

Nerve Agents Countermeasures – Where to Go?

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Organophosphorus (OP) acetylcholinesterase (AChE; EC 3.1.1.7) inhibitors are widely utilized in agriculture as pesticides (e.g. chlorpyrifos, parathion, diazinon) and in industry as softening agents, additives or lubricants. They are also used in medicine as ophthalmic agents (echothiophate, isoflurophate) or they were tested for their potential benefit as drugs for Alzheimer's disease (e.g. trichlorfon). Some of most toxic OP inhibitors were developed before and during the World War II as chemical warfare agents and were called Nerve Agents (NA) [1]. Among them, sarin is probably the most known member of this family, because of its misuse by terrorists in Japan (1995). At that time, several kilograms of this agent were spread in Tokyo subway by a Japanese religious cult AumShinrikyo. Although just several kilograms of low purity sarin were released, it resulted in over 5000 poisoned victims and 12 deaths [2]. Soman, tabun, cyclosarin, VX, or nowadays well-discussed Novichoks are other members of this family (Figure 1) [3].

Routes of NA exposure differ depending on their physico-chemical properties (volatile or non-volatile agents). All NA can be absorbed through eyes, respiratory system and skin. The toxic effect comes in less than one minute to several minutes depending on the route of administration and amount of absorbed NA. For example, if the liquid NA is absorbed through the skin, the toxic effect is delayed from minutes to several hours. On the contrary, if respiratory route is affected, immediate signs are developed. Lowered AChE activity in blood is an indicator of either NA intoxication [4].

The effects of NA poisoning are well known and have been extensively described. NA were called according to their mode of action – interaction with nerve system. Toxicity of NA is connected with inhibition of enzyme AChE, which is splitting the neuromediator acetylcholine (ACh) at the synaptic clefts. They covalently bind via phosphorylate or phosphonylate moiety to the serine hydroxyl group at the esteratic part of the enzyme active site. Irreversibly inhibited enzyme is unable to further split ACh, which accumulates in the synaptic cleft and over stimulates receptors that continue to stimulate the affected organ. The clinical effects from NA exposure are caused by excess of ACh (cholinergic crisis). Intoxicated organism could mostly die due to the respiratory failure [5].

The signs, symptoms and the severity of NA poisoning are also depending on the absorbed amount, which entered the body. At muscarinic receptors (parasympathetic effects), they cause constricted pupils (miosis), glandular hypersecretion (salivary, bronchial, lacrimal, bronchoconstriction, vomiting, diarrhoea, urinary and faecal incontinence, bradycardia). At nicotinic receptors (motor and post-ganglionic sympathetic effects) they cause sweating of the skin. On the skeletal muscle, they cause initial defasciculation followed by weakness and flaccid paralysis. At central nervous system, they produce irritability, giddiness, fatigue, emotional lability, lethargy, amnesia, ataxia, fasciculation seizures, coma and central respiratory depression [6].

Recently, multiple approaches are used to counteract deleterious effect of NA. Among them, prophylaxis (e.g. using drugs in advance) is used prior the intoxication by NA. After the intoxication with NA, decontamination of the skin is applied to prevent the NA adsorption into the organism. Subsequently, adequate treatment consisted of anticholinergic drug and AChE reactivator is applied. In the following paragraphs, all three approaches are more thoroughly discussed [7].

Prophylaxis: The term - pharmacological prophylaxis - means medical countermeasures against NA intoxication, which are administered usually several hours before possible exposition to the NA. There are two fundamental prophylactic approaches - firstly, the protection of AChE against its inhibition (currently available antidotes); and secondly, the decrease of the inhibitor concentration in blood (enzyme scavengers, commonly called bioscavengers).

Carbamates (e.g. pyridostigmine and physostigmine), oximes (e.g. asoxime; Transant patch) belong to the first group prophylactics, which protect AChE against its inhibition. Bioscavengers (e.g. butyrylcholinesterase; BChE, paraoxonase, phosphotriesterase) are recently well investigated throughout the world as the most promising prophylactic drug candidates. Moreover, if pharmacological prophylaxis is combined with subsequent medical treatment, the best possible protection against various toxic effects of NA is obtained [8].

Decontamination: Decontamination is the first requirement after contact with any contaminant (in this case NA). Purpose of the decontamination means is to remove the NA from the skin surface and thanks to it to prevent its penetration through the skin. Currently recommended washing solutions are based on surfactants (e.g. Argos,

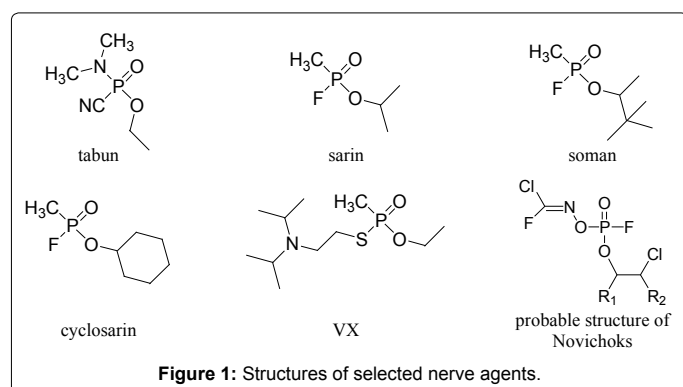


Figure 1: Structures of selected nerve agents.

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Anios). Specific products were developed for decontamination against chemical warfare agents, absorbent powders such as clay (bentonite, IBP-80), activated charcoal (M291) or Fuller's Earth (FE) or a liquid form FDA-approved RSDL (Reactive Skin Decontamination Lotion), which is an aqueous solution containing KBDO as oxime. Active decontamination combining the removal and degradation of toxicant seems to be a promising solution to increase decontamination efficacy [9].

Post exposure treatment: Main drugs used for post-exposure treatment are anticholinergics (functional antidotes) that antagonize the effects of accumulated ACh at the cholinergic synapses. Atropine, which has peripheral action, is the most used anticholinergic drug. If AChE reactivators are not available, atropine alone should be applied. Several new anticholinergics were tested; however, replacement of this compound within post-exposure treatment strategy is currently not realistic. AChE reactivators (called oximes according to the functional oxime group) reactivate AChE inhibited by NA (causal antidotes). Nowadays, there are only five commercially available AChE reactivators (pralidoxime, trimedoxime, obidoxime, methoxime and asoxime) spread across the world for military or civilian use. Unfortunately, none from these oximes is sufficiently effective against all known NA. Effects of anticholinergic drugs and AChE reactivators are synergistic. If anticonvulsants are discussed, diazepam seems to be the most promising drug of the first choice. However, several countries prefer to use its prodrug avizafone due to its better solubility [10].

Although, the development of novel countermeasures against NA begun already shortly after their first synthesis, there is still no universal approach for complex protection of the soldiers and, also civilians in the case of possible terroristic attack. There are lots of limitations in this scientific field. In the following paragraphs, there are listed several severe limitations of recently available countermeasures.

Prophylaxis

Possible toxicity and subsequent side effects of several prophylactic means, if overdosed—due to their narrow therapeutic range (pyridostigmine, physostigmine, etc.) (toxicity of prophylactic means).

High immunoresponse, if exogenic enzyme bioscavengers are applied (low half-life of bioscavengers in the blood).

High cost of bioscavengers (estimated price of such antidote is thousands USD).

Timing of application of appropriate prophylactic means (wrong timing).

Decontamination

The need of the shortest interval between contamination with NA and subsequent decontamination to reach a sufficient decontamination protection (short time for decontamination application).

Relatively corrosive components are used as a part of the decontamination means (wrong selection of decontamination components).

If non-corrosive components with low reactivity are used in decontamination means, there is usually low rate of NA degradation (low rate of NA decomposition).

Post exposure treatment

Every NA is reactivator-specific; it means there is no single AChE reactivator able to counteract every NA-poisonings (no universal oxime exists).

Recently used commercial reactivators are only peripherally acting drugs, thus their blood-brain barrier penetration should be enhanced (low BBB penetration).

Possible toxicity and subsequent side effects of AChE reactivators and consequent limited dosing (e.g. obidoxime- possible hepatotoxicity) (toxicity of reactivators);

For the above-mentioned reasons, research in this field continues throughout the world and novel improved prophylactics, decontamination means and post-exposure drug candidates are designed and tested [11-13].

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