally in smooth muscle and exocrine glands.

The excess of ACh causes cholinergic crisis and two general types of end-organ responses – hyperstimulation and eventual fatigue and failure. The effects of nerve agents are easily organized by organ system according to the possible responses of the tissue. Thus, overstimulation of neurons in the brain leads to seizures (clinically manifested as convulsions) and other derangements of neural activity, whereas fatigue and failure of the respiratory center in the medulla lead to central apnea. Hyperstimulation of skeletal muscle causes twitching and fasciculations, whereas subsequent muscle fatigue and failure are responsible for the weakness and paralysis (sometimes rigid, but usually flaccid) that can lead to respiratory arrest. Excess ACh postsynaptically in smooth muscle is responsible for miosis, bronchoconstriction (including bronchospasm), and hyperperistalsis (manifested by nausea, cramping, vomiting, and diarrhea). Hypersecretion of exocrine glands explains the lacrimation, rhinorrhea, salivation, and bronchorrhea that render a patient "wet all over." **This constellation of symptoms and signs is referred to as the cholinergic toxidrome, and its presence is crucial in diagnosing nerve agent poisoning**. See Table 2 for a summary of the clinical effects on the nicotinic and muscarinic systems.

The heart is affected both directly by ACh released from the vagus nerves and also indirectly by ACh-induced stimulation of neurons in sympathetic ganglia to release norepinephrine. Although cholinergic crisis in animals usually leads to bradycardia, the heart rate in humans is unpredictable after nerve agent poisoning and is more frequently elevated than depressed.

Table 2. The Clinical Effects of Overstimulated Acetylcholine Receptors

	Location of Receptor	Clinical Effects
Nicotinic	Skeletal muscle	Fasciculations, muscle fatigue, weakness, paralysis, and respiratory arrest
	Sympathetic ganglia and vagus nerve	Often tachycardia and hypertension
Muscarinic	Exocrine glands	Lacrimation, rhinorrhea, salivation, bronchorrhea
	Brain	Seizures
	Medulla	Central apnea
	Smooth muscle	Miosis, bronchoconstriction, hyperperistalsis

First responders wearing personal protective equipment arrive on the scene and instruct the moviegoers to evacuate the building. Due to the cold weather, they are escorted into the lobby of an adjacent office building. The moviegoers are instructed to remove their clothing and place them in designated plastic bags. They are then washed thoroughly with soap and water and given clean robes to wear.

DUMBBELS is a useful mnemonic that summarizes the muscarinic effects on the body caused by nerve agent exposure:

Diarrhea

Urinary Incontinence

Miosis/Muscle Fasciculations

Bronchorrhea

Bronchospasm

Emesis

Lacrimation

Salivation

COMMENT: When the identity of the agent is in doubt, all liquid must be considered to have the potential to cause systemic toxicity via absorption and must be removed as quickly as possible. In general, immediate management of a chemical casualty should involve **ABCDD**: **A**irway, **B**reathing, **C**irculation, spot **D**econtamination, and administration of **D**rugs (specific antidotes) as available.

Prompt decontamination of liquid chemicals may be one of the simplest and yet most effective and important life-saving measures that can be taken at the scene of an exposure. Because many toxic liquid chemicals may quickly penetrate the eyes, skin, and wounds, decontamination of liquid must occur as soon as possible and should begin with removal of liquid-soaked clothing. **Removing outer clothing can eliminate 85% to 90% of contamination**.[1] Decontamination is conducted by trained personnel wearing protective gear and includes washing with soap and water. High concentrations of chemical decontaminants such as hypochlorite solutions (bleach) may damage the skin and lead to increased penetration of agent. Casualties pass from the hot zone, or contaminated area, to the warm zone where they disrobe and wash before they pass to the cold zone, or safe area. Ideally, decontamination should occur in the field, but the hospital must also be prepared to decontaminate, as many ambulatory patients will arrive on their own. Decontamination must be accomplished as soon as possible, but even delayed decontamination can prevent contamination of medical staff and facilities and prevent continued absorption from liquid remaining on the skin or clothes.

Factors that affect the decontamination process can include: weather (temperature and wind), number of patients, triage category of patients, type of exposure (liquid vs. gas), severity of exposure, and available resources (trained personnel and equipment).

The arriving ambulance carries a cyanide antidote kit and three nerve agent antidote kits, each with one autoinjector of atropine and one of 2-PAM chloride. Just after the ambulance arrives, one of the passengers who has just left the multiplex falls to the ground and stops breathing. The EMT administers the three nerve agent antidote kits, but the patient does not respond.

QUESTION 3

What action should be considered after a patient fails to respond to three nerve agent antidote kits?

a. Observe the patient for an hour in order for the antidote to take effect.

b. Administer an additional nerve agent antidote kit.

c. Administer the cyanide antidote kit.

COMMENT: Treatment of nerve agent casualties depends upon the severity and nature of exposure and effects.[5] General supportive management includes attention to ABCs (airway, breathing, and circulation), decontamination (D), administration of supplemental oxygen, and observation. Mild effects from exposure to vapor will resolve spontaneously and may not need antidotal treatment.

In general, effects from liquid exposure merit earlier and more aggressive treatment because of the likelihood that the agent is still in transit through the skin.

Nerve agent antidotes (the second D in the ABCDDs) include an anticholinergic compound — atropine sulfate, and an oxime — such as 2-pralidoxime chloride (2-PAM chloride). These two antidotes are often packaged together in one kit as two autoinjectors (2 mg of atropine in one autoinjector and 600 mg of 2-PAM chloride in the other autoinjector) for intramuscular administration. Standard dosage protocols are readily available from a variety of sources. Table 3 summarizes the clinical effects and treatment for both vapor and liquid sarin exposure.

Atropine, a competitive inhibitor of ACh, works at muscarinic receptor sites but has no nicotinic effects such as resolution of twitching or weakness. It can be thought of as a kind of "Pepto-Bismol®" that "coats" muscarinic end-organs and thereby prevents ACh end-organ effects. Following administration of the first three autoinjectors, atropine should be repeated at five- to ten-minute intervals until muscarinic effects decrease. The use of additional 2-PAM chloride should be delayed for approximately an hour. The endpoints for atropine administration are a decrease in secretions and a decrease in airway resistance. Nerve agent casualties seldom require more than a total of 20 mg of atropine. In contrast, patients poisoned by organophosphate pesticides (which are also anticholinesterases) may require up to one to two grams of atropine.

Pralidoxime chloride, or 2-PAM chloride, breaks the bond between the nerve agent molecule and the AChE molecule. It can be visualized as a "2-PAM crowbar" that "pries" the nerve agent away from the enzyme. It is effective as long as the bond has not been modified by a process called aging, which is analogous to the setting of glue. Once aging has occurred, 2-PAM chloride will be ineffective at regenerating AChE. The half-life of aging for sarin is approximately five hours. However, 2-PAM chloride should never be withheld out of concern that it may be administered too late after exposure.[1] Although 2-PAM chloride acts at the bond between the nerve agent and AChE, its clinical effects are mostly nicotinic, that is, resolution of skeletal-muscle twitching, weakness, and paralysis. 2-PAM chloride is indicated for the treatment of poisoning by nerve agents and organophosphate pesticides. It is not indicated for the treatment of poisoning by carbamate pesticides or anticholinesterases that do not contain phosphorus.

In the emergency room waiting area, several of the ambulatory patients are complaining of pain in the eyes; physical examination reveals red eyes with tearing and miosis. The emergency room physicians conduct a quick but thorough assessment of the victims.

COMMENT: It is important to generate a differential diagnosis and to determine a presumptive clinical diagnosis in terms of the agent involved. One must also estimate the agent dose, the state of the agent in the environment, the route of exposure, whether effects are local or systemic, and whether effects are likely to progress or to resolve with or without therapy. The state of the agent is important, because the time course of effects resulting from vapor and liquid exposure differ in clinically significant ways. Miosis can occur after both vapor and high-dose liquid exposure. Following removal from the agent, symptoms should not worsen if the exposure was to vapor only. However, if there was liquid exposure, symptoms may develop or worsen as the absorbed agent makes its way through the skin.

Asking questions about the time course can provide a valuable estimate of the dose of agent, since the length of the clinically asymptomatic period is usually inversely correlated with dose. Pertinent questions for the past, present, and future include the following:

Past:	Duration of exposure? Time from exposure? Time of onset of symptoms?
Present:	Is the patient getting better, getting worse, staying the same, or fluctuating in condition?
Future:	What is the prognosis without therapy and with therapy?

Table 3. Summary of Nerve Agent Effects and Treatment*

	Clinical Effects	Treatment
Vapor exposure		
Mild	• Uni- or bi-lateral miosis (pinpoint pupils) • Rhinorrhea (runny nose) • Shortness of breath (due to bronchoconstriction or bronchosecretions) • Combination of above	• No treatment • 2 mg atropine if rhinorrhea or discomfort are severe • 2 mg atropine if mild or moderate; 4 mg if severe • Treat most severe effect
Moderate	• Shortness of breath	• 2-4 mg atropine, depending on severity; repeat 2 mg doses every 5 minutes until improvement • Ventilate as needed via bag-valve-mask
Severe	• Unconscious, convulsing, postictal, gasping for air; effects in 2 or more systems	• 6 mg atropine IM; repeat 2 mg doses every 5 minutes until improvement • 1.8 g 2-PAM IM • Diazepam • Ventilate via bag-valve-mask • Suction airways if secretions are copious
Liquid exposure		
Mild	• Localized sweating; fasciculations	• 2 mg atropine • 600 mg 2-PAM IM
Moderate	• Gastrointestinal effects	• 2 mg atropine • 600 mg 2-PAM IM
Severe	• Same as for vapor	• Same as for vapor

*Adapted and reprinted with permission from Briggs and Brinsfield.[6]

QUESTION 4

A medical student in the emergency room is taking a history from one of the decontaminated asymptomatic patients, when the patient suddenly gasps, falls over, and starts convulsing on the floor. Which of the following conclusions about this scenario is correct?

a. The patient is likely to have residual agent on his skin and needs to be decontaminated again.

b. There is a probable pocket of residual sarin vapor, and the medical student should immediately hold his or her breath and leave the area.

c. The collapse is likely to be from liquid nerve agent no longer on the skin.

COMMENT: The effects of nerve agents such as sarin depend in large measure on the state of the agent in the environment, the route(s) of exposure, and whether the dose and the circumstances of exposure cause local or systemic effects. Individual facial exposure to a very small amount of sarin vapor may cause miosis, rhinorrhea, salivation, mild bronchorrhea and bronchoconstriction, all from local effects. As the dose increases, progression to systemic effects may occur, usually beginning with nausea. Local effects from vapor may occur almost immediately and usually do not worsen in severity following removal from the agent. A small droplet of liquid on the skin will lead to localized twitching, fasciculations, and sweating. As the absorbed dose increases, systemic effects progressively develop; progression, however, varies. A large dose of sarin may lead to sudden collapse with apnea and convulsions whether the exposure is from inhalation or percutaneous absorption. The difference is that

sudden collapse from high vapor concentrations will occur within seconds, whereas sudden collapse from a significant amount of liquid on the skin will occur after a period of minutes to hours. The length of the latent period after liquid exposure can help in estimating the absorbed dose; fatal doses of liquid agent usually cause sudden effects after as little as 20 to 30 minutes. It is important to realize that early appearance and successful treatment of vapor-induced effects do not exclude liquid exposure, and sarin casualties should be observed for 24 to 48 hours.

Several patients in the emergency room develop moderate to severe signs of nerve agent exposure, and supportive care is continued. Antidotal treatment is also continued.

QUESTION 5

When should repeat intravenous or intramuscular doses of atropine be discontinued?

a. When miosis resolves

b. When twitching and muscle weakness resolve

c. When secretions and airway resistance decrease

d. When the heart rate rises above 110 beats per minute

Before discharge from the hospital, several patients ask about the likelihood of long-term complications from their exposure.

QUESTION 6

What would be the expected long-term complications for the victims described in the case?

a. Most victims of acute exposure should recover without sequelae.

b. Subtle neurological effects have not been conclusively demonstrated following recovery from nerve agent exposure.

c. Chronic organophosphate-induced delayed neurotoxicity (COPIDN), a "dying-back" neuropathy, has been seen after poisoning with organophosphate insecticides but, curiously, has never been seen after nerve agent exposure.

d. "Intermediate syndrome," with weakness of neck, limb, and respiratory muscles, has occurred in a small number of nerve agent victims.

Ticket receipts show that a total of 1,233 patrons had been issued tickets to movies showing in the multiplex at the time of the release of sarin. In addition, 32 theater employees had been working that evening. A total of 6,430 patients, including movie patrons, employees, first-responders, and hospital staff, were evaluated at several hospitals and clinics throughout the city. Of these, 433 had objective evidence of sarin exposure, including 15 emergency-response personnel and 7 hospital staff members. Of the 25 deaths attributed to the release, 8 were among those known to have been exposed to liquid sarin; one of these died after having been supported for 7 months on a ventilator, without regaining consciousness. Autopsies indicated that 2 deaths had occurred outside the theater in casualties who had been carried outside by other patrons and then left on the sidewalk without attention to airway management; these victims might have

survived had it not been for positional airway obstruction. Hypothermia was a contributor to a third death. Two middle-aged men were determined to have coronary-artery disease that could have led to myocardial infarctions, although nerve agent release was still listed as the cause of death for these victims.

The morning after the incident, a local newspaper received a letter claiming responsibility for the event and describing details that were later confirmed by forensic investigation. Despite an intensive criminal and terrorist investigation, the perpetrators remain at large and their individual identities unknown. One year after the incident, 735 people, including many with no objectively demonstrated exposure, report continued or recurrent largely nonspecific symptoms including weakness, lethargy, memory problems, and flashbacks. Apart from hypoxic damage attributed to prolonged apnea at the scene in 5 patients, the only demonstrated physiological abnormalities are minor memory deficits.

ANSWER KEY & DISCUSSION

QUESTION 1

Which of the following signs and symptoms suggest a nerve agent rather than a cyanide or pulmonary agent?

a. Increased secretions
b. Cough
c. Headache
d. Sore throat

ANSWER: The correct answer is a. Increased secretions are a hallmark feature of nerve agent exposure. A useful tools for remembering the classic presentation of sarin is the mnemonic DUMBBELS (see sidebar on page 7). Cough and sore throat are typical presentations of pulmonary and blister agents, while headache is a symptom of cyanides.

QUESTION 2

Which of the following statements is TRUE about the mechanism of action that produces stumbling, chest tightness, and difficulty breathing after sarin exposure?

a. Stumbling is probably secondary to excess cholinergic stimulation of the constrictor muscles of the irises, leading to miosis.
b. Chest tightness is probably a pre-cursor of sarin-induced damage to alveolar-capillary membranes and incipient pulmonary edema.
c. Because sarin causes weakness and then paralysis of the diaphragm, tightness of the chest would not be expected and would imply the mixture of sarin with a pulmonary agent.
d. Stumbling is probably an early manifestation of damage to cerebellar pathways involving balance from direct effects of sarin on the central nervous system.

ANSWER: The correct answer is a. Sarin, like other nerve agents, inhibits the enzyme that hydrolyzes ACh. Excess ACh, or cholinergic crisis, leads to miosis and therefore problems seeing, especially at nighttime or in the dark. Chest tightness may occur from ACh-induced bronchospasm, or cholinergic crisis leading to skeletal muscle overstimulation which may result in fatigue and failure. A

pulmonary agent would cause alveolar-capillary membranes and incipient pulmonary edema. Sarin can affect the central nervous system with high dose exposure, and seizures are the common manifestation.

QUESTION 3

What action should be considered after a patient fails to respond to three nerve agent antidote kits?

a. Observe the patient for an hour in order for the antidote to take effect.
b. Administer an additional nerve agent antidote kit.
c. Administer the cyanide antidote kit.

ANSWER: The correct answer is c. Weakness, nausea, lacrimation, salivation, and apnea, although part of the cholinergic toxidrome and thus highly suggestive of nerve agent poisoning, may also be seen after exposure to pulmonary agents, blister agents, and especially cyanide. In fact, if a suspected nerve agent fails to respond to initial administration of nerve agent antidotes, administration of the cyanide antidotes should be considered.[4] The full standard initial antidotal treatment for a severely poisoned nerve agent casualty is three nerve agent antidote kits plus a benzodiazepine, even if the casualty has not yet begun to seize. Even if a fourth nerve agent antidote kit were available at this point, only the atropine autoinjector from that kit would be used; the use of additional 2-PAM chloride should be delayed for approximately an hour.

QUESTION 4

A medical student in the emergency room is taking a history from one of the decontaminated asymptomatic patients, when the patient suddenly gasps, falls over, and starts convulsing on the floor. Which of the following conclusions about this scenario is correct?

a. The patient is likely to have residual agent on his skin and needs to be decontaminated again.
b. There is a probable pocket of residual sarin vapor, and the medical student should immediately hold his or her breath and leave the area.
c. The collapse is likely to be from liquid nerve agent no longer on the skin.

ANSWER: The correct answer is c. This situation illustrates the importance of assessing whether exposure was to vapor, liquid, or both. Whether exposure is to vapor or liquid, effects may be initially minor and progress, or they may be major and occur all at once. One useful difference is that effects from inhalation of nerve agent vapor usually occur within seconds to minutes of exposure and once present do not worsen once a casualty has been removed from exposure. However, liquid nerve agent starts being absorbed through the skin soon after exposure, and effects are delayed while agent traverses the epidermis to reach the dermis, where it can be picked up by dermal blood vessels and then distributed systemically. Skin decontamination will not remove agent already in transit through the skin and therefore will not prevent delayed effects from liquid. In this case, liquid exposure occurred from contact with liquid sarin in the theater and the surface of the skin was decontaminated several minutes later, but severe systemic effects from the sarin that had already started to penetrate the skin were delayed until the agent had time to reach the circulation. This occurred, suddenly and dramatically, after the patient reached the emergency room.

QUESTION 5

When should repeat intravenous or intramuscular doses of atropine be discontinued?

a. When miosis resolves
b. When twitching and muscle weakness resolve
c. When secretions and airway resistance decrease
d. When the heart rate rises above 110 beats per minute

ANSWER: The correct answer is c. Atropine is a competitive inhibitor of ACh at muscarinic receptor sites and as such, counteracts only muscarinic effects such as secretions and bronchoconstriction. Miosis is a muscarinic effect, but it occurs in a relatively isolated tissue that may not receive a full therapeutic dose of atropine from intramuscular or intravenous administration. In the absence of topical administration of atropine, miosis may take up to six weeks to resolve. The heart rate in nerve agent poisoning may be low, high, or normal and is in fact more likely to be high than low. The heart rate is always an important vital sign, but it should not be used either as an estimate of the severity of nerve agent poisoning or as an endpoint for atropine administration.

QUESTION 6

What would be the expected long-term complications for the victims described in the case?

a. Most victims of acute exposure should recover without sequelae.
b. Subtle neurological effects have not been conclusively demonstrated following recovery from nerve agent exposure.
c. Chronic organophosphate-induced delayed neurotoxicity (COPIDN), a "dying-back" neuropathy, has been seen after poisoning with organophosphate insecticides but, curiously, has never been seen after nerve agent exposure.
d. "Intermediate syndrome," with weakness of neck, limb, and respiratory muscles, has occurred in a small number of nerve agent victims.

ANSWER: The correct answer is a. Subtle and mostly subclinical chronic neurological effects have been seen in low-dose exposures in nerve agent production facilities and in a few survivors of acute high-dose exposures.[7] Weakness of neck flexors and of proximal limb muscles with respiratory depression characterized as "intermediate syndrome," was seen after intentional ingestions of anticholinesterase insecticides in Sri Lanka, but this syndrome appears not to occur after nerve agent exposure. "Ginger jake paralysis" from an anticholinesterase that contaminated Prohibition-era whiskey was an example of a chronic axonal "dying-back" and demyelinating syndrome called chronic organophosphate-induced delayed neurotoxicity (or COPIDN). This syndrome appears to be associated with an enzyme (neuropathic target esterase, or NTE) not affected by nerve agents. COPIDN after nerve agent exposure has been documented in only a single case, the atypical case of a 51-year-old man who inhaled sarin during the attack on the Tokyo subway system and who died 15 months later without regaining consciousness.[8] Prompt diagnosis, repeated systematic assessments, supportive treatment, and specific antidotal treatment should lead to complete recovery without sequelae in most acute victims of sarin exposure.

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SUGGESTED READING

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EVALUATION FORM
TERRORISM AND DISASTER: WHAT CLINICIANS NEED TO KNOW
Sarin

Participant Information

Name/Degree _____ Practice setting: ❑ Hospital/In-patient ❑ Outpatient/Clinic ❑ Other

Address _____ Email _____

City _____ Clinical Specialty _____

State _____ Zip _____ Signature _____

Telephone _____ Date _____

Instructions for Physicians Receiving Credit

The questions that follow may be used to obtain continuing medical education credit. To obtain 1 hour of Category 1 credit towards the AMA Physician's Recognition Award, read this case study, which will take one hour of your time, circle the correct answer to each of the CME questions, complete the evaluation form, and return both the CME question page and the evaluation form via mail or fax to:

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Case Study Evaluation

Please rate this case study according to the following scale: 1=Very Poor 2=Poor 3=Fair 4=Good 5=Very Good 6=Excellent

1. Accredited CME activities must be "free of commercial bias for or against any product." In this regard, how would you rate this activity? If you perceived any bias, please provide specific comments below. 1 2 3 4 5 6 ☐ ☐ ☐ ☐ ☐ ☐

   _____

2. How well did the case study satisfy your purpose for reading it? ☐ ☐ ☐ ☐ ☐ ☐
3. To what extent were the stated objectives of the case study achieved? ☐ ☐ ☐ ☐ ☐ ☐
4. In general, was the case study well organized and presented? ☐ ☐ ☐ ☐ ☐ ☐
5. To what extent has this CME activity improved your preparedness to recognize and care for victims of a terrorism attack or other public health disaster? ☐ ☐ ☐ ☐ ☐ ☐
6. What was your overall rating of this case study? ☐ ☐ ☐ ☐ ☐ ☐
7. I would recommend this case study to a colleague. ☐ Yes ☐ No
8. Based upon your review of this case, what specific action(s) could you take to enhance disaster preparedness in your workplace?

   Please estimate the probability that you will act on this item (0-100% where 100% = certainty)

   A. _____ A. _____

   B. _____ B. _____

   C. _____ C. _____

☐ Please check this box if you prefer not to be contacted for follow-up about the impact of this activity on your clinical practice.

QUESTIONS FOR CONTINUING MEDICAL EDUCATION

1. **What is the pathophysiology of sarin poisoning?**
   a. Sarin quickly binds to acetylcholinesterase (AChE), leading to an excess of acetylcholine (ACh) at receptors.
   b. Sarin exposure leads to paralysis because of decreased stimulation of muscles by acetylcholine (ACh).
   c. Sarin competes with acetylcholine (ACh) for binding to muscarinic receptors.
   d. Sarin causes increased release of acetylcholine (ACh) from the axons of neurons.

2. **Which of the following best describes a patient exposed to sarin?**
   a. "Blind as a bat, dry as a bone, hot as a hare, red as a beet, and mad as a hatter"
   b. Paranoid, hypertensive, sweating, mydriatic (dilated pupils), and hyperpyrexic
   c. Weak, twitching, miotic (pinpoint pupils), tearing, salivating, sweating, vomiting, diarrhetic, and seizing
   d. Miotic (pinpoint pupils), comatose, hypotensive, hypothermic, hyporeflexive, seizing, and with decreased bowel sounds

3. **How would victims exposed by inhalation of sarin differ clinically from those exposed solely to liquid sarin?**
   a. Miosis is never seen after exposure to liquid sarin.
   b. With high doses, sudden collapse may be the first clinical effect after either kind of exposure but with liquid exposure would occur after several minutes rather than immediately.
   c. Twitching is not commonly seen after exposure only to sarin vapor.
   d. Unlike liquid-exposed patients, victims from sarin vapor may exhibit a gradual onset of symptoms even after removal from exposure.

4. **In a hospital setting, what is the role of decontamination for sarin victims?**
   a. No decontamination is needed by the time victims reach the hospital.
   b. Late decontamination is performed solely to protect hospital personnel and facilities.
   c. Decontamination of sarin requires hypochlorite solutions (bleach).
   d. Removal of clothing may eliminate most but not all sarin in an exposed victim.

5. **Which statement most accurately describes the action of a nerve agent antidote?**
   a. Diazepam acts as a competitive inhibitor of acetylcholine at muscarinic receptors.
   b. Atropine acts as a little "crowbar" to "pry" the nerve agent away from bound enzyme.
   c. Because 2-PAM chloride acts primarily at nicotinic receptors, its main clinical effects are on smooth muscle.
   d. Atropine acts as the "Pepto-Bismol®" of nerve-agent antidotes by "coating" muscarinic receptors.

Terrorism and Disaster

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