CHEMICAL WARFARE AGENTS-MECHANISMS OF ACTION, SYMPTOMS AND TREATMENT REGIMENS

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ABSTRACT

In society today, large amounts of chemicals are routinely stored, handled and transported. Some of these are products ready for marketing whereas others are used for military purposes.

Not all chemical substances imply risks when released. Risk chemicals are classified according to several different criteria, e.g., range effect, toxicity and chemical stability. The number of people who will be injured following the release of chemicals, and the extent of the damage, will depend on numerous factors. Some factors are the properties of the substance, the size of the discharge, the period during which people are exposed, and the length of time that passes between exposure and treatment.

Chemicals were used for the first time on a large scale as weapon during the First World War. About 1.3 million people were injured and 100,000 killed by chemical weapons during the first World War. Since then, large quantities of different chemical warfare (CW) agents have been produced, stored and dispersed during warfare. This paper describes in a concise form the mechanisms of action and antidotes for the most important CW agents.

KEYWORDS: *nerve agents, mustard agents, tear gases, hydrogen cyanide, mechanism of action, antidotes.*

INTRODUCTION

Chemical weapons are used as alternatives or supplements to both conventional and nuclear weapons. They have the ability to affect only human beings, animals and plants, yet leave terrain and buildings practically undamaged.

There are three main reasons for the use of CW agents. One is to disable the enemy within a relatively restricted area by killing or by more or less severely injuring him. Another is to prevent or delay certain activities within restricted areas. The third reason which can only be achieved under suitable weather conditions will be to disturb or exhaust personnel within large areas by compelling them to wear respirators or to remain in gas-proof chambers for lengthy periods.

Attacks by CW agents can be made in different ways, depending on the objective of the attack and the nature of the target. In some cases the intention may be to release the agent in liquid form, in others as gas or aerosol. In actual fact, a combination of liquid, aerosol and gas occurs in all forms of dispersal methods but by choosing the appropriate type of substance it is possible to make the desired type of dispersal the dominant one.

Chemical weapons can be used for sabotage in the introductory phase of a conflict. Since they are extremely toxic, small easily handled quantities may be sufficient also for fairly comprehensive employment. Volatile substances can be poured into air intakes or sprayed out in crowds, possibly by means of remote-controlled spray containers, food and drink can be poisoned, e.g., at a dairy or at a food-processing industry.

NERVE AGENTS

A characteristic of nerve agents is that they are extremely toxic and that they have very rapid effect. The nerve agent, either as a gas, aerosol or liquid, enters the body through inhalation or through the skin. Poisoning may also occur through consumption of liquids or foods contaminated with nerve agents.

The route for entering the body is of importance for the period required for the nerve agent to start having its effect. It also influences the symptoms developed and, to some extent, the sequence of the different symptoms. Generally, the poisoning works faster when the agent is absorbed through the respiratory system than via other routes. This is because the lungs contain numerous blood vessels and the inhaled nerve agent can therefore rapidly diffuse into the blood circulation and thus reach the target organs. If a person is exposed to a high concentration of nerve agent, e.g., 200 mg sarin/m³ death may occur within a couple of minutes (Table 1). The values express the dose at which 50 per cent of the exposed population will die as a result of their injuries.

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TABLE 1: TOXICITY OF THE MOST IMPORTANT NERVE AGENTS TO MAN

	Inhalation mg.min/m³	Skin mg/individual
Tabun	200	4000
Sarin	100	1700
Soman	100	300
VX	50	10

Poisoning takes longer when the nerve agent enters the body through the skin. Nerve agents are more or less fat-soluble and can penetrate the outer layers of the skin. However, it takes some time before the poison reaches the deeper blood vessels. Consequently, the first symptoms do not occur until 20 - 30 minutes after the initial exposure but subsequently the poisoning process may be rapid if the total dose of nerve agent is high.

The toxic effect of nerve agents depends on the substance inhibiting the enzyme acetylcholinesterase in the cholinergic nerve system. This enzyme is responsible for breaking down the signal substance acetylcholine, a process requiring two steps - acetylation by means of a serine in the active site and hydrolysis (Fig.1).

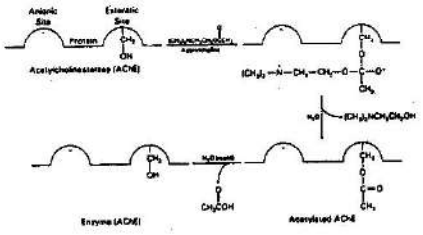

Fig. 1: Hydrolysis of acetylcholin by acetylcholinesterase (AChE)

The reaction mechanism for nerve agents is similar but with the important difference that the rate of the final hydrolysing step is negligible. Consequently, the enzyme becomes irreversibly inhibited, with the nerve agent covalently bound to the enzyme via the serine in the active site (Fig.2). Inhibition of acetylcholinesterase is thus a progressive process and the degree of inhibition depends not only on the concentration of nerve agent but also on the time of exposure. Soman is the most potent inhibitor of acetylcholinesterase among the nerve agents. A concentration of 10^{-9}M is sufficient to inhibit the enzyme by more than 50 per cent within 10 minute.

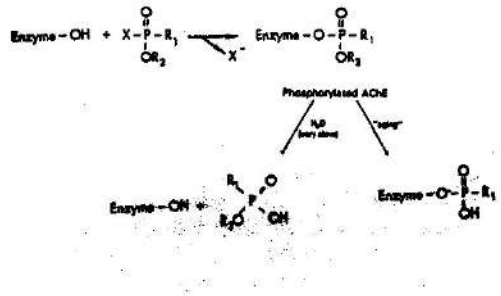

Fig. 2: Reaction of nerve agent with acetylcholinesterase

Symptoms

When exposed to a low dose of nerve agent, causing minor poisoning, characteristic symptoms are increased production of saliva, a running nose and a feeling of pressure on the chest. The pupil of the eye becomes contracted which impairs night-vision. The accommodation capacity of the eye is also reduced so that short-range vision deteriorates and the victim feels pain when he tries to focus on an object nearby. This is accompanied by headache. More unspecific symptoms are tiredness, slurred speech, hallucinations and nausea.

Exposure to a higher dose leads to a more dramatic development and symptoms are more pronounced. Broncho-constriction and secretion of mucus in the respiratory system leads to difficulty in breathing and to coughing. Discomfort in the gastro-intestinal tract may develop into cramp and vomiting. Involuntary discharge of urine and defecation may also form part of the picture. The discharge of saliva is powerful and the victim may experience running eyes and sweating. Symptoms from the skeletal muscles are very typical. If the poisoning

is moderate, this may express itself as muscular weakness, local tremors or convulsions.

When exposed to a high dose of nerve agent, the muscular symptoms are more pronounced. The victim may suffer convulsions and lose consciousness. To some extent, the poisoning process may be so rapid that earlier mentioned symptoms may never have time to develop.

Muscular paralysis caused by nerve agents also affects the respiratory muscles. Nerve agents also affect the respiratory centre of the central nervous system. The combination of these two effects is the direct cause of death. Consequently, death caused by nerve agents is a kind of death by suffocation.

The toxic effect depends on both the concentration of nerve agent in the air inhaled (C) and the time of exposure(t). In extremely high concentrations there is a simple relationship C.t, which gives a certain toxic effect. Inhalation of sarin vapour with a concentration of 100 mg/m³ for one minute gives the same result as inhalation of 50 mg/m³ for two minutes. However, at low concentrations this relationship does not apply since the human body is capable of some degree of detoxification. In order to obtain a corresponding effect, it is then necessary to have relatively longer periods of exposure.

Antidotes and Methods of Treatment

Nerve agents have an extremely rapid effect. If medical methods or treatments are to serve any purpose, they must be introduced immediately. Generally, the Armed Forces have access to an auto-injector containing antidotes to nerve agents. It is so simple to use that the soldier can easily give himself or another person an intra-muscular injection.

The auto-injector usually contains two active components: an oxime and atropine. Oximes, with the general formula R-CH=NOH, can reactivate the phosphorylated enzyme. The oxime attacks the P - O bond whereby an operational enzyme and a phosphorylated oxime, which is rapidly hydrolyzed to non-toxic products, are formed. The efficiency of such reactivation depends strongly on the types of all the three components involved - enzyme, oxime and nerve agent.

The various nerve agents cause poisoning which are more or less easy to treat with oximes. From this standpoint, VX and sarin are the easiest to treat and all oximes used increase the chances of surviving poisoning with these nerve agents. Soman causes the most difficultly treated poisoning. Soman poisoning is complicated by the inhibited enzyme going through an "ageing" process. Following the ageing the enzyme cannot be reactivated by any oxime.

The other component in the auto-injector, atropine, is the classical antidote in cases of poisoning by organophosphorus compounds. It is a medication which relieves the symptoms but does not attack the cause of the injury. Atropine thus gives protection against the excess of acetylcholine which results from inhibition of acetylcholinesterase.

An additional auto-injector can be given to victims of nerve agents if their situation does not improve within ten minutes. Subsequently, the victim should be treated by qualified medical staff who may initially inject additional atropine and an anticonvulsant drug, diazepam. In cases of severe poisoning by nerve agents, large doses of atropine (grammes) may be required. The level of operational acetycholinesterase is gradually restored by the body's own production but this process requires at least two weeks. During this period, and possibly also later, the victim may require medical care not only for mental disorders such as difficulty in sleeping, amnesia, difficulties in concentrating, and anxiety, but also for muscular weakness. Mental problems may also occur after long exposure to extremely low concentrations of nerve agents.

There are also medical antidotes which can be taken preventively. These antidotes are taken as tablets. One of the tablets contains a carbamate, pyridostigmine, as active ingredient. Carbamates, with the general formula $R_1R_2 - N - C(0) - 0 - R_3$, inhibit acetylcholinesterase and protect the enzyme against inhibitory effects of nerve agents. The dose is low and leads to about 25 per cent inhibition. The pyridostigmine-inhibited enzyme is continuously released to active state and thereby can reasonably and effectively maintain the transfer of nerve impulses despite injury caused by nerve agents.

Pretreatment with carbamate should be combined with oxime therapy (the auto-injector) after the poisoning in order to provide maximum effect. This combination reduces the toxic effects of all nerve agents.

Pretreatment has best effect if a warning system is available and operative, since the tablets need about 30 minutes to have effect after being swallowed. The best protective effective is achieved after about two hours, which is followed by decreasing efficacy.

MUSTARD AGENTS

The toxic effects of mustard agent depend on its ability to covalently bind to other substances. The chlorine atom is spiked off the ethyl group and the mustard agent is transferred to a reactive sulphonium ion. This ion can bind to a large number of different biological molecules. Most of all it binds to nucleophiles such as nitrogen in the base components of nucleic acids and sulphur in SH - groups in proteins and peptides. Since mustard agent contains two "reactive groups", it can also form a bridge between or within molecules. Mustard agent can destroy a large number of different substances in the cell by means of alkylation and thereby influence numerous processes in living tissue.

Symptoms

In the form of gas or liquid, mustard agent attacks the skin, eyes, lungs and gastro-intestinal tract. Internal organs may also be injured, mainly blood-generating organs, as a result of mustard agent being taken up through the skin of lungs and transported into the body. Mustard agent gives no immediate symptoms upon contact and consequently a delay of between two and twenty-four hours may occur before pain is felt and the victim becomes aware of what has happened. By then cell damage has already been caused.

Symptoms of mustard agent poisoning extend over a wide range. Mild injuries consist of aching eyes with abundant flow of tears, inflammation of the skin. irritation of the mucous membrane, hoarseness, coughing and sneezing. Normally, these injuries do not require medical treatment. Severe injuries which are incapacitating and require medical care may involve eye injuries with loss of sight, the formation of blisters on the skin, nausea, vomiting and diarrhoea together with severe respiration difficulty.

Acute mortality arising from exposure to mustard agent is low. The dose needed to directly kill a person upon inhalation is, e.g., about 50 times larger than the dose giving acute mortality upon poisoning with the nerve agent soman. People who die after exposure to mustard agent usually do so after a few days up to one or mor week.s

Minor skin damage may be caused by mustard agent in the gaseous state whereas the most severe injuries are caused after contact with liquid mustard agent. Skin damage first appears as a painful inflammation. Depending on the level of exposure, the injury may develop into pigmentation, which flakes-off after a couple of weeks, small surfaces blisters or deep liquid-filled blisters with subsequent skin necrosis. In extreme cases, the skin necrosis may be so comprehensive that no blisters occur, skin injuries are more severe in humid and warm climates. Similarly, the injuries will be more severe where the skin is moist and warm, e.g., in the groin and armpits.

Experience has shown that even extremely extensive skin damage, 80 - 90 per cent, can be cured if the patient is kept free of infection. However, injuries to the skin require a very long period of recuperation, much longer than thermal burns, and may require care and plastic surgery over a period of several months.

Injury to the eyes appear initially as irritation with eye inflammation and a strong flow of tears. Depending on exposure, the symptoms thereafter may successively develop to sensitivity to light, swollen eyelids, and injury to the cornea. Severe damage to the eye may lead to the total loss of vision. Victims suffering damage to the eyes may encounter problems persisting up to 30 - 40 years following exposure.

The most common cause of death as a result of mustard agent poisoning is complications after lung injury, caused by inhalation of mustard agent. Lung injuries become apparent some hours after exposure and will first appear as a pressure across the chest, sneezing and hoarseness. Severe coughing and respiration difficulties will gradually occur and after a couple of days, a "chemical pneumonia" may develop. Most of the chronic and late effects are also caused by lung injuries.

The effect on inner organs which is most pronounced is injury to the bone marrow, spleen and lymphatic tissue. This may cause a drastic reduction in the number of white blood cells 5 - 10 days after exposure, a condition very similar to that after exposure to radiation. This reduction of the immune defence will complicate the already large risk of infection in people with severe skin and lung injuries.

Antidotes and Methods of Treatment

There is no treatment or antidote which can affect the basic cause of mustard agent injury. Instead, efforts are made to treat the symptoms. By far the most important measure is to rapidly and thoroughly decontaminate the patient and thereby prevent further exposure. Clothes are removed, the skin is decontaminated with a suitable decontaminant and washed with soap and water. Eyes are rinsed with water or a physiological salt solution for at least five minutes.

In medical treatment, efforts are made to control infections by means of antibiotics. Pain can be eased by local anesthetics. After skin injuries have healed, it may be necessary to introduce plastic surgery. Lung injuries are treated with bronchodilatory treatment. Medicine to relieve coughing and also cortisone preparations may be used. Eye injuries are treated locally with painkillers and with antibiotics if required. Despite treatment, inflammation and light sensitivity may remain for long periods.

Modern knowledge on the mechanisms behind mustard agent injuries may lead mainly to new ways of treatment. The first step, alkylation, takes place extremely rapidly and is probably very difficult to influence. Future treatment may concentrate on suppressing and alleviating the development of symptoms and thereby improve the opportunities for good recovery.

HYDROGEN CYANIDE

The most important toxic effect of hydrogen cyanide is by inhibiting the metal-containing enzymes. One such enzyme is cytochrome oxidase, containing iron. This enzyme system is responsible for the energy-providing processes in the cell where oxygen is utilized, i.e., cell respiration. When cell respiration ceases, it is no longer possible to maintain normal cell functions, which may lead to cell mortality.

Symptoms of cyanide poisoning vary and depend on, for example, route of poisoning, total dose and the exposure time. If hydrogen cyanide has been inhaled, the initial symptoms are restlessness and increased respiratory rate. Other early symptoms are giddiness, headache, palpitations and respiratory difficulty. If the

poisoning occurs rapidly, e.g., as a result of extremely high concentrations in the air, there is no time for symptoms to develop and exposed persons may then suddenly collapse and die.

Antidotes and Treatment

Today, there is no specific medical antidote against cyanide poisoning. The treatment given to civilians is based on encouraging and speeding-up the body's own ability to excrete cyanide and to bind cyanide in the blood. The enzyme rhodanese is present in the body, mainly in the liver, and together with sulphur transforms cyanide into thiocyanate, which is passed out in the urine. By supplying sulphur in the form of sodium thiosulphate ($Na_2S_2O_3$), the detoxification can be speeded up. The cyanide ion has high affinity to trivalent iron (Fe^{3+}). The divalent ion in blood haemoglobin can be oxidized to trivalent, which leads to the formation of methaemoglobin which binds cyanide ions. The formation of methaemoglobin can be achieved by supplying sodium nitrate ($NaNO_3$) or dimethylaminophenol (DMAP).

Cyanide can also be bound by metallic ions to the blood in suitable form. Among others, cobalt can be supplied in the form of a cobalt complex or as hydroxycobalamin (vitamin B_{12}).

In cases of poisoning with hydrogen cyanide it is of the utmost importance that counter-measures are immediately introduced. For this reason, a medical antidote (PAPP, para-aminopropiophenone) for use as a pretreatment is being developed in the United Kingdom.

TEAR GASES

All tear gases have in common that they cause almost instant pain in the eyes, flow of tears and cramp of the eyelids. The strongly irritating effect leads to a more or less pronounced incapacitation of exposed persons. Apart from the effects on the eyes, most tear gases cause irritation in the nose and mouth, throat and airways and sometimes also in the skin, particularly in moist and warm parts. In situations of massive exposure, tear gas which is swallowed may also cause vomiting.

Disagreeable sensations caused by exposure to tear gas are so strong that victims cannot behave rationally, which explains why tear gases cause incapacitation. The irritating effect remains as long as there is sufficient concentration of tear gas present but disappears fairly quickly (15 - 30 min.) after exposure has ceased.

The irritating properties of tear gases depend on nerves in mucous membrane and skin being affected. Sensitivity to tear gases varies considerably between different individuals. Factors influencing individual reactions may be emotional state, motivation, physical activity, ambient temperature and humidity.

The expressions "threshold concentration" (TC) and "incapacitating or intolerable concentration" (IC) are frequently used to express the efficiency of a tear gas. TC_{50} thus implies the concentration required to obtain no more than a perceptible effect on 50 per cent of the people exposed to the gas for one minute. IC_{50} is the concentration felt to be intolerable by 50 percent of the people exposed to the gas for one minute. TC_{50} and IC_{50} values for the most important tear gases are listed in Table 2.

TABLE 2: THRESHOLD CONCENTRATIONS (TC_{50}) AND INCAPACITATING CONCENTRATIONS (IC_{50}) FOR TEAR GASES (mg/m^3).

	CN	CS	CR
TC50 ((eyes)	0.3	0.004	0.004
TC50 (airways)	0.4	0.023	0.002
IC50	20-50	3.6	0.7

Acute toxicity of tear gases is very low, i.e., the margin between the concentration giving intolerable effect and that which may cause injury is large. It is not until very high concentrations are reached that injury may be severe of lethal. In practice, this requires exposure in closed spaces. Toxicological investigations have been unable to demonstrate effects of tear gases on genetic material or on foetal development in experimental animals or humans.

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