Nerve Agents

Fact Sheet

Background

Nerve agents are a class of chemicals grouped together based on their common mechanism of action, which is interruption of vital nerve transmissions to various organs.[1,2] Nerve agents are usually organophosphates (OP)—esters of phosphoric acid—which, as a group, can range in toxicity from relatively harmless to lethal at certain dosages.[2] Indeed, many commonly used insecticides in the United States contain organophosphates.[2]

Military nerve agents can be extremely lethal even at small doses.[3] The most well-known of these are tabun, sarin, soman, GF, and VX. Like other organophosphates, the military nerve agents are manmade compounds; none are found in nature.[2]

Use as a Chemical Warfare Agent

The first nerve agent of military relevance was inadvertently discovered in 1937 by the German chemist Gerhard Schrader while he was conducting research on ethyl-N-dimethyl-phosphoroamidocyanate, now more commonly known as tabun (GA). After his discovery of GA's toxicity and lethality, Dr. Schrader reported his findings to the German War Ministry, which went on to weaponize GA, sarin (GB), and soman (GD)—known collectively as the G-series.[2] In the late 1940s, researchers in England produced a group of nerve agents known as the V-series, which includes the chemical weapon VX, or O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate.[2]

Despite the 1925 Geneva Protocol, "For the Prohibition of the Use in War of Asphyxiating, Poisonous or other Gases, and of Bacteriological Methods of Warfare," many countries have developed and maintained their own stores of chemical weapons.[4] The United States and the Soviet Union both built stockpiles of chemical weapons, including nerve agents, during the Cold War.[2] The Chemical Weapons Convention (CWC), which became effective in April 1997, effectively bans development, stockpiling, or use of all chemical weapons.[5] As signatories to the CWC, the US and Russia, as well as the other 163 signatories, are compelled to reduce and ultimately eliminate their stockpiles of chemical weapons, including nerve agents.[2,5-7]

Despite the large stores of these nerve agents around the world, the actual use of military nerve agents has been limited.[2] The Iran-Iraq War (1980-1988) saw the first use of nerve agents in modern warfare, when Iraq released GA on Iranian troops in 1984.[4] Toward the end of that war, the Iraqi military reportedly deployed a cocktail of chemical weapons—possibly including GB, GA, and VX—against its own Kurdish population living in the north of the country.[2,4]

Aum Shinrikyo, the Japanese cult/terrorist organization is also known for use of nerve agents. In 1994, the group released sarin gas in a failed attempt to assassinate local judges in Matsumoto, Japan; that action resulted in 8 civilian deaths.[8] The following year, Aum released sarin gas into the Tokyo subway system, killing 13 people and sending more than 6,000 to the hospital.[8]

In December 2012, during the ongoing civil war in Syria, there were reports of a release of nerve agents against Syrian civilians in the town of Aleppo.[9] The Assad government and the opposition forces have since both claimed that it was the other who released the nerve agents.[9] While details about the alleged release remain unclear, both Britain and France have said that there is credible evidence indicating that Syria's government has released chemical weapons multiple times during the civil war.[10] The US continues to investigate the claim.[10]

Mechanism of Action & Physical Properties

At room temperature, nerve agents are primarily liquid.[2] The G-series agents are clear, colorless, and tasteless.[11] Sarin is the most volatile nerve agent.[11] VX, is the least volatile, is odorless, and can be clear or amber-colored.[11]

These agents act primarily by interfering with the nervous system, generating an overstimulation of muscles.[2] The primary mechanism of toxicity results from the inhibition of the enzyme acetylcholinesterase (AChE) at the neuromuscular junction,[1,12] which causes overstimulation of the muscles through the excessive accumulation of the neurotransmitter acetylcholine (ACh).[12] This over stimulation results in muscle paralysis.

Signs & Symptoms

Nerve agents can enter the body through inhalation or through the skin.[2] G-series agents are significantly more toxic when inhaled.[2] Symptoms from exposure to nerve agents will vary depending on the type of agent and the type and extent of exposure, though generally, symptoms will include miosis (constriction of the pupils), rhinorrhea (runny nose), dyspnea (shortness of breath), convulsions, and a loss of muscle control, with an onset of symptoms potentially occurring within seconds

Table 1: Nerve Agents Overview

Agent	Chemical Name	Range of Toxicity	State at Room Temperature	Color	Odor
Tabun (GA)	Ethyl-N-dimethyl-phospho-ramidocyanidate	Rapid onset of action; exposure can be lethal within 10 minutes Fatal dose is ~0.01mg/kg LCt50 of vapor: 400mg/min/m(3) LD50 (percutaneous): 1.0g/70 kg man	Liquid, giving off colorless vapor Vapor possible at high temperature or when aerosolized by an explosion	Brown	None in pure state; when impure, has been described as fruity, almond-like
Sarin (GB)	Isopropyl-methylphosphoro-fluoridate	Rapid onset of action; small drop on skin can cause death LCt50 of vapor: 100mg/min.m(3)	Liquid, giving off colorless vapor Vapor possible at high temperature or when aerosolized by an explosion	None	Almost none in pure state; weak, fruity; nondescript
Soman (GD)	Trimethyl-propylmethyl-phosphoro-fluoridate	Poisoning occurs quickly, making therapy less effective Can be lethal at dose as low as 0.01 mg/kg LCt50 of vapor: 50mg/min/m(3)	Liquid, giving off colorless vapor Vapor possible at high temperature or when aerosolized by an explosion	None	In pure state, slightly fruity, or similar to oil of camphor; when impure, has been described as smelling like pinacolyl, alcohol, nutmeg, orange peel
Cyclosarin (GF)	Cyclohexyl-methyl-phosphoro-fluoridate	Rapid onset of action, and high level of toxicity Evaporates slowly	Liquid Vapor possible at high temperature or when aerosolized by an explosion	None	Nondescript; has been described as sweet or musty; often not detectable by smell
VX	o-ethyl S-[2-diiospropylamino) ethyl] methylphosphoro-fluoridate	Droplets evaporate slowly, resulting in systemic absorption LCt50 of vapor: 10mg/min/m(3) LD50 (percutaneous): 10mg/70 kg man	Liquid Vapor possible at high temperature or when aerosolized by an explosion	Amber; colorless in pure form	None in pure state; when impure, has been described as smelling of rotten fish

or minutes.[13] Nerve agents are lethal at certain levels of exposure,[2] with death resulting from respiratory failure, depression of the central nervous system, and excessive secretions.[3]

Inhalation exposure at a large enough dose, depending on vapor concentration and duration of exposure, can result in an onset of symptoms within 30 seconds to 2 minutes.[1] Symptoms may include loss of consciousness, convulsions, flaccid paralysis, and respiratory failure.[3,14] Symptoms after an inhalation exposure to a more limited quantity of vapor will still begin quite soon after exposure, though are generally not as severe. Symptoms may include miosis, red conjunctiva, dimmed or blurry vision, pain, nausea and vomiting, rhinorrhea, increased salivation, tightness in chest, cough, and dyspnea.[14]

Transdermal exposure to nerve agents generally results in a slower onset of systemic symptoms, as the toxins are gradually diffused through the skin. The latency and severity of symptoms are affected by the temperature of the surrounding area, the dose, and the anatomical area of exposure.[1] With exposure on parts of the body where the dermal layers are thin, such as the ears and eyelids, the toxins will be absorbed more rapidly.[1] Effects may begin within 30 minutes, or as long as 18 hours after initial exposure.[14]

Table 2: Onset and Symptoms of Nerve Agent Exposure

	Inhalation	Transdermal
Small Exposure	**Onset:** Seconds to minutes following exposure **Symptoms**: Miosis, rhinorrhea, dyspnea	**Onset:** Up to 18 hours after exposure **Symptoms:** Sweating, twitching at site of exposure; possibly nausea, vomiting, diarrhea
Large Exposure	**Onset:** Seconds to minutes following exposure **Symptoms:** Loss of consciousness, seizures, apnea, flaccid paralysis; miosis, nose and mouth secretions	**Onset:** Within 30 minutes of exposure **Symptoms:** Loss of consciousness, seizures, apnea, flaccid paralysis

With an exposure that is limited to a very small drop, symptoms may include sweating and twitching at the site of exposure.[14] Slightly greater exposure can result in nausea, vomiting, and diarrhea.[14] Following exposure to a full drop, symptoms may include loss of consciousness, convulsions, and flaccid paralysis.[14]

Diagnosis

For clinical diagnosis, the most reliable indicator of exposure to a chemical nerve agent is generally miosis, though it will not always occur in victims who have come in contact with nerve agents through transdermal exposure.[1,14] Following inhalation exposure to nerve agents in vapor form, however, nearly all victims will present with miosis, usually in both eyes.[14] Indeed, after the Tokyo subway sarin release, more than 90% of victims who were exposed to the vapor presented with miosis.[1]

Treatment

The effectiveness of treatments for exposure to a nerve agent depends on the dose, type of exposure, and the specific agents involved.[2] Some nerve agents can produce irreversible effects within just a few minutes of exposure, though others take much longer.[2] Exposure to soman, for example, must be treated within minutes of exposure for treatment to be effective.[2] Exposure to tabun, by comparison, can be treated several hours later and be effective.[2]

Atropine and pralidoxime chloride are the 2 drugs used to treat nerve agent exposure.[2] Diazepam (valium) or similar benzodiazepines can be used to mitigate the convulsions associated with exposure.[2]

Atropine[1] works by counteracting the effects of the excessive amount of acetyl choline while the body works to clear the nerve agent.[1,2] Pralidoxime chloride works by reversing the agent's mechanism of action, and reactivating AChE.[1,2] Early treatment with pralidoxime can prevent the otherwise irreversible nerve damage associated with exposure.[1] Pralidoxime should continue to be administered for a period of time after symptoms resolve.[1]

Control Measures & Prophylaxis

Exposure to organophosphate pesticides is relatively common.[13] In the US, where these pesticides are widely used, many emergency medical teams are familiar with the diagnosis and treatment of exposure and have access to atropine and pralidoxime.[13] However, in widespread exposure to military nerve agents, which would likely result in multiple victims, local supplies of these drugs would be quickly depleted.[13]

Further protective measures against nerve agents include gas masks and protective clothing.[4] Soldiers who are at risk of exposure to nerve agents will often carry atropine and pralidoxime injectors in an antidote kit, so as to be able to have quick access to treatment if they are exposed.[2,4] Iranian troops were known to carry atropine injectors during the Iran-Iraq War,[4] and US troops carried both of these drugs in their antidote kits during the Persian Gulf War.[2]

Some drugs, such as pyridostigmine bromide, can serve as prophylaxis. Prophylactic treatment with pyridostigmine bromide may allow for a longer treatment window after exposure to nerve agents,[2] and may improve survival rates.[1]

References

1. Geoghegan J, Tong JL. Chemical warfare agents. *Continuing Education in Anaesthesia*, Critical Care & Pain. December 1, 2006 2006;6(6):230-234.
2. Shea DA. Chemical Weapons: A Summary Report of Characteristics and Effects: CRS Report for Congress; December 13, 2012: http://www.fas.org/sgp/crs/nuke/R42862.pdf. Accessed April 18, 2013.
3. Sifton DW, Kelly GL. *PDR guide to biological and chemical warfare response*. 1st ed. Montvale, NJ: Thomson/Physicians' Desk Reference; 2002.
4. Ali J. Chemical Weapons and the Iran-Iraq War: A Case Study in Noncompliance. *The Nonproliferation Review*. 2001;Spring:43-58. http://cns.miis.edu/npr/pdfs/81ali.pdf. Accessed April 18, 2013.

5. Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction, (1992).
6. CDC. Chemical Weapons Elimination - Closing U.S. Chemical Warfare Agent Disposal Facilities. 2012; July 18, 2012 Available at: http://www.cdc.gov/nceh/demil/closing_facilities.htm. Accessed April 18, 2013.
7. Pan PP. Plant to Destroy Chemical Weapons Opens in Russia. *The Washington Post*. May 30, 2009. http://articles.washingtonpost.com/2009-05-30/world/36772555_1_shells-and-warheads-nerve-agents-chemical-safety. Accessed April 18, 2013.
8. Richard Danzig MS, Terrance Leighton, Lloyd Hough, Hidemi Yuki, Rui Kotani, Zachary M. Hosford. *Aum Shinrikyo: Insights Into How Terrorists Develop Biological and Chemical Weapons*: Center for a New American Security;2011.
9. DeYoung K. Britain, France claim Syria used chemical weapons. *The Washington Post*. April 18, 2013. http://www.washingtonpost.com/world/national-security/britain-france-claim-syria-used-chemical-weapons/2013/04/18/f17a2e7c-a82f-11e2-a8e2-5b98cb59187f_story_1.html. Accessed April 19, 2013.
10. Gladstone R, Schmitt E. Syria Faces New Claim on Chemical Arms. *The New York Times*. April 18, 2013. http://www.nytimes.com/2013/04/19/world/middleeast/Syria.html?_r=0. Accessed April 19, 2013.
11. CDC. Nerve Agents (GA, GB, GD, VX). *Toxic Substances Portal* 2011; March 3, 2011 Available at: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=93. Accessed April 19, 2013.
12. Golomb BA, Marshall GN, Harley NH, et al. *A review of the scientific literature as it pertains to Gulf War illnesses*. Santa Monica, CA: Rand; 1998.
13. Institute of Medicine (U.S.). Committee on R & D Needs for Improving Civilian Medical Response to Chemical and Biological Terrorism Incidents., National Research Council (U.S.). Board on Environmental Studies and Toxicology. *Chemical and biological terrorism : research and development to improve civilian medical response*. Washington, D.C.: National Academy Press; 1999.
14. Sidell FR, Patrick WC, Dashiell TR. *Jane's chem-bio handbook*. Alexandria, Va.: Jane's Information Group; 1998.