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## **Sarin Nerve Gas: A Rationale for Vigilance amidst War and Peace**

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## Background

Today more than ever, the world remains vulnerable to the deliberate use of chemical agents as weapons of mass destruction. The World Health Organization (WHO) and other international organizations have already made efforts to upgrade preparedness for chemical incidents, such as industrial and domestic accidents.<sup>1</sup> However, many existing emergency preparedness plans have not been developed for response to terrorist attacks. The challenge remains to identify and implement the additional actions needed to allow relevant international organizations to fulfill their public health role in relation to the deliberate use of chemical agents to cause harm.

Chemical warfare has existed for millennia. As far back as 1000 BC, the Chinese used arsenical smoke as a weapon.<sup>2</sup> In the last century, chemical agents have been used in warfare on numerous occasions, from World War I to the Iran-Iraq conflict. While many military physicians routinely receive training in the management of chemical and environmental catastrophes, such training has not been widely disseminated to civilians until recently.<sup>3</sup>

Chemical attacks can be delivered with almost any type of conventional ballistic weapon, spray device, or by nontraditional means.<sup>3</sup> Such nontraditional means were used by the Aum Shinrikyo religious cult to launch two attacks in public places in Japan using sarin gas.<sup>1</sup> The first attack occurred in Matsumoto, Japan in June 1994.<sup>4</sup> The second attack occurred in a Tokyo subway in March 1995.<sup>5</sup> In the Tokyo attack, terrorists carried diluted sarin solution in plastic bags into subway trains and simultaneously punctured the bags with sharpened umbrella tips. This released diluted sarin vapor into

three convergent lines of the Tokyo subway system.<sup>6</sup> To date, the Tokyo subway sarin attack is the largest disaster caused by nerve gas in peacetime history.<sup>5</sup> These attacks revealed how an ill-prepared disaster management system can be overwhelmed by the chaos and confusion following such an event.

Sarin is a highly toxic nerve agent which can be fatal within minutes to hours.<sup>7</sup> It was first synthesized in Germany in 1937 as an insecticide, although its battlefield potential was soon recognized.<sup>8</sup> During World War II, Germany prepared thousands of tons of the potent nerve agents tabun and sarin but refrained from using them. Sarin's first use in war did not occur until the Iran-Iraq conflict in the 1980s.<sup>9</sup>

### **Sarin Toxicology**

Sarin (*o*-isopropyl methylphosphonofluoridate) is a high potency organophosphate ester. It is a clear, colorless liquid that is highly volatile. Thus, sarin presents both a liquid and vapor hazard. In the liquid state it can rapidly penetrate skin as well as clothing. In the vapor state it can rapidly penetrate the mucous membranes of the eye or be inhaled into the lungs, whereupon it is rapidly absorbed.<sup>7</sup>

### **Mechanisms of Acute Toxicity**

The principal mechanism of toxicity after sarin exposure is through inhibition of acetylcholinesterase (AChE) and a consequent rise in acetylcholine, leading to hyperstimulation at cholinergic synapses.<sup>10 11</sup> These effects are dose related.<sup>12</sup>

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.<sup>13</sup> 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.<sup>14</sup> Several compounds can remove sarin from AChE if administered prior to aging. The most important group of compounds is the oximes.<sup>15</sup> 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 acute cholinergic syndrome.<sup>16</sup>

Sarin may also exert its effects through cholinergic mechanisms unrelated to AChE inhibition. New research suggests that sarin may act as a muscarinic receptor antagonist inhibiting the release of GABA.<sup>17 18</sup> It is reasonable to consider that reductions in levels of GABA, an inhibitory neurotransmitter, may contribute to the convulsive properties of sarin.

### **Exposure Variables and Toxicokinetics**

Nerve agents such as sarin pose both a liquid and vapor hazard. Vapors heavier than air and tend to sink into basements and other low-lying areas. This likely played a factor in the Tokyo subway attack. The potential number of injuries and deaths from a

sarin attack is determined by whether it occurs in an indoor or outdoor setting, and by environmental conditions such as wind, humidity, rainfall, and temperature.<sup>15</sup>

Nerve agents rapidly penetrate clothing, skin and mucous membranes. They can be absorbed through inhalation, ingestion, or dermal contact. Following dermal contact, symptoms can be delayed up to 18 hours; however, inhalation symptoms can occur within seconds.<sup>3 19</sup>

Sarin is absorbed rapidly and 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.<sup>14</sup> Systemic effects occur as a result of absorption of sarin into the circulation from the respiratory tract, gastrointestinal tract, or the skin.<sup>20</sup> The fate of sarin in the blood plays a major role in determining how much sarin reaches the central nervous system (CNS) and other sites. Once in the blood, sarin interacts with several types of esterases. Some of these esterases hydrolyze sarin to inactive metabolites, while others irreversibly bind to sarin.<sup>20 21</sup> The latter class of esterase is often described as a "false target" because it in effect sequesters sarin in the blood, preventing some or all from reaching the CNS.<sup>11</sup> High doses of sarin can overwhelm these "false targets". Acute cholinergic syndrome occurs when red blood cell (RBC) AChE is inhibited by 75-80 percent.<sup>14</sup>

In animal models, radiolabeled sarin administered intravenously was distributed to the brain, lungs, heart, diaphragm, kidneys, liver, and plasma within 1 minute. Within 15 minutes, sarin concentrations declined by 85 percent. A major sarin metabolite, isopropyl methylphosphonic acid (IMPA), was detectable within the first minute.<sup>22</sup> In animal models, the kidneys are the major route of elimination of sarin or its metabolites.

<sup>22</sup> The distribution, metabolism, and elimination of sarin in humans appear to be similar to that found in animal models. IMPA was detected in the urine of human victims of the terrorist attack on the Tokyo subway system. Peak levels of IMPA was found in the urine of victims 10-18 hours after exposure. The levels of IMPA in the urine correlated with clinical symptoms. The distribution of sarin to the human brain had occurred in 4 of the 12 people who died after exposure.<sup>23</sup>

### **Acute Clinical Manifestations and Diagnosis**

The acute health effects to sarin exposure are dependent on dose. Exposure to high doses of sarin produces acute cholinergic syndrome featuring a variety of signs and symptoms affecting the peripheral and central nervous systems.<sup>24</sup> Peripheral effects may be categorized as either muscarinic or nicotinic, depending on the type of receptor stimulated by acetylcholine. Muscarinic signs and symptoms include pinpoint pupils (one of the earliest signs of sarin exposure<sup>24</sup>), blurring of vision, frontal headache, rhinorrhea, dyspnea, nausea, vomiting, diaphoresis, increased salivation, and urinary frequency.<sup>24</sup> Nicotinic signs and symptoms include fatigue, weakness, and flaccid paralysis.<sup>24</sup> Central nervous system involvement causes depression of respiratory and circulatory centers leading to cyanosis and hypotension.<sup>24</sup> If the dose is sufficient, death results after convulsions and respiratory failure.<sup>20</sup>

Because the actual doses to 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 acute cholinergic syndrome is

present. An intermediate-level exposure may be presumed to have occurred when signs and symptoms are limited to miosis, rhinorrhea, and depressed blood cholinesterase levels. Low-level exposure may be presumed to have occurred even when there are no cholinergic signs and symptoms when a well-documented history of exposure exists.<sup>9</sup>

Patients who survive exposure to nerve agents may experience eye problems, easy fatigability, headaches, and psychological symptoms for months afterwards.<sup>5</sup>

As previously mentioned, sarin is an organophosphorous cholinesterase inhibitor. It can inhibit AChE on the red cell, butyrylcholinesterase in the plasma, and AChE at cholinergic receptor sites in tissue.<sup>3</sup> These three enzymes are not the same. The most reliable parameter for monitoring the biological effects of acute exposure to sarin is the erythrocyte AChE activity.<sup>25</sup>

Although the erythrocyte AChE activity is considered a reliable parameter for monitoring the biological effects of nerve agents, a study of 80 patients treated for sarin exposure on the day of the 1995 Tokyo terrorist attack concluded that miosis is a more sensitive index of exposure to sarin vapor than erythrocyte AChE. The same study also found that systemic poisoning is less likely to develop if the patient's pupil size is normal on arrival at the hospital.<sup>25</sup>

As with any trauma situation, treatment for sarin toxicity begins with assessment of airway, breathing, and circulation. Victims should be separated from the exposure source and decontaminated. Clothing should be removed from the victim. The eyes should be flushed with water for 10 minutes. The victim's skin should be washed with soap and water or 0.5% sodium hypochlorite solution (bleach and isotonic sodium chloride solution).<sup>3 15 19 24 26 27</sup>



Antidotes for sarin and other nerve agent poisoning are atropine sulfate and pralidoxime chloride. The initial dose of atropine sulfate is 2 to 6 mg intramuscularly, depending on the severity of exposure, followed by 2 mg intramuscularly every 5 to 10 minutes until dyspnea or secretions are minimized. pralidoxime chloride is an oxime that acts as an AChE reactivator that binds the nerve agent and removes it from the enzyme. The initial dose is 600 to 1800 mg intramuscularly, depending on exposure severity. A benzodiazepine such as diazepam may be used as an adjunct to control convulsions.<sup>3 15 19 26</sup>

### **Historical and Public Health Perspective**

The Tokyo subway sarin attack was a wake-up call to the world. Prior to this attack, there had never been such a large-scale disaster caused by nerve gas in peacetime history. Initially the media reported that approximately 5500 subway passengers had been injured; however, a U.S. team that went to Japan shortly after the attack found that less than 1000 passengers were actually injured. 12 passengers died as a consequence of the attack.<sup>28</sup> To quote Fred Sidell of the U.S. Army Medical Research Institute for Chemical Defense, "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."<sup>29</sup> 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 uncovered in the aftermath of the Tokyo sarin attack. St. Luke's Hospital had 3 entrances and had not set up a definite plan for the guidance of mass casualties. Victims, their families, television crews, and onlookers streamed into the hospital from all 3 entrances creating a chaotic situation on the inside. In the chaos, many medical records were lost.<sup>5</sup>

Many hospital staff were secondarily exposed to sarin for several reasons. First, the cause of the victim's illnesses was not known until some 3 hours after the sarin had been released. Second, although the hospital staff wore gloves and masks, they had no access to chemical-resistant personal protective equipment (PPE). Third, ventilation was poor in some patient treatment areas. Finally, hospitals lacked decontamination facilities.<sup>5</sup>

Antidote availability was crucial for the treatment of victims. St. Luke's Hospital alone used up 700 ampules of pralidoxime chloride and 2,800 ampules of atropine sulfate. The hospital depleted its original stockpile of antidote and had to airlift in additional supplies.<sup>5</sup>

The lack of an efficient chemical disaster information network posed a significant communication problem.

After reviewing the disaster management problems, St. Luke's Hospital arrived at the following conclusions. Each hospital should have a decontamination area and have chemical PPE available. Ventilation in the ER and main treatment areas should be well designed. Hospital disaster planning should include an efficient emergency medical chart system and an emergency staff call-up system.<sup>5</sup> The development of a legal basis for the concentration of authority during major disasters was also recommended.<sup>30</sup>

## Conclusion

Sarin and other chemical agents remain a threat in today's altered political climate because they are relatively simply to produce, transport, and deploy. They leave affected persons at risk for long-term effects.<sup>15</sup> Sarin is a highly toxic nerve agent, and bears the notorious reputation of being the agent used in the largest nerve gas terrorist attack in peacetime history. Sarin's principle mechanism of toxicity leads to hyperstimulation at cholinergic synapses.

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 PPE, ventilation, and decontamination facilities to prevent secondary exposure to medical staff. Hospital and community organizations must coordinate disaster drills and disaster management planning.

On a national and international level, every effort must be made to prevent the deliberate use of chemical agents. Primary prevention through relevant treaties banning development, production, stockpiling, and transfer of chemical weapons should be implemented.

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Very respectfully,

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