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Education

Novichok: An overview of the world's deadliest nerve agent

EDUCATION

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ABSTRACT

Relevance

The Novichok class of nerve agents are noxious chemical-weaponized organophosphates. Though its use is prohibited under the 1997 Chemical Weapons Convention, the attempted murder of an ex-Russian spy and his daughter has turned a spotlight on one of the world's deadliest poisons.

Summary

Novichok was developed by the Soviet Union in the 1970s and is reportedly ten times more lethal than VX, the nerve agent used to assassinate the half-brother of North Korean leader Kim Jong-un. Novichok produces its toxic effect by irreversibly inhibiting acetylcholinesterase. Unlike other nerve agents, it is thought to target both the central and peripheral nervous systems. Exposure to Novichok invariably leads to death.

Take Home Messages

With an increase in worldwide chemical weapons usage, including recent use in the United Kingdom, clinicians should know how to rapidly recognize symptoms of nerve agent poisoning, lend their expertise in the education and treatment of such attacks and administer life-saving antidotes.

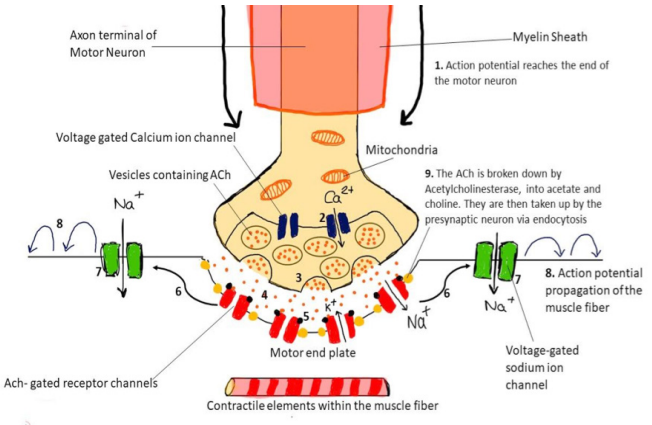
In March 2018, the United Kingdom, along with the rest of the world, were shocked by news of the poisoning of an ex-Russian spy. Less than three months later, paramedics were called to a flat in Amesbury, England, after a local couple were exposed to the very same agent used earlier in the year. (1) Subsequent confirmation that the substance used in these attacks belonged to the Novichok class of nerve agents has turned a spotlight on what are considered amongst the world's deadliest chemical weapons. This article aims to explore Novichok and its effects on the human body, given the high likelihood of future usage of these agents.

The name Novichok means *"newcomer"* in Russian, highlighting the fact that its development marked a breakthrough in chemical weapons. (2) Novichok is a series of organophosphate nerve agents. Nerve agents are organic substances which disrupt the body's normal nervous communication to muscles and organs. (1)

Novichok was developed as part of the Russian classified nerve agent program named FOLIANT over a period of two decades from 1971. (3) It has never been used on the battlefield as its use is forbidden under the terms of the Chemical Weapons Convention of 1993. It is believed that Novichok was developed as the Soviet Union's response to false information that the USA was producing its own nerve agents during the Cold War. (2,4)

The effects of Novichok, like all nerve agents, are due to the blocking of acetylcholinesterase (AChE) which catalyses the breakdown of acetylcholine (ACh). (4) ACh is a neurotransmitter found in vesicles of pre-synaptic neurons at neuromuscular junctions. As an action potential passes down a neuron, the depolarisation causes an influx of calcium ions, triggering exocytosis of ACh from the pre-synaptic neuron and diffusion across the synaptic cleft. ACh then binds onto nicotinic ACh receptors (nAChRs) on the post-synaptic membrane, causing sodium ion channels to open. An influx of sodium ions through the post-synaptic membrane causes depolarisation. The subsequent action potential results in contraction of a muscle or release of a hormone. Once the action has been produced, the enzyme AChE catabolises the neurotransmitter to allow the muscle or organ to relax. (See Figure 1)

Figure 1 - Events at a neuromuscular junction



Novichok is a non-competitive inhibitor of AChE, accounting for its irreversible inactivation. (5) The nerve agent causes a build-up of ACh, preventing further re-depolarisation of the post-synaptic membrane, so that impulse transmission ceases. This results in muscles remaining in their contracted states. Symptoms of poisoning appear within seconds of exposure and death occurs rapidly by asphyxiation or cardiac arrest due to failure of contraction of the diaphragm and heart. Whilst most nerve agents affect the central nervous system exclusively, Novichok also affects the peripheral nervous system, leading to peripheral weakness and paraesthesia. (6)

Exposure to Novichok is generally by inhalation, although absorption may also occur percutaneously. (7) Early symptoms include rhinorrhea, chest tightness, and miosis. Later stages involve involuntary salivation, loss of continence and abdominal pain. This is followed by myoclonic jerks and status epilepticus. (6) If treatment is not initiated timely, death will ensue. Most of the literature on Novichok is based on testimonies from the scientists involved in developing the agent. As it is still a relatively new chemical which few people have been exposed to, our understanding of the symptomology and treatment are limited. Andrei Zheleznyakov, a scientist involved in the Novichok's development, was accidentally exposed to the agent in 1987. He was unconscious for 10 days post-exposure. Zheleznyakov then began to suffer from *"chronic weakness in his arms, a toxic hepatitis that gave rise to cirrhosis of the liver, epilepsy, spells of severe depression, and an inability to read or concentrate that left him totally disabled and unable to work"*. (8) Five years following exposure, Zheleznyakov died.

"Circles appeared before my eyes: red and orange. A ringing in my ears, I caught my breath. And a sense of fear: like something was about to happen. I sat down on a chair and told the guys: it's got me!" – Andrei Zheleznyakov, Russian military researcher after he was exposed to Novichok from a malfunctioning fume hood (1987). (8)

Initial management of Novichok poisoning includes removal of contaminated clothing and contact lenses. This should be followed by thorough rinsing of the skin with soap and water to prevent further exposure. Patients will then require basic life support and oxygen should be administered. (9) The mainstay treatment of Novichok poisoning is with anticholinergic drugs. (5) Atropine, an ACh receptor antagonist, blocks receptors to prevent poisoning.

Other antidotes include pralidoxime and diazepam. Pralidoxime binds to AChE causing the phosphate group of the nerve agent to be displaced. The poison/antidote complex then unbinds from the active site, thus regenerating the fully functional AChE enzyme. (10) It is possible to survive a Novichok attack; however, victims may be left with permanent disabilities such as chronic muscle weakness and reduced cognitive ability.

Since its creation, seven people are known to have been exposed

by Novichok; of which three have died. Today, news of such chemical attacks is rapidly circulated and information about the poison and the risk of exposure can become misconstrued by the public. Therefore, it is increasingly important that clinicians can be called upon to lend their expertise in the education and treatment of attacks caused by dangerous chemical weapons.

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