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A Systematic Review on Nerve Chemical Warfare Agents

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Abstract: ***The recent poisoning of Russian opposition figure and critic Alexei Navalny on August 20th, 2020 with a Soviet-era Novichok nerve agent reminded the world of the use of chemical agents, especially nerve agents to eliminate individual targets or for mass destruction. Nerve agents are a class of organophosphorus compounds. Soman, Sarin, Tabun, Cyclosarin, VX are a few examples of nerve agents. Nerve agents affect a person by disrupting the mechanism by which nerve signals are passed in the body. They inhibit the action of acetylcholinesterase enzyme which is responsible for the breakdown of acetylcholine neurotransmitters leading to accumulation of acetylcholine in the body. Nerve agents have a range of chemical effects on the eye, gastro-intestinal (GI) tract, Central nervous system (CNS), Respiratory system, Cardiovascular system and Neurological system. The management of nerve agent poisoning is done by administering Atropine or Pralidoxime chloride or also by administering anticonvulsants like Benzodiazepines or Diazepam. This review presents all such detailed information on this class of chemical Warfare agents.***

Keywords: Chemical Warfare Weapon, Nerve Agents, Acetylcholinesterase, Toxicity, Instrumentation

I. INTRODUCTION

The Sarin gas attack of August 2013 in Damascus which killed more than 1400 civilians is one among many examples of use of chemical agents for mass destruction [1]. Nerve agents are one such chemical agent which are used for mass destruction purposes. Nerve agents are organophosphorus compounds that affect the nervous system when present in the body. Tabun, the first nerve agent was discovered by German scientist Dr. Gerard Schrader in the 1930s [2]. Nerve agents include Tabun, Sarin, Soman, GF and VX. Tabun, Sarin, Soman are also called G-Agents [3]. Nerve agents affect a person by inhibiting the action of acetylcholinesterase enzymes responsible for breakdown of acetylcholine neurotransmitters.

This leads to the accumulation of acetylcholine in the body and excess stimulation of muscarinic and nicotinic receptors in the body [4,5].

The most common clinical findings of nerve agent poisoning are Miosis (constriction of pupil) and Rhinorrhea (runny nose). Other signs of nerve agent poisoning are hypertension, tremors, respiratory distress, status epilepticus (long lasting seizures) and death [2]. Excess acetylcholine in synapses causes the release of Glutamate which further sustains Status epilepticus.

A. Chemical Properties

Nerve agents are colorless, tasteless and liquid at room temperature. G-agents are more volatile than V-agents which accounts for their higher vapor hazard when present in air. Nerve agents can be mixed with water or other solvents for dispersion [3,6]. The vapour pressure of a nerve agent determines its volatility, higher the vapour pressure implies higher is the volatility. Sarin is considered as the most volatile nerve agent (22,000 mg/m^3) [5]. The less volatile a nerve agent is, the more persistent it is in the environment i.e., greater ability of the nerve agent to remain active in the environment [2].

B. Toxicokinetics

Nerve agents that are dispersed in vapour form enter the body through the respiratory tract and nerve agents that are dispersed in liquid form enter the body by absorption through skin. Small doses of the nerve agents cause localized effects like irritation, sweating etc. Large doses of the nerve agents cause systemic effects affecting major systems in the body like cardiovascular system or neurological system [3]. Toxicokinetic of a nerve agent also depends upon latency of the nerve agent i.e. the time delay between the exposure and the start of symptom [2].

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C. Toxicity

Toxicity of a nerve agent is expressed in the form of two terms: LC_{50} (Lethal Concentration 50%) and LD_{50} (Lethal Dose 50%). LC_{50} expresses vapour toxicity, and it denotes the quantity of the nerve agent that is required to show lethal effect in 50% of the exposed population [2,3]. It is expressed in mg-min/m^3. Tabun is found to have the highest LC_{50} value of 400mg-min/m^3. LD_{50} expresses liquid toxicity, and it denotes the quantity of nerve agent that is required to show lethal effect in 50% of the exposed population [3]. Sarin is found to have the highest LD_{50} value of 1700 mg.

D. Toxicodynamics

Nerve agents inhibit the acetylcholinesterase enzyme that is responsible for breakdown of acetylcholine neurotransmitter into acetic acid and choline [6]. The inhibition of that enzyme causes excessive accumulation of acetylcholine neurotransmitters in the body which causes the occurrence of various clinical effects. There are two types of acetylcholine receptors in the body: Muscarinic and Nicotinic [8].

The excessive stimulation of these receptors causes the onset of clinical symptoms and if left untreated may lead to death. Acetylcholinesterase enzyme is inhibited by a reaction between the enzyme and the nerve agent. The enzyme reacts with nerve agent by cleaving a portion of the nerve agent and forming a covalent bond which leads to inactivation of the enzyme. This is called *Aging* or *Maturation.*

Aging is an irreversible process, and the action of the enzyme can be restored only by synthesis of a new enzyme [9]. The aging time varies with different nerve agents. Soman has an aging time of 2 minutes, Sarin has an aging time of 3-4 hours, VX has an aging time of upto 24 hours. Aging can be reversed by administering an oxime (example: Pralidoxime chloride). But administering an oxime is of no use when aging has already occurred [10]. Routes of exposure include inhalation of vapour (vapour exposure) or absorption of droplets on skin (dermal exposure). Clinical effects vary with routes of exposure. The symptoms of vapour exposure include shortness of breath, nausea, vomiting etc. The symptoms of dermal exposure include fasciculations (muscle twitch), vomiting, urination, seizures etc. [2]

E. Clinical Effects

Nerve agent poisoning causes a range of clinical effects in the body. Most of the clinical effects are due to accumulation of acetylcholine neurotransmitters in neural junctions. Clinical effects depend on the mode of administration and the dosage. A vapour exposure to a nerve agent initially affects eyes, nose and airway whereas a liquid exposure to a nerve agent initially affects gastrointestinal tract. The mismanagement of the initial effects causes severity, eventually leading to death [3].

1) *Eye:* One of the early symptoms of nerve agent poisoning is Miosis (excessive constriction of pupil). The onset of miosis is rapid when poisoning occurs due to vapour exposure, and it's delayed when caused due to dermal exposure. Administration of Atropine relieves miosis [11].
2) *Respiratory system:* Nerve agents affect the Autonomic nervous system of the body which controls involuntary systems like respiratory system, cardiovascular system etc. Symptoms of the respiratory system include bronchoconstriction, airway resistance, apnea (halting of breathing) and rhinorrhea [2].
3) *Gastrointestinal tract:* The continuous stimulation of muscarinic receptors in the GI tract causes gastrointestinal hyperactivity, decreased water reabsorption, relaxation of anal sphincter causing uncontrolled defecation, diarrhea, vomiting and nausea [12].
4) *Cardiovascular system:* The symptoms of cardiovascular system include repetitive episodes of Tachycardia (abnormally increased heartbeat) and Bradycardia (abnormally decreased heartbeat). A higher dose also causes ventricular dysrhythmias followed by respiratory failure [2].
5) *Central Nervous System (CNS):* CNS is the most affected system of the body. Symptoms of CNS include loss of consciousness, seizures, tremors, headache, drowsiness, lack of concentration etc [12].
6) *Glands:* Symptoms of the various glands in the body due to nerve agent exposure include excessive stimulation of lacrimal glands, salivary glands, gastric cells and pancreatic secretion leading to excess salivation and gastric secretions [2].
7) *Musculoskeletal:* Initial manifestation of a nerve agent is similar to Succinylcholine chloride (neuromuscular blockade). Initial symptoms include cramps, weakness which when stimulated by higher dose of nerve agent causes muscle twitch and paralysis [13].

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MODERATE EXPOSURE	LETHAL EXPOSURE
HEAD: confusion, drowsiness and headache *EYES:* watery eyes, eye pain, blurry vision, small/pinpoint pupils *MOUTH AND NOSE:* cough, drooling, runny nose *CARDIOVASCULAR:* abnormal blood pressure and heart rate, weakness *LUNGS:* rapid breathing, chest tightness *DIGESTION:* nausea, vomiting, abdominal pain, increased urination, diarrhea *SKIN:* Excessive sweating, muscle twitching at the site of contact	*CONVULSIONS:* nerve agents trigger muscles into overdrive as they reach the nerves connected to them. *LOSS OF CONSCIOUSNESS:* muscles that control breathing can be affected, causing the brain to be starved of oxygen. *BREATHING FAILURE:* if a person breathes in roughly a rice grain worth of VX (the most toxic nerve agent on Earth), it can be enough to kill. *PARALYSIS:* by interfering with enzymes that help muscles relax, the body can freeze up. *DEATH:* lethal exposure to nerve agents if left untreated, typically kills in 20-30minutes.

Table I: What Nerve agent does to the body [14]

F. Treatment

Two main treatment procedures are followed to treat nerve agent exposure: Atropine and Pralidoxime. *Atropine* is an anticholinergic agent i.e., acts by inhibiting the action of acetylcholine. The dosage of administration depends on the lethality of symptoms and exposure dose of the nerve agent. Administration of *Pralidoxime* is helpful as it helps in reactivation of acetylcholinesterase enzymes. But administration of Pralidoxime is helpful only when aging of the enzyme has not occurred [2,13]. Administration of *Mark-I kit* consisting of 2mg atropine autoinjector and 600mg pralidoxime autoinjector is also a treatment for nerve agent poisoning.

Administration of anticonvulsants like Diazepam and Benzodiazepines is also found to reduce seizures and the lethality of other symptoms followed by nerve agent exposure. Administration of Pyridostigmine is also effective as it prevents the breakdown of acetylcholine in body [3].

G. Laboratory Findings

Nerve agents inhibit the action of acetylcholinesterase enzyme thereby leading to accumulation of acetylcholine neurotransmitters. A sample of blood is tested for the estimation of the activity of the enzyme. Erythrocytes are more sensitive for exposure to nerve agents than plasma enzyme activity. A lowered erythrocyte enzyme activity may be an active sign of nerve agent exposure along with symptoms like miosis and rhinorrhea. However, a normal or near to normal enzyme activity may indicate the presence of moderate symptoms in other organs [15].

Technical progress in terms of analytical identification methods have been highly achieved in verification analysis [16]. Few examples from sophisticated published work are mentioned there forth. In the latest advancements, Qian and Wengi in their independent works described Colorimetric and Fluorescent Sensor based methods for identification of various nerve agents [17,18]. Modern instruments [19] can be used to directly detect the Hydrolysis products of nerve agents from body fluids after negative electrospray ionization (ESI) using LC-MS [20,21,22]. Van der Meer et al. quantified IMPA (hydrolysis product of Sarin) from serum samples in Japanese victims of the 1995 Tokyo-GB attack using GC-TOF-MS [23].

H. International Legislation

The use of chemical warfare agents like nerve agents poses emerging threats in the currently evolving geopolitical events. Although there are many international legislations governing the use of nuclear weapons, there is only one such legislation internationally governing the use of chemical weapons for mass destruction. Chemical Weapons Convention (CWC) was signed on January 13th, 1993 and came into force on April 29th,1997. 193 countries have signed the treaty as of 2021. CWC prohibits the manufacture, purchase, possession, movement, stockpiling or any sort of usage of chemical weapons [24].

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I. Case Studies

1) *The Alexei Navalny poisoning case:* Alexei Navalny, a critic of Vladimir Putin and an anti-corruption activist, fell ill during his flight on August 20th, 2020 from Tomsk to Moscow. In a few hours Alexie's condition worsened and he fell into a coma. Since he was an open critic of the president, suspicions arose that the SVR was involved. He was airlifted to Berlin for further treatment on August 24th, 2020. Upon examination, the doctors reported that he was poisoned by *Antipsychotics* and *Neuroleptics* and found Industrial chemicals such as *2-ethylhexyl diphenyl phosphate* in his system. CCTV footage showed that before boarding the flight from Tomsk to Moscow, Alexie was seen drinking tea at the airport. Critics of the Russian government, majority of intelligence agencies, journalists and experts suggest that Alexei Navalny was poisoned and the tea at the Tomsk airport cafe was contaminated by a nerve agent belonging to the novichok family and speculate involvement of the SVR and the government [25].
2) *The Attack on former soviet spy in England in 2018:* Long after the dissolution of the Soviet Union, on March 4th, 2018 in Salisbury, England, a 66 year old man and a 33 year old woman were seen to have fallen unconscious at a diner, their mouths were filled with froth and pupils were constricted. The man was Sergei, a former soviet spy and a double agent working for the British intelligence, and the woman was his daughter Yulia Skripal. They both defected to the United Kingdom on March 3rd, 2018. The next day when they were at a restaurant, they were poisoned. The investigation concluded by stating that the poison used to attack Sergei was a rare military grade nerve agent from the *novichok family* and was in a liquid form. The Russian intelligence agents had used a perfume bottle to carry this nerve agent and had applied it onto Sergei's front door handle, where both the daughter and the father were exposed to the poison [26].
3) *Usage of nerve agents in the Syrian war:* On April 4th, 2017, the town of Khan Shaykum in Idlib, Syria, was attacked by Syrian-Arab Air force, where chemical substances such as *Sarin* and similar compounds were released which resulted in the death of 89 civilians and injured 541 civilians [27].

II. CONCLUSION

Nerve agents are organophosphorus compounds that affect a person by inhibiting the action of acetylcholinesterase enzymes. The blocking of the enzyme leads to accumulation of acetylcholine neurotransmitters in the neural junctions, causing excessive stimulation of muscarinic and nicotinic receptors. Nerve agent poisoning includes a wide range of symptoms affecting the neurological system, respiratory system, cardiovascular system, gastrointestinal tract, eyes and glands. A severe exposure and lack of timely medical intervention leads to the death of the person. The toxicity of a nerve agent is expressed in terms of LD_{50} and LC_{50}. The treatment for nerve agent poisoning includes administration of atropine, pralidoxime chloride or anticonvulsants like diazepam, benzodiazepines. A lowered erythrocyte acetylcholinesterase enzyme activity may be used for diagnostic purposes, although treatment should be started immediately in suspected cases of nerve agent poisoning. CWC is an international legislation restricting the development and use of chemical warfare agents. Medical personnel should be efficiently prepped up for handling any chemical agent outbreak as it forms an important step in lowering the number of casualties caused by chemical warfare agents in the future.

III. ABBREVIATIONS

1) *CWC:* Chemical Weapons Convention
2) *GC-TOF-MS:* Gas Chromatography- Time of flight- Mass Spectrometry
3) *IMPA:* Isopropyl Methyl Phosphonic Acid
4) *LC:* Lethal Concentration
5) *LC-MS:* Liquid Chromatography-Mass Spectrometry
6) *LD:* Lethal Dose

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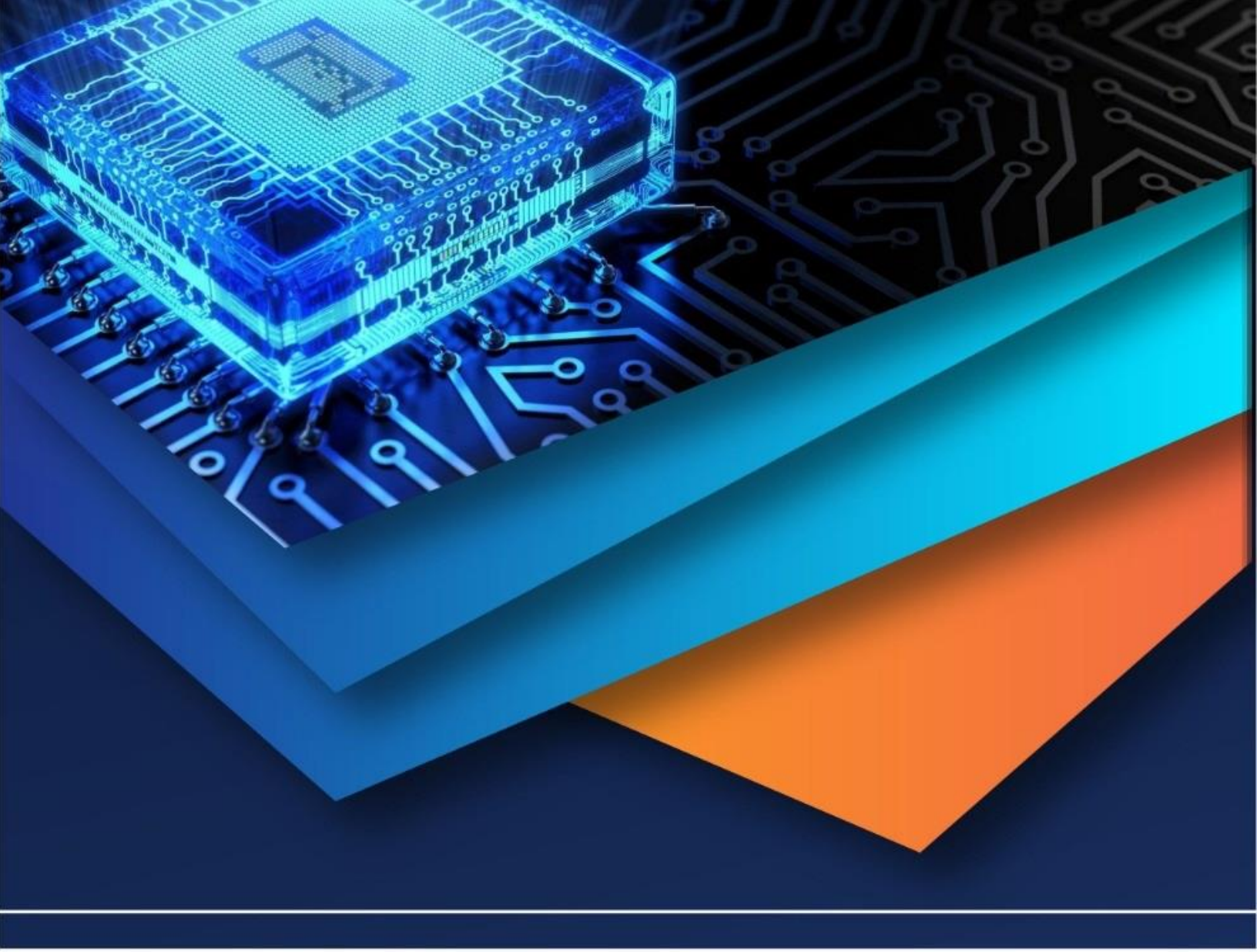

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