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NERVE AGENTS: A BRIEF REVIEW

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Abstract:

Nerve agents, are organic chemicals that interrupt the cholinergic transmission to organs by irreversible inhibition of enzyme acetylcholinesterase.(1) This leads to the accumulation of neurotransmitter acetylcholine (ACh), which can ultimately lead to fatality. presently employed antidotal therapy, focused on the reactivation of inhibited AChE, include quaternary pyridinium aldoxime reactivators , is limited to the peripheral circulation because it cannot cross the blood brain barrier (BBB) at therapeutic dose levels due to their positive charge. This review mainly focusesd on the chemistry, and effects of nerve agents and illustrates the description regarding their antidotes.

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INTRODUCTION:

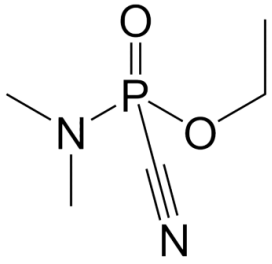
Nerve agents are acetylcholinesterase inhibitors, which possess actions such as constriction of pupils, convulsions, increased salivation, involuntary urination and defecation. Death by asphyxiation or cardiac arrest can occur within minutes owing to the loss of the body's control over respiratory and other muscles depending upon the dose received and the agent used. Some nerve agents are readily vaporized or aerosolized, and the primary portal of entry into the body is the respiratory system[(2)]. Nerve agents can also be absorbed through the skin. This review mainly focusesd on the chemistry of nerve agents and illustrates detailed description regarding their antidotes.

These nerve agents can be classified into four types: (1) the G-series agents which were developed by Germans and include tabun (GA), sarin (GB), soman (GD), and cyclosarin (GF) , (2) V-series agents, where V stands for venomous, include VE, VG, VM, and VX , and Chinese VX and Russian VX [(3)]. (3) GV-series which have the combined properties of both series G and V, for example, GV, 2-dimethylaminoethyl-(dimethylamido)-fluorophosphate [(4)]. Generally, the G-series agents are less toxic compared to the V series[(5)]; (4) Novichok series of compounds, for example, substance-33, A230, A232, A234, Novichok-5, and Novichok-7 [(6)(7)]. Dr. Mirzayanov was first person to detail the development of the first three compounds, namely, substance-33, A230, and A232 at the GosNIIOKhT facility, Russia [(8)].

G-SERIES

TABUN

Tabun is the first of the *G-series* nerve agents along with GB (sarin), GD (soman) and GF (cyclosarin).



The symptoms of exposure include restlessness, rhinorrhea (runny nose), excessive salivation, dyspnea (difficulty in breathing due to bronchoconstriction/secretions), miosis (contraction of the pupil),sweating, loss of consciousness, convulsions, bradycardia(slow heartbeat), flaccid paralysis, apnea (breathing stopped), loss of bladder and bowel control, and lung blisters. The actual symptoms of overexposure are like to those created by all nerve agents. Tabun is toxic even in small doses. The number and harshness of symptoms which appear differ according to the amount of the agent absorbed and rate of entry of it into the body[(9)]. Very little skin dosages sometimes cause local sweating and tremors accompanied with typically constricted pupils with few other effects. Tabun is about partially as toxic as sarin by inhalation, but in very low concentrations it is highly irritating to the eyes than sarin. Tabun also breaks down slowly, which after repetitive exposure can lead to build up in the body.[(10)]

SARIN

Sarin is an extremely toxic synthetic organophosphorus compound[(11)]. A colourless, odourless liquid, it is used as a chemical weapon due to its extreme potency as a nerve agent. Exposure is lethal even at very low concentrations, where fatality can occur within one to ten minutes after direct inhalation of a lethal dose,[(12)] due to suffocation from respiratory paralysis, unless antidotes are quickly administered[(13)]. People who absorb a non-lethal dose and do not receive immediate medical treatment may suffer permanent neurological damage.

Sarin attacks the nervous system by interfering with the degradation of the neurotransmitter acetylcholine at neuromuscular junctions. fatality will usually occur as a result of asphyxia due to the failure to control the muscles involved in breathing.

Primary symptoms follow exposure to sarin are, tightness in the chest, a runny nose and constriction of the pupils. Soon after, the person will have difficulty breathing and they will experience nausea and drooling. As they continue to lose control of bodily functions, they may vomit, defecate, and urinate. This phase is followed by twitching and jerking. Ultimately, the person becomes comatose and suffocates in a series of convulsive spasms. Moreover, common mnemonics for the symptomatology of organophosphate poisoning, including sarin, are the "killer Bs" of bronchorrhea and bronchospasm because they are the leading cause of death[(14)] and SLUDGE – salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis (vomiting). Death may follow in one to ten minutes after direct inhalation.

It is almost always manufactured as a racemic mixture (a 1:1 mixture of its enantiomeric forms) as this involves a much simpler synthetic process whilst providing an adequate weapon.[15][16]

A number of production pathways can be used to create sarin. The final reaction typically involves attachment of the isopropoxy group to the phosphorus with an alcoholysis with isopropyl alcohol. Two variants of this process are common. One is the reaction of methylphosphonyl difluoride with isopropyl alcohol, which produces a racemic mixture of sarin enantiomers with hydrofluoric acid as a byproduct:[17]

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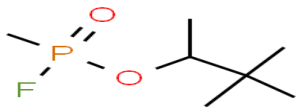
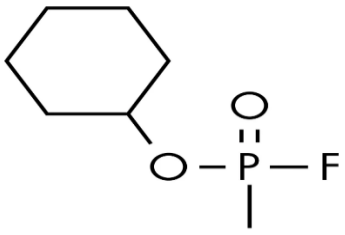
SOMAN



Soman is synthesized by reacting pinacolyl alcohol with methylphosphonyl difluoride. The result of this reaction is the forming of soman which is described as “colorless liquid with a somewhat fruity odor.” The low vapor pressure of soman will also produce the volatile gas form of soman. Also, the acid hydrogen fluoride will form due to the elimination of fluoride and a proton. This acid is indirectly dangerous to humans. Skin contact with hydrogen fluoride will cause an immediate reaction with water which produces hydrofluoric acid.[18]

soman is closely related to compounds such as sarin, indications for a soman poisoning are relatively similar. One of the first observable signs of a soman poisoning is miosis. Some, but not all of the later indications are vomiting, extreme muscle pain and peripheral nervous system problems. Those symptoms show as soon as 10 minutes after exposure and may last for many days.[19]

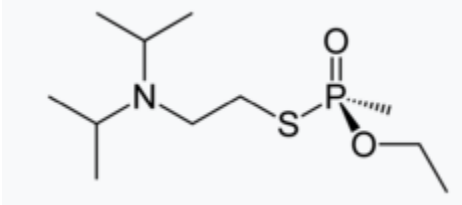
CYCLOSARIN



Hypersecretions, tremors, *status epilepticus*, respiratory distress and death, Miosis and rhinorrhea are the most common clinical findings in those individuals acutely exposed to OP nerve agents. Prolonged seizures are responsible for the neuropathology.(20).

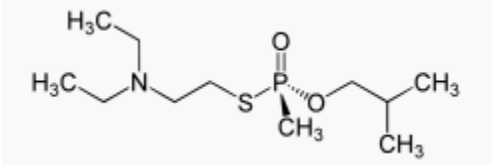
V SERIES

VX



On such exposure, these agents severely disrupt the body's signaling between the nervous and muscular systems, leading to a prolonged neuromuscular blockade, flaccid paralysis of all the muscles in the body including the diaphragm, and death by asphyxiation.[21]

VR

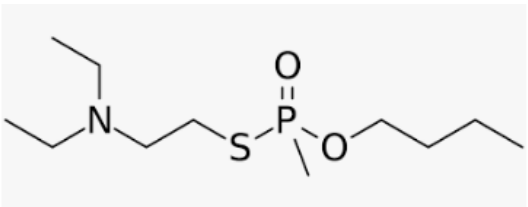


VR (Russian VX, VXr, Soviet V-gas, GOSNIIOKhT substance No. 33, Agent "November") is a "V-series" unitary nerve agent closely related (it is an isomer) to the better-known VX nerve agent.[1] It became a prototype for the series of Novichok agents

V series seizures is shorter, as they rapidly denature the acetylcholinesterase In addition to the standard seizures, some of the second generation V series agents are known to cause comas(22)

CVX

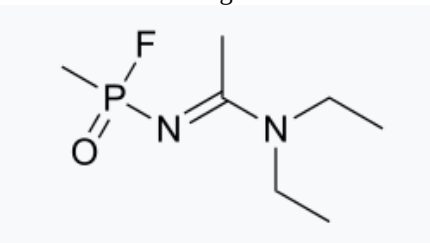
Chinese VX (CVX), also known as EA-6043, is an organophosphate nerve agent of the V-series. It is a structural isomer of both VX and Russian VX.[23][24]



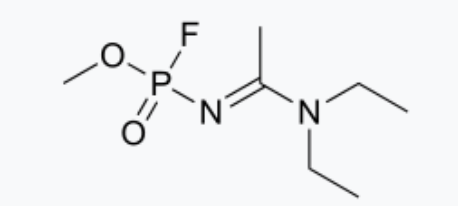
A SERIES

A 230

A-230 is an organophosphate nerve agent. It was developed in the Soviet Union under the FOLIANT program and is one of the group of compounds referred to as Novichok agents that were revealed by Vil Mirzayanov. A-230 is possibly the most potent nerve agent for which specific toxicity figures have been published, with a human lethal dose estimated to be less than 0.1 mg.

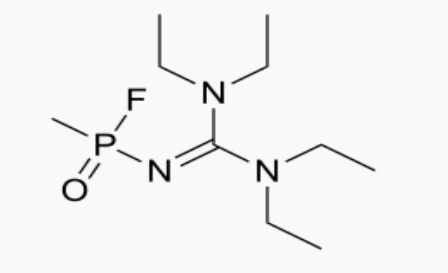


A 232



A-232 is an organophosphate nerve agent. It was developed in the Soviet Union under the FOLIANT program and is one of the group of compounds referred to as Novichok agents that were revealed by Vil Mirzayanov. A-232 is reportedly slightly less potent as a nerve agent compared to some of the other compounds in the series such as A-230 and A-234, having similar potency to the older nerve agent VR. However it proved to be the most versatile agent as it was chemically stable and remained a volatile liquid over a wide temperature range, making it able to be used in standard chemical munitions without requiring special delivery mechanisms to be developed.[25][26]

A 242

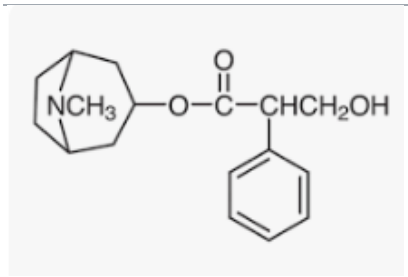


A-242 is an organophosphate nerve agent. It was developed in the Soviet Union under the FOLIANT program and is one of the group of compounds referred to as Novichok agents hat were revealed by Vil Mirzayanov. Mirzayanov gives little specific information about A-242, stating that it is highly toxic but no figures are given to compare it to other related agents. It is reportedly a solid rather than a volatile liquid as with most nerve agents, and in order to weaponise it successfully, it had to be milled into a fine powder form that could be dispersed as a dust.[27]

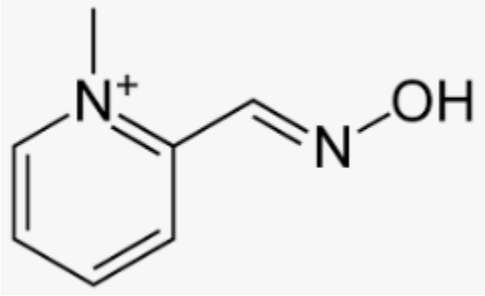
Antidotes

The backbones of medical therapy in organophosphate (OP) poisoning include atropine, pralidoxime (2-PAM), and benzodiazepines (eg, diazepam).

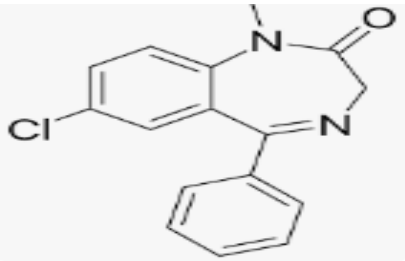
Primary management must focus on adequate use of atropine. Optimizing oxygenation prior to the use of atropine is recommended to minimize the potential for dysrhythmias.Much larger doses of atropine are often needed for OP pesticide poisoning than when atropine is used for other indications. In order to attain adequate atropinization quickly, a doubling approach typically used, with escalation of doses from 1 mg to 2 mg, 4 mg, 8 mg, 16 mg, and so on.[28]



Pralidoxime has approval as an antidote for nerve agent poisoning. Reports point out that chemical weapons like sarin, tabun, soman, and cyclosarin were used in the 1980 Iran-Iraq war, the 1995 Tokyo subway attack, the Gulf war, and the 2013 Syrian civil war. Pralidoxime also has approval as an antidote for organophosphate-based pesticides. Pralidoxime has also received approval to succeed an overdose of acetylcholinesterase drugs prescribed for myasthenia gravis and Alzheimer dementia.[29]



The utmost standpoint antidotal mixture against soman, consisting of the oxime HI-6 and atropine, should be complemented by diazepam not only because of the prevention of poisoned organisms from centrally mediated seizures and subsequent tonic-clonic convulsions but also because of the increase in the ability of antidotal treatment to eliminate soman-induced acute lethal effects.[30]



CONCLUSION:

This review mainly focusesd on the chemistry of nerve agents and illustrates the description regarding their antidotes. Medical Practitioners and Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies. This review help to know in detail about the nerve agents and also the antidotes of nerve agent poisoning.

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