Nerve agents

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Published in:
Emergency Nurse
Publication date:
2019

Abstract

Recent events in the United Kingdom (UK) and the alleged chemical attacks on the Syrian people by the Bashir Al Assad regime have brought the subject of chemical weapons back into the public domain. To date these events have been relatively rare, as terrorist plans to harm large numbers have been thwarted. This is the first article in a two article series that gives an overview of nerve agents and provides emergency nurses with information about the historical background of nerve agents, their manufacture and how these agents affect normal physiology. The second article will consider the initial treatment that will include effective triage, decontamination and medical management.

Gas! GAS! Quick, boys! — An ecstasy of fumbling,
Fitting the clumsy helmets just in time;
But someone still was yelling out and stumbling,
And flound'ring like a man in fire or lime ...
Dim, through the misty panes and thick green light,
As under a green sea, I saw him drowning.
In all my dreams, before my helpless sight,
He plunges at me, guttering, choking, drowning.
(Wilfred Owen, 1917)

Historical Background

The military recognises that the enemy may attempt to inflict harm through nerve agents. This possibility is registered in armed forces medical philosophy and dates back to stories of chemical weapons delivered through poison arrows stemming back to ancient Greece (Mayor, 2003). World War I witnessed the emergence of killing or maiming the opposition on a massive scale, through novel mechanisms of delivery in mines, mortars, tanks and lethal nerve gas. It was impossible for nurses and clinical staff to prepare for the emerging injuries. Since then, military clinical practitioners prepare for the worst case scenario so that they can respond, both emotionally and with competency, when faced with the most severe and traumatic of cases. If they can cope with the worst scenarios, then everything else should be within the practitioner's scope of practice.

The military mental health (MH) philosophy and doctrine of priming staff to deal with emotionally distressed patients also stems back to World War 1. The ramifications of the introduction of lethal chemical weapons led to widespread shock, panic and public revulsion at the news of slow and painful deaths. Soldiers themselves coined the term Shell Shock (Myers, 1915), although many of those presenting with the symptoms of fatigue, tremor, confusion, nightmares, sight / hearing difficulties and being unable to function had been no-where near the battlefield. It was their thoughts and associated fear of being exposed to gas and the horrendous implications that led to their presentation (Jones, 2002). These anxieties shaped practical training in World War II, (Munro et al, 1990) and the real threat of chemical warfare rose after the 9th November 2011 terrorist attacks in New York (Martin & Lombard, 2003). In contemporary society the response chemical, biological, radiological and nuclear (CBRN) hazards generally relates to either attacks by non-state actors or clandestine organizations to the accidental release of Hazmat material (Calder & Bland, 2018).

In 2018, the audacious attack on former soviet spy Sergei Skirpal and his daughter Yulia in Salisbury, England brought one of the most dangerous nerve agents into the public eye (Brunning, 2018) Prior to this, other than serving members of the military, scientists and our intelligence services, few had heard the name Novichok. The consequences of the Novichok incident in Salisbury on emergency services personnel was clear. It was well documented that a first responder had the symptoms of nerve agent poisoning (Brunning, 2018). The fact that a first responder felt the effects of the nerve agent clearly demonstrated that the substance had a much higher degree of persistency. This was due to the nerve agent being contained within a liquid as a opposed to a gas, which would be less persistent and thus a lower threat of secondary contamination to emergency personnel Calder & Bland, 2018).

Almost 100 Wiltshire police officers and affiliated staff sought psychological support after this nerve agent incident, and continued to do so for months afterwards (Morris, 2018). Their reports of disorientation, anxiety and concern, over the potential long-term health impact on the wider community would have to be acknowledged and addressed in the ED. The group of nerve agents called Novichok was developed by the Russians between 1971 and 1993 and has a total of five variants numbered one to five. All nerve agents are chemically related to organophosphate insecticides that were originally developed to protect crops (Bailey et al, 2014). However, at the

beginning of World War 2 the German military began to develop organophosphate based nerve agents for military purposes (Barthold & Schier, 2005). Following WW2, the nerve agent tabun was used during the Iran – Iraq war with devastating effects (Barthold & Schier, 2005). More recently, a Japanese terrorist group called Aum Shinriko used sarin gas during two attacks of the Tokyo underground which affected 5000 people with 19 fatalities (Brunning, 2018). Whilst many countries have decommissioned their stocks of nerve agents, the recent attack in England proves that nerve agent reserves still exist.

Classification

As previously mentioned nerve agents are organophosphate derivatives of phosphoric acid and are generally divided into the V and G series of agents. However, after March 13th 2018, the general public were made aware of a more dangerous type of nerve agent called Novichok (Brunning 2018). The name Novichok is Russian and means "*newcomer"* and from a chemical perspective is similar to the V series of organophosphate nerve agents that includes VX and the older G series of agents e.g. sarin. Due to the clandestine nature of nerve agent development there is minimal tangible evidence within the public domain and much of what scientists know about Novichok was disclosed by Vil Mirzayanov and Lev Fedorov, both Russian chemical weapons scientist who state that they were involved in the development of Novichok during the early 1970s through to the early 1990s (Brunning, 2018). Although the exact chemical structure of Novichok is uncertain, it is thought that the group of Novichok nerve agents are ten times more potent than VX, which is lethal with just ten milligrams landing on a victims skin (Brunning, 2018). The G type nerve agents were initially developed by the Germans just before and during World War 2. The V agents were developed much later and attract the letter V due to their much higher level of potency at much lower doses (Newmarket, 2004). See table 1 for a list of the know nerve agents. See Diagram 1 for more specific information on Novichok.

Table 1 Nerve Agents

G Nerve Agents	V Nerve Agents	Novichok
Sarin (GB)	VX	Novichok 5
Cyclosarin (GF)	VR	Novichok 7

Soman (GD)		
Tabun (GA)		

Pathophysiology

Exposure to nerve agents is most likely to be via the dermal or inhaled route although ingestion is also possible. Presenting symptoms vary in nature and the rate of onset depends on the dose and characteristics of the causative agent, the exposure route and the pre-morbid health status of the affected individual. Generally, nerve agents and insecticides that are organophosphate based act by altering the effects of the neuro-transmitter acetylcholine (Sidell & Borak, 1992). In the human nervous system, acetylcholine regulates both nicotinic and muscarinic receptors that can be found in the central, sympathetic, parasympathetic nervous systems and in skeletal muscles (Bailey et al, 2014). Normally, neuro-transmission takes place when an action potential is conducted along a neuron to the distal portion of the telodendria called the axonal terminus, where acetylcholine is released (Huether & McCance, 2016). Once released, acetylcholine is then able to cross the neuromuscular junction separating one neuron from another. The net effect of the binding of acetylcholine to the postsynaptic receptor is to produce an action potential that will induce contraction of muscle. Following contraction, acetylcholine detaches from the postsynaptic receptor, hydrolysed and then deactivated by acetylcholinesterase (Sidell & Borak, 1992). Therefore, the consequences of blocking acetylcholinesterase will result in the presence of overpowering amounts of acetylcholine in the synaptic cleft (Bailey et al 2014). Classically, nerve agents will attach themselves at the active site of acetylcholinesterase, thus blocking the deactivating function of acetylcholinesterase on acetylcholine.

Signs and Symptoms

Nerve agents are chemically related to organophosphate insecticides and are among the most toxic and lethal substances known to mankind (Bailey et al. 2014). Therefore early recognition is paramount in order to manage patients safely and effectively and to assure the personal health and safety of healthcare staff (Candiotti 2017).

In the acute post-exposure phase excess acetylcholine accumulation is signalled by the production of copious respiratory and oral secretions, gastrointestinal effects including diarrhoea and vomiting, profuse sweating, autonomic instability and generalised muscle weakness that can progress rapidly leading to paralysis, respiratory arrest and death. Subsequent to the acute cholinergic effects of nerve agent exposure survivors may develop an 'intermediate syndrome' (Bailey et al. 2014). This may result in appreciable ongoing morbidity characterised by cranial nerve and proximal muscle weakness and respiratory failure. This is thought to reflect ongoing, sustained (and sometimes irreversible) acetylcholinerase inhibition at nerve junctions (Abdollahi & Karami-Mohajeri 2012).

Nerve agents affect virtually all body systems (Candiotti 2017). The attributable signs and symptoms can be classified in terms of time of onset, the specific nerve receptor (muscarinic or nicotinic) or major body system affected. For the purpose of this clinically focussed article the latter classification has been adopted and is summarised in Table 1. It should be noted that the presence, ordering and intensity of specific signs and symptoms varies and does not necessarily correlate with the level of nerve agent exposure or predict the anticipated outcome.

Table 2: Toxic Nerve Agent Syndrome: Signs and symptoms attributable to nerve agent exposure from all variants

System	Potential Signs and Symptoms
Central Nervous	Miosis (unilateral or bilateral) Blurred vision Headache Altered consciousness (irritability to coma) Seizures
Respiratory	Rhinorrhoea Bronchorrhea Wheezing, Dyspnoea, Chest tightness Altered respiratory rate and depth: tachypnoea (early), bradypnoea (late)

	Respiratory Arrest
Cardiovascular	Altered Heart Rate: Tachycardia (early), bradycardia (late) Altered Blood Pressure: Hypertension (early), Hypotension (late) Cardiac arrhythmias e.g. prolonged QT on EKG, ventricular tachycardia
Gastrointestinal	Abdominal pain Nausea and vomiting Diarrhoea
Urogenital	Urinary frequency Incontinence
Musculoskeletal	Fasciculations (localised or general) Generalised weakness (may lead to paralysis)
Skin and Mucous Membranes	Profuse perspiration Salivation Runny eyes Conjunctival injection

Implications for Clinical Practice

The existence of large stockpiles of nerve agents, along with the ease of producing new nerve agents, leads experts to believe that further incidents involving nerve agents are inevitable. Most recently, the Novichok attack in Salisbury was targeted and had relatively minimal impact on the general public. However, it is important to recognize that the intent of nerve agents is to create a more widespread impact and disorder. Specifically, in the 1990s, Osama bin Laden planned to smear nerve agents on the handles of cars, and al Qaeda developed a viable distribution device

for a nerve agent to be delivered in the New York subway system (Newmarket, 2004). Emergency Nurses have a vital role to play in reducing the mortality and morbidity of such attacks. Whilst many countries have decommissioned their stocks of nerve agents, the recent attack in England proves that nerve agent reserves still exist. Within this context, emergency nurses must be have a knowledge of the differing nerve agents and how they interact with human physiology and know how to use the existing treatments available. It is also worth noting that emergency nurses should be vigilant for those patients who have an occupational exposure. A history of working with sheep dip, pesticides or insecticides should be noted. This article has considered the historical background, development and classification of nerve agents as well as the potential pathophysiological impacts and presentation in affected individuals. The second article will consider the pre-hospital response that will include effective triage and decontamination and the in-hospital treatment.

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