

# Nerve Agents: Implications for Anesthesia Providers

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*Anesthesia providers may be called to treat injuries from chemical weapons or spills, for which prompt treatment is vital. It is therefore important to understand the mechanism of action of nerve agents and the resultant pathophysiology and to be able to quickly recognize the signs and symptoms of nerve agent exposure.*

*This review article addresses the different types of nerve agents that are currently being manufactured as*

*well as the symptomatic and definitive treatment of the patient who presents with acute nerve agent toxicity. This article also reviews the physiology of the neuromuscular junction and the autonomic nervous system receptors that nerve agent toxicity affects.*

**Keywords:** Chemical weapons, cholinesterase inhibitors, nerve agents, nerve gas.

After the terrorist attacks of September 11, 2001, there was a considerable amount of media coverage dedicated to the potential for future biological or chemical attacks. Since then, these issues have been pushed aside and, for many people, complacency has set in. The prospect of a chemical weapons attack with nerve agents, however remote, is still a possibility, and the best way to prepare for such an event is to understand these agents. Anesthesia providers are considered the airway specialists in many institutions and may be called on to help, particularly in a mass casualty or disaster. Understanding the complexities and mechanisms of action of the most commonly used nerve agents can help the anesthesia provider recognize the signs and symptoms of nerve agent poisoning. More importantly, understanding how the nerve agents affect the neuromuscular junction and autonomic receptors can guide lifesaving treatment when time is of the essence.

## History

Of all the chemical weapons that have ever been developed, the organophosphate nerve agents are by far the most toxic. Germany was the first country to develop this class of agents and synthesized tabun (also known as GA) and sarin (GB) between 1936 and 1945.<sup>1</sup> Although Germany never used these agents, the Nazi army did manufacture and stockpile them. Thus far, the only time these agents have been used in warfare was the Gulf War of 1981 to 1987, in which Iraq reportedly used tabun and sarin against Iran.<sup>1</sup>

Sarin has been used in a terrorist attack. On June 27, 1994, sarin was released over the city of Matsumoto, Japan. There were more than 600 casualties and 7 deaths.<sup>2</sup> On March 20, 1995, the Japanese cult "Aum Shinrikyo" released sarin vapor on a Tokyo subway, killing 12 people. Thousands of people presented to emergency departments for possible exposure and treatment.<sup>3</sup>

Death can result from only a small dose of nerve agent. In addition, nerve agents can be readily transported in their liquid form. Since only a small amount of the liquid is needed, it can be transported in sealed vials or bags and is virtually undetectable by standard security measures.

## Review of Literature

The organophosphorus compounds that have been developed for use as chemical weapons are commonly referred to as "nerve agents." They are closely related to the organic phosphorus pesticides but are much more deadly. The nerve agents exert their mechanism of action by inhibiting acetylcholinesterase.<sup>4</sup> Acetylcholinesterase belongs to a class of enzymes that hydrolyzes esters. Esters are compounds that have an alcohol group connected to an acid group. When acetylcholine is hydrolyzed by acetylcholinesterase, it is broken down into choline and acetic acid. Choline is the alcohol group and acetic acid is the acid group.<sup>5</sup> This results in the binding of acetylcholinesterase, leading to an accumulation of acetylcholine at both the muscarinic and nicotinic receptors.<sup>6</sup> The symptoms of nerve agent poisoning are directly related to the effects of excess acetylcholine at the autonomic receptors.

Acetylcholine is the primary neurotransmitter of the parasympathetic nervous system. The 2 principal autonomic receptors in the parasympathetic branch of the autonomic nervous system are the muscarinic and nicotinic receptors. The receptors are named so because they are stimulated by muscarine and nicotine, respectively; however, they are both responsive to acetylcholine.<sup>6</sup> Muscarinic receptor stimulation causes defecation, urination, miosis, bronchospasm, bronchorrhea, bradycardia, emesis, lacrimation, and salivation. This may be best remembered by the use of the mnemonic "DUMBBELS" because it contains the 3 "Bs" that are the most life threatening.<sup>5</sup>

Nicotinic receptors are found in the ganglia of both

the sympathetic and parasympathetic nervous systems. Excitation of the receptor by either nicotine or acetylcholine will produce hypertension and tachycardia at low doses and will produce hypotension and neuromuscular weakness at higher doses.<sup>6</sup> Central nicotinic stimulation can result in seizures, coma, and depression of the respiratory center. Signs and symptoms of excessive nicotinic stimulation may best be remembered by the use of the mnemonic "MTWHF" (mydriasis, tachycardia, weakness, hypertension, and fasciculations).<sup>5</sup> Someone who is poisoned with a high dose of nerve agent may experience a depolarizing block similar to that produced by succinylcholine. The detrimental effect of this would be fasciculation followed by paralysis<sup>5</sup> and would require immediate intervention to assist the person's respirations. In acute poisonings involving nerve agents, acute respiratory insufficiency is the primary cause of death.<sup>5</sup>

The initial presenting symptoms of exposure to nerve agents depend on the dose received and the route of exposure. These include myosis, which leads to blurred vision, bronchospasm, dyspnea, rhinorrhea, sweating, and fasciculations. The patient may exhibit bradycardia or tachycardia, depending on whether a muscarinic or nicotinic receptor is stimulated. It is important to remember that the dose capable of producing symptoms is only slightly less than the lethal dose,<sup>5</sup> and so all victims should be regarded as having been exposed to a potentially lethal dose. The nerve agents can gain entry into the body via inhalation through the respiratory tract or via direct contact with the skin.<sup>7</sup> The following discussion concerns the chemical properties of the various agents and the most likely route of exposure.

### Review of Specific Nerve Agents

The nerve agents can be synthesized fairly easily and inexpensively by anyone with an understanding of organic chemistry. The G-type agents (sarin, soman, and tabun) are colorless, clear, tasteless liquids that are easily mixed in water and most organic solvents.<sup>7</sup> Sarin is the most volatile of all the nerve agents and has no odor. Tabun has a fruity odor, whereas soman has a camphorlike odor.<sup>7</sup> All of the nerve agents have a vapor density greater than 1 and are thus heavier than air. The nerve agents, therefore, tend to sink to lower lying areas.

The nerve agent VX is the least volatile but the most persistent. Although it is difficult to aerosolize VX, it is an oily liquid that can be absorbed through the skin with minimal contact time. Even after a victim's clothing has been removed and the skin decontaminated, the body can continue to absorb VX from the inner layers of the skin, resulting in delayed symptoms.<sup>5</sup> Temperature of the ambient air is also a factor in absorption of this agent. Temperature and absorption are positively correlated; thus, the higher the temperature, the more the agent is absorbed through the skin.

### Decontamination and Treatment

The initial care and treatment of someone who has been exposed to a nerve agent involves immediate and rapid removal of all clothing and removing the patient from the source of nerve agent exposure. Decontamination of the skin may be accomplished with either soap and water<sup>7</sup> or 0.5% sodium hypochlorite solution (dilute household bleach solution).<sup>5</sup> The dilute bleach solution is preferable because the alkaline pH of the bleach hydrolyzes the nerve agent more rapidly, thus rendering it inactive. For example, the half-life of sarin when exposed to water (pH 7) is 5.4 hours compared with 15 minutes when exposed to a bleach solution (pH 9).<sup>5</sup> For inhalation exposures, the primary means of decontamination is to get the victim to an area with adequate ventilation.<sup>5</sup>

Anesthesia providers who are involved in the initial care and rescue of victims exposed to nerve agents must wear proper personal protective equipment to prevent a secondary exposure. In situations in which there is lingering nerve vapor, responders should wear adequate respiratory protection in the form of a pressure-demand, self-contained breathing apparatus (SCBA).<sup>8</sup> In situations in which it is possible that nerve agent may come into contact with skin, chemical protective clothing and butyl rubber gloves should be worn because even a tiny amount of liquid nerve agent can be rapidly absorbed through the skin, producing toxicity.<sup>8</sup>

Atropine is used to control life-threatening muscarinic symptoms such as bronchoconstriction, bronchorrhea, and bradycardia. Atropine is a competitive antagonist at muscarinic receptors and thus blocks the effects of acetylcholine at peripheral and central muscarinic receptors. The dose of atropine is 1 to 2 mg given intravenously (IV) or intramuscularly (IM). The IV route is preferred; however, the IM route may be used when IV access cannot be established readily. In cases of severe exposure, up to 6 mg of atropine may be given initially, followed by 2 mg every 5 to 10 minutes until secretions have dried up and ventilation is improved.<sup>5</sup>

Atropine is not effective for nicotinic symptoms and will not be effective in the treatment of paralysis, fasciculations, or muscle weakness.<sup>7</sup> Treatment for nicotinic symptoms at this time is supportive and involves assisting respiratory effort with ventilatory support and treating hypotension with vasopressor drugs. There is no specific nicotinic antagonist available to treat nicotinic symptoms. Instead, care is directed at treating symptoms produced by the excessive nicotinic stimulation. Seizures occurring as a result of nerve agent toxicity can be best controlled with diazepam.<sup>9</sup>

The treatments discussed so far have been directed at controlling the symptoms of nerve agent toxicity that are directly related to an excess of acetylcholine. A more definitive treatment involves the use of an oxime such as pralidoxime chloride. When the nerve agent enters the

body and deactivates the acetylcholinesterase enzyme, there is a set window of time before the bond becomes covalent and thus becomes irreversible. This phenomenon is also known as aging. Once aging has occurred, the acetylcholinesterase complex will never again be able to metabolize acetylcholine.<sup>5</sup> Oximes work by removing the organophosphoryl moiety of the nerve agent from the acetylcholinesterase enzyme, allowing the enzyme to spontaneously regenerate.<sup>7</sup>

The problem, however, is that the rate of aging varies widely for the various nerve agents. Soman, for example, is irreversibly aged after only 10 minutes and is 50% aged in less than 2 minutes. In contrast, VX may take up to 48 hours to age, whereas sarin is 50% aged after approximately 5 hours.<sup>5</sup> In the case of a nerve agent exposure, it is doubtful that the identity of the agent will be known immediately.

Therefore, it becomes important that the patient be promptly treated with an oxime such as pralidoxime to prevent aging of the nerve agent-cholinesterase complex. In the hospital setting, pralidoxime chloride is administered at dose of 15 mg/kg and is given via a 1- to 2-g IV loading dose over 5 to 10 minutes. Dosing, however, can vary widely based on the type of nerve agent used and the severity of the exposure. The maximum daily infusion dose for adults is 12 g.<sup>5</sup> In the military setting, troops are given kits containing autoinjectors of atropine and pralidoxime chloride that can be administered IM in case of nerve agent exposure. At the same time, muscarinic effects should still be controlled with atropine.

## Summary

The possibility of encountering a person who has been exposed to a nerve agent is a reality today. The outcome of that patient depends on the responder's quick recognition of the signs and symptoms of nerve agent poisoning and the swift implementation of the appropriate drug therapy. Initial steps are aimed at decontamination of the patient and basic principles of life support using the ABC (airway, breathing, and circulation).

Pralidoxime should be given as soon as it is available if the patient has the appropriate symptoms to suggest nerve agent toxicity; it should be given regardless of whether the

patient has a confirmed exposure to a nerve agent. Atropine should be titrated to the patient's individual symptoms and should be given until secretions have dried and breathing is easier. Seizures should be managed with a benzodiazepine such as diazepam. The rest of the treatment is directed at stabilization of the patient's vital signs and giving ventilatory support as needed.

As anesthesia providers, we are very familiar with airway management and understand the complexities of the autonomic nervous system. Having the knowledge to recognize and treat nerve agent toxicity incorporates existing knowledge of these 2 body systems and can only enhance the anesthetist's skills as an anesthesia provider and first responder.

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