Review Article

Novichok Toxicology: A Review Study

Florica Voiţă-Mekereş[1], Cristian Delcea[2*], Camelia Liana Buhaş[1], Veronica Ciocan[3,4]

[1]Department of Morphological Discipline, Faculty of Medicine and Pharmacy, University of Oradea, 410087 Oradea, Romania. [2]Department of Forensic Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, 400000 Cluj-Napoca, Romania. [3]Department of Forensic Medicine, University of Medicine and Pharmacy "Victor Babes" Timisoara, Romania. [4]Institute of Forensic Medicine, Timisoara, Romania.

Abstract

One of the most important types of chemical weapons is nerve agents. In recent years, a group of the newest, most unknown, and at the same time the most common nerve agents known as Novichok has been used in terrorist attacks. It is necessary to become more familiar with the basic and clinical chemical and pharmacologic features of this group of nerve agents for all the employees of the medical group. In this article, while reviewing the history of development and production, chemical structure, mechanism of action, toxicokinetic, and toxicology of these agents, the latest information regarding the methods of diagnosis and treatment of poisoning with these agents was also reviewed. Contrary to early information, it appears that Novichok poisoning is similar to other organophosphate agents and can be managed with prompt and appropriate treatment. Considering the existence of global threats in the field of terrorist incidents with these agents, the medical team must be familiar with these poisons to diagnose and treat the victims optimally.

Keywords: Toxicology, Novichok, Nerve agents, Toxicokinetic

Introduction

Chemical weapons (Chemical weapons) or chemical warfare agents (Chemical Warfare Agents) refers to any type of weapon that is designed and used intentionally to cause injury, disability, or death based on the toxic properties of chemical agents [1-3]. These weapons, due to the ability to cause damage and killing in a high amount along with biological, radiation, and nuclear weapons (Radologic and Nuclear weapons) as weapons Weapons of Mass Destruction; WMD) are classified [1, 4, 5]. Chemical weapons can be classified based on various criteria such as chemical structure, physical state, degree of toxicity, toxic effects, and target organs. Commonly, chemical weapons are divided into different types such as Nerve Agents, Vesicants or Blistering Agents, Chemical Asphyxiants, Pulmonary Irritants, Tearing Agents or Riot Control Agents, and Incapacitating Agents [6, 7].

One of the most important types of chemical weapons is nerve agents. In terms of their chemical structure, these agents are among phosphorous organic compounds or organophosphates, which are considered one of the strongest and most toxic chemical weapons by inhibiting the acetylcholinesterase enzyme. Nerve agents such as Tabun and Sarin were used as chemical weapons in the history of wars, including the Iran-Iraq War (1359-67), and other types of these agents, Sarin and VX, have been used in terrorist attacks in some countries. In recent years, a group of the newest, most unknown, and at the same time most toxic nerve agents called Novichok has been used in terrorist attacks [2-9]. It is necessary to become more familiar with the basic and clinical chemical and toxicological properties of this class of nerve agents for all medical professionals, especially those specialists who are involved in responding to chemical terrorism incidents, diagnosing and managing the treatment of poisoned people, and investigating and confirming the cause. Poisoning and death caused by incidents of chemical terrorism are involved, including emergency medicine specialists, clinical toxicology, forensic medicine, and forensic toxicology, it seems necessary [7-11].

The purpose of this article is to review the toxicological aspects of Novichok, including its history, chemical structure, physicochemical properties, mechanism of action, toxicokinetic toxicity, clinical signs and symptoms, diagnosis, and review of the latest treatment of poisoning.

History

Before the start of World War II in Germany in 1934, to make new industrial insecticides, a project was started at the Farben Chemical Industries Company under the supervision of the

Address for correspondence: Cristian Delcea, Department of Forensic Medicine, "Iuliu Hațieganu" University of Medicine and Pharmacy, 400000 Cluj-Napoca, Romania. cristian.delcea.cj@gmail.com

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German chemist, Dr. Gerhard Schreider [12-15]. In 1936, Schrader's research group started systematic research for the synthesis of new insecticides based on chemical compounds from the organophosphorus category and was able to synthesize more than 2000 chemicals with an organophosphorus structure by the end of this project in about 10 years [15, 16]. In 1936, for the first time, the Germans succeeded in synthesizing the first highly toxic substance from the organophosphate group called Tabun (Tabun, GA). In 1939, the second substance of this chemical group called Sarin (Sarin, GB) was synthesized, which was 10 times more toxic than tabon.

Until the early 1950s, most chemical weapons were considered unitary. This means that ammunition (bombs, bullets, cannons, mortars, and grenades) was directly filled with a toxic chemical agent and stored and kept in the same way until use. The existing problems related to the possibility of poisoning in the processes of production, storage, and destruction of defective or outdated ammunition and the need for complex and expensive equipment and methods in the destruction process, and on the other hand, the existence of environmental hazards related to the storage of these weapons, cause to reduce the risks of these weapons, research for the production of chemical weapons in the form of a project called the Binary Lethal Weapons System was implemented in the United States [17, 18].

The word Novichok in Russian means newcomer [15-20]. Novichok is not a substance but refers to several two-component chemical agents that are analogs of Class A nerve agents. These substances were known as A-242 (Novichok-5), A-262 (Novichok-7), and Nonname Novichok along with A-234 and Substance-33 as new nerve agents. Novichok is considered the third generation of nerve agents and the fourth generation of chemical weapons (the first generation of chemical weapons is sulfur mustard [15-18]. Providing information about the nature and physicochemical and toxicological properties of Novichok until the end of the Foliant project was prohibited from the 1970s to the early 1990s for approximately 20 years and before the signing of the International Convention on the Prohibition of Chemical Weapons by Russia. In September 1992, after the collapse of the Soviet Union, Will Mirzayanov, an expert in analytical chemistry and a member of the Soviet State Institute of Organic Chemistry and Technology (GosNIIOKAT) and one of the researchers participating in the Foliant project, for the first time in an article that It was published in the Moscow news newspaper and disclosed this project [15, 18, 21]. After the publication of this article, he was arrested for the crime of treason, but a few months later, due to the pressure of public opinion, he was released from prison and immigrated to America. In this way, the Western world became aware of the existence of secret research in the Soviet Union on a new generation of nerve agents with more toxic effects than existing nerve agents. However, many of the physicochemical properties, synthesis methods, toxicity, and military properties of these agents have remained unknown to this day due to the top secrecy of the plan. Most of the available information about Novichok is also based on articles, books, and interviews published by some scientists such as Mirzayanov, Vladimir O. Golf, and Andrey Zheleznyakov, who participated in this project in the past [18, 21]. To understand the unknown dimensions of this category of nerve agents, it should be noted that until 2018 there were no articles related to these agents in the reliable database PubMed, and only after the use of these agents in the terrorist incidents that occurred in 2018 and After that, it happened that these events will be mentioned in the rest of the article. Until the time of writing this review article, only 22 articles related to some of the chemical and toxicological properties of this class of nerve agents have been published in the journals indexed in this database.

The Use of Novichok in Chemical Terrorism

Although Novichok has never been used as a chemical weapon in the history of wars, chemical terrorist attacks in recent years using Novichok as a nerve agent have increased the attention of the international community to this group of agents. The possible use of Novichoks for the chemical assassination of the famous Russian banker, Ivan Kiolidi and his secretary Zara Ismailova in Moscow in 1995 was reported by impregnating his office phone. In this terrorist incident, at the age of 46 (three days after the poisoning), his 35-year-old secretary (one month after the poisoning) died in the hospital due to the use of an unknown agent from the military-grade organophosphorus nerve agents. However, only after Skripal's chemical assassination of his 33-year-old daughter, Yulia, did the world's attention turn to the use of these nerve agents [18-22].

Signs and Symptoms of Poisoning

Considering that Novichok nerve agents are organophosphorus agents and irreversible inhibitors of acetylcholinesterase and other non-specific cholinesterases including butyrylcholinesterase, the signs and symptoms of acute poisoning with these agents are similar to other nerve agents. The severity of clinical manifestations depends on the type of agent, the dosage, and the way the poison enters the body. Signs and symptoms can appear in the body 30 seconds to 2 minutes after consuming poison orally. There are signs and symptoms of cholinergic toxic syndrome in this poisoning [1-3, 14, 23-25]. In case of exposure to small amounts of poison, especially through the respiratory route, the symptoms and signs are mostly in the respiratory system, with a runny nose, nasal congestion, shortness of breath, chest burning, bronchial contraction, and increased airway secretions that cause wheezing and Cough and shortness of breath are accompanied, and depending on the amount of exposure, it may last for several days [14, 26-30]. Constriction in the pupils of the eye (miosis) is the first sign of local poisoning (exposure to the liquid or vapor form of the poison) or systemic poisoning. Pain in the eyeballs or behind it is caused by the strong contraction of the ciliary muscles. Eye pain increases when focusing on near vision or squinting in bright lights. Tears, misalignment, blurred vision, photophobia, eyelid spasms, and conjunctival hyperemia are other eye effects of these factors. Gastrointestinal signs and symptoms after oral consumption include nausea, vomiting, abdominal pain, diarrhea, and incontinence [14, 31-35]. The sequence of occurrence of general clinical manifestations in poisoning with these multiple factors is different depending on the route of entry of the poison. Respiratory signs and symptoms appear first in the case of inhalation of these agents, as well as gastrointestinal manifestations occur more quickly when these agents are taken orally. General toxicity is associated with muscarinic, nicotinic, and central nervous system involvement [14, 36-43].

In severe poisoning, due to the increased effects of acetylcholine on the nicotinic receptors in the neck ganglia, dilated pupils (mydriasis), tachycardia, and increased blood pressure occur. Muscle weakness that worsens with increased activity, twitching, fasciculation, muscle cramps, flaccid paralysis, and vasoconstriction that leads to pale skin are other symptoms of nicotine poisoning with these agents. In severe poisoning, the occurrence of general body muscle weakness with the involvement of respiratory muscles can cause respiratory failure and death [43, 44]. Anxiety, restlessness, emotional instability, insomnia, nightmares, and increased dreams are some of the effects of these toxins on the central nervous system in mild doses. Headache, tremors, drowsiness, impairment of judgment, coordination, recall, memory, and slowing of reactions may occur. Confusion, balance disorder, generalized seizures, lack of reflexes, and Cheye-Stoke coma breathing pattern are other signs and symptoms of poisoning. Death occurs as a result of respiratory arrest due to paralysis of the diaphragm muscles and weakening of the respiratory centers in the brain stem and anoxia, although the weakening of the blood circulation centers in the brain can also cause bradycardia and hypotension [1, 14, 43, 44]. Most of the information about the late and long-term effects of acute Novichok poisoning is based on observations made in limited cases of this type. There is the first report of accidental acute poisoning in Andrei Zheleznyakov, one of the Russian scientists involved in the project to make these agents known as Foliant. In 1987, while working on 5-Novichok, this scientist was exposed to the aerosols of this agent due to a sudden malfunction of the laboratory's chemical hood. He quickly suffers from mydriasis, shortness of breath, drooling and convulsions, bradycardia, respiratory paralysis, shortness of breath, and coma. After being treated and discharged from the hospital, he developed severe movement disorders and memory impairment and died 5 years after poisoning due to advanced liver cirrhosis, epilepsy, and inflammation of the trigeminal nerves [18]. Examining other cases of acute poisoning with Novichok shows the occurrence of a wide range of neurological and psychological complications in the victims. Delayed neurotoxicity has been reported 1-3 weeks after acute poisoning with severe motor and respiratory muscle weakness, and mental and memory disorders in poisoned people [21, 43].

Treatment

The basis of treatment for acute poisoning caused by Novichok, like other organophosphorus compounds, includes emergency treatment measures (maintaining the patient's airways, breathing control, and blood circulation), decontamination, stabilization of the patient, antidote treatment, and other supportive measures. It is a sign [14, 43, 44]. In critically ill patients, it is necessary to admit the patient to a special care unit and perform intubation and mechanical ventilation along with cardiovascular support and monitoring.

Laboratory Diagnosis

Although the treatment should never be delayed due to the impossibility of laboratory diagnosis, nevertheless, the use of various laboratory methods to detect the cause of poisoning, especially in environmental samples (water, soil, and air) or biological samples of the poisoned patient or the deceased help diagnose, confirm, or differentiating poisoning from other poisoning agents or diseases or in determining the cause of death. It should be noted that accurate diagnosis of the type of nerve agent is not possible in all laboratories due to the lack of access to high purity standards and the need to use high-tech analytical devices, and at the same time, it is a time-consuming and expensive process.

The use of simple colorimetric methods to measure the activity of acetylcholinesterase and butyrylcholinesterase enzymes is one of the common methods for detecting exposure or poisoning with inhibitory agents of this enzyme, including organophosphorus compounds, in hospitals. In this method, the patient's blood sample is used to evaluate the level of acetylcholinesterase enzyme activity in red blood cells or plasma butyrylcholinesterase. The Ellman method is commonly used to measure enzyme activity in the blood of patients poisoned with organophosphorus agents, and the amount of inhibition of acetylcholinesterase has a good proportion with the severity of poisoning. It should be noted that in this method, the type of enzyme inhibitor couldn’t be identified [40, 45]. Evaluation of the activity level of other enzymes such as beta-glucuronidase and paraoxonase enzymes is also among the methods of diagnosing organophosphate poisoning in patients [40].

Today, detection tubes are widely used to identify nerve agents (such as Suman, Sarin, VX, and Novichoks) in non-biological and environmental samples such as water, air, and soil. These detectors work based on enzymatic color reactions. These detectors include carriers in the form of pellets on which acetyl or butyrylcholinesterase enzymes are fixed along with substrate and reagent. Among the advantages of these devices are portability, high sensitivity, simplicity of operation, and the ability to be used on all types of weather samples in war zones or terrorist incidents [45-48]. Butyrylcholinesterase enzyme is mostly used in these devices. The immobilization of this enzyme on the carrier plays a very important role in the stability of the results. Recently, Magnesium Aluminometasilicate with high contact surface has been used as a protective layer to prepare pellets in these devices [49]. The most sensitive and accurate methods for identifying and confirming nerve agents, including Novichoks, especially in very small amounts in all kinds of biological samples, such as blood, urine, tissue samples, including liver and lung tissue, and non-biological samples, water, soil, air, clothing, and food samples, using gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-mass spectrometry (LC-MS-MS) methods [50].

Conclusion

Novichoks, as the fourth generation of chemical weapons and at the same time unknown, are considered nerve agents of category A. These agents, like other nerve agents, belong to the group of organophosphorus compounds in terms of chemical structure and are considered non-competitive and irreversible inhibitors of the acetylcholinesterase enzyme. However, the structural differences with other G and V class agents have caused them to estimate more toxicity for these agents compared to other nerve agents of older generations. However, based on the new information obtained from the observation of toxic clinical effects, these compounds seem to be present in the victims of chemical terrorism incidents in recent years, and on the other hand, the data obtained from the computer simulation of the molecules of these agents. Despite the high intrinsic toxicity of these compounds, contrary to the initial information published about these agents, the toxicity of these substances is not greater than other nerve agents such as VX, and in case of rapid and standard treatment measures in acute and severe poisoning with nerve agents including measures Symptomatic and supportive, the use of mechanical ventilation and the administration of standard drugs and antidotes such as atropine, oximes, and benzodiazepines, the treatment management of poisoned people can be done successfully. Therefore, due to the increasing international threat of using these agents in chemical terrorism attacks, it is necessary to familiarize the employees of the medical group with the various aspects of basic and clinical toxicology of these agents.

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