

Cyanogen Agents

GENERAL

Introduction

Cyanogen agents produce their effects by interfering with oxygen utilization at the cellular level. Their toxicity is primarily derived from the liberation of the CN-group. Inhalation is the usual route of entry. The term "blood agents" has, in the past been used to describe cyanogen agents and is still in widespread use. It should be noted, however, that not all "blood agents" are cyanogens (e.g. carbon monoxide).

The commodity industrial chemical hydrogen cyanide (HCN (AC)) was used during WWI and is still attractive as an improvised weapons fill because of its availability. Hydrogen cyanide is released when cyanides (e.g. acetone cyanohydrin, sodium cyanide, potassium cyanide) are spilled in water or subjected to acid. The cyanogen halides, cyanogen chloride (ClCN (CK)) and cyanogen bromide (BrCN), were used during WWI. The toxicity of cyanogen halides is due to the CN-group and the irritant properties of the halogen moiety. The commodity chemical hydrogen sulphide (H₂S) has a toxicity comparable to hydrogen cyanide and appears to act by a similar mechanism.

HYDROGEN CYANIDE

Properties

Physical Properties

Under most field conditions, hydrogen cyanide is a colourless gas and represents a non-persistent hazard. The vapour is less dense than air and has a faint odour, somewhat like bitter almonds, although about up to 40 % of people are unable to smell this. It is highly soluble and stable in water.

Chemical Properties.

The CN compounds hydrolyse slowly in water with subsequent gradual loss of toxicity. They are readily oxidised by strong oxidants; e.g. potassium permanganate. Hydrogen cyanide has an affinity for oxygen and is flammable; hence it is less efficient when dispersed by artillery shells.

Compounds which contain labile sulphur atoms (R-S=S₂-) react with HCN even in vivo, for example:



This reaction with sodium thiosulphate forms the basis of a therapy of cyanide poisoning. Metal ions easily form complexes with cyanide ions for example:



These types of reaction are employed in reactive carbons where the charcoal is impregnated with metal ions in order to increase the absorptive capacity of charcoal. Similar reactions with complexed metal ions are also utilised in some forms of therapy.

Detection

Automatic detectors are available which detect attack concentrations of cyanide vapour. Draeger™ tubes are also available, as are water testing kits.

Protection

Hydrogen cyanide, because of its volatility and low molecular weight, is poorly absorbed by the charcoal in the canister of the respirator. This charcoal is made more reactive by impregnating it with metal salts. In field conditions the respirator gives good protection against gas. Modern NBC filters are effective against attack with hydrogen cyanide, but should be changed immediately afterwards.

Decontamination

Because of its physical properties the agent will not remain for long in its liquid state; decontamination should not be necessary.

Mechanism of Action

The cyanide ion forms a reversible complex with the respiratory cytochrome oxidase, an enzyme system essential for oxidative processes within cells. This results in impairment of cellular oxygen utilisation. The central nervous system, particularly the respiratory centre, is especially susceptible to this effect and respiratory failure is the usual cause of death.

Signs and Symptoms

As a result of the high rate of detoxification in the body, high concentrations of cyanide for short periods produce greater toxicity.

- *High concentrations:* At high concentrations there is an increase in the depth of respiration within a few seconds. This

stimulation may be so powerful that a casualty cannot voluntarily hold his or her breath. Loss of consciousness with possible convulsions occur after 20 to 30 sec with cessation of respiration within 1 min. Cardiac failure follows within a few minutes. Sudden loss of consciousness in the absence of other characteristic features of nerve agent intoxication is a key indicator of potentially lethal cyanide poisoning.

- *Low Concentrations:* At low concentrations, the early symptoms are weakness of the legs, vertigo, nausea and headache. Convulsions may follow with coma which may last for hours or days depending on the duration of exposure to the agent. Recovery from prolonged coma may disclose residual damage to the central nervous system manifested by irrationality, altered reflexes and unsteady gait which may last for several weeks or longer; temporary or permanent nerve deafness has also been described. In mild cases there may be headache, vertigo and nausea for several hours before complete recovery.

Casualty Management

First Aid Measures. The casualty should be removed from the source of hydrogen cyanide. Rescue workers should wear adequate individual protective equipment (IPE).

Therapy. The key to treatment of patients poisoned with hydrogen cyanide is speed. Although there is disagreement regarding the ideal drugs for use in the treatment there is no doubt that urgent action is necessary.

Treatment

Any casualty who is fully conscious and breathing normally more than 5 min after presumed exposure to cyanide agents has ceased will recover spontaneously and does not require treatment (cyanide is detoxified very rapidly in the body). Successful treatment for acute cyanide poisoning depends upon rapid fixation of the cyanide ion, either by methaemoglobin formation or by fixation with cobalt compounds. Artificial ventilation is not likely to be helpful in the absence of administration of antidote.

Treatment Approaches

Two major approaches are involved in the treatment by antidote of cyanide poisoning:

1. By providing alternative binding sites for the cyanide ions, the cytochrome oxidase enzyme activity is restored. Binding sites may be provided by drugs such as dicobalt edetate and hydroxocobalamin or by the production of methaemoglobin in the blood. Methaemoglobin avidly binds cyanide ions and may be produced by compounds such as sodium nitrite, amyl nitrite and dimethylaminophenol (4-

DMAP). Methaemoglobin-forming compounds should be used cautiously in patients suffering from concurrent carbon monoxide poisoning or hypoxia.

2. Cyanide is detoxified at a rate that is of practical importance, about $17 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Provision of additional sulphur groups to enhance the detoxification of cyanide to thiocyanate by endogenous rhodanese is accomplished by giving sodium thio-sulphate.

It is generally agreed that binding the cyanide ions is the main priority of treatment but that thiosulphate should be provided with most treatment regimen to promote conversion of cyanide to non-toxic thiocyanate ions.

Drugs That Induce The Binding Of Cyanide Ions

Sodium Nitrite

Sodium nitrite must be administered intravenously. Ten millilitres of a 3% solution (300 mg) of sodium nitrite should be injected intravenously over a period of 3 min. The sodium nitrite is administered in order to produce methaemoglobin, thus sequestering the cyanide on the methaemoglobin. Subsequent intravenous administration of sodium thiosulphate is required to promote the conversion of cyanide to thiocyanate ion which is then excreted from the body.

The decrease in blood pressure following sodium nitrite injections is negligible unless the patient is allowed to get into an upright position. The development of a slight degree of cyanosis may be associated with the production of methaemoglobin (methaemoglobinaemia) and does not in itself call for artificial ventilation. It is not anticipated that an extreme or injurious degree of methaemoglobinaemia will develop at the dosages stated above. If it does occur, treatment is oxygen administration. If methaemoglobin formation is severely symptomatic, methylene blue may be given to convert methaemoglobin to haemoglobin. Methylene Blue is given $1-2 \text{ mg}\cdot\text{kg}^{-1}$ by slow IV injection over 5 - 10 min; repeated once after 1 h if there is no response.

4-Dimethylaminophenol-hydrochloride (4-DMAP)

4-DMAP induces the rapid formation of methaemoglobin and must be injected intravenously at a dose of 250 mg over 3 - 5 min. Muscular necrosis may follow intramuscular injection and this route should be avoided. Subsequent intravenous administration of sodium thiosulphate is required to promote the conversion of cyanide to thiocyanate ion which is then excreted from the body. If sodium thiosulphate is not immediately available,

250 mg of 4-DMAP should be given every hour until thiosulphate can be given; the latter completes the treatment.

Amyl Nitrite

Amyl nitrite may be of benefit when used as a first aid measure, prior to the use of intravenous antidotes. Crushing the ampoule around the face or even inside the facepiece of the respirator is worthless unless the casualty is breathing. It should not be used with concurrent oxygen administration due to the risk of explosion. Treatment with amyl nitrite should be followed by sodium thiosulphate.

Hydroxocobalamin

Hydroxocobalamin (vitamin B12a) is a fast acting antidote that binds cyanide to form non-toxic cyanocobalamin (vitamin B12). Both are excreted by the kidneys. It must only be given intravenously. The initial dose of 5g (ca. 70 mg.kg⁻¹) has to be infused over 30 min. One or 2 further injections may be administered depending on the severity of poisoning. In practice, there are no known side effects. Association with thiosulphate is usually not necessary however, if performed, care should be taken not to mix both drugs in the same infusion.

Dicobalt Edetate

Dicobalt edetate releases cobalt ions that react with cyanide ions. Highly stable cyanide-cobalt complexes are excreted by the kidneys. It must be given intravenously in doses of 600 mg followed immediately by 50 ml of a glucose hypertonic solution. The injection should be followed by an intravenous injection of sodium thiosulphate. Another 300 mg dose may be injected. It should be noted that cobalt edetate is toxic to the kidney and causes hypotension, hypoglycaemia, vomiting, diarrhoea and headaches. These effects are more prominent in non-intoxicated casualties.

Provision of Sulphur Groups

Sodium thiosulphate provides additional thiosulphate ions and these combine with cyanide ions in a reaction catalysed by rhodanase to produce thiocyanate. With most treatment regimen it should be given to supplement other forms of treatment for cyanide poisoning. The dose is 12.5 - 25 g diluted for intravenous administration over a 10 minute period.

Additional Therapy

If available, 100% oxygen should be given, with or without positive pressure ventilation.

Course and Prognosis

Death may occur within minutes without treatment, but a casualty who is fully conscious and breathing normally 5 min after presumed exposure has ceased does not

require antidotal treatment and will be expected to make a full recovery. Occasionally, when tissue hypoxia has been prolonged, residual injury of the CNS may persist for weeks and some damage may be permanent.

CYANOGEN HALIDES

Introduction

Cyanogen chloride and cyanogen bromide were used during WWI (usually in mixtures with other warfare agents - hydrogen cyanide, bromoacetone). Their effects on the body are similar to those of hydrogen cyanide but they also have irritant effects on the eyes and upper respiratory passages. The threshold concentration for cyanogen chloride is approximately 2.5 mg.m⁻³.

Physical and Chemical Properties

Under most field conditions, cyanogen chloride is a colourless, strongly irritant gas. Although only slightly soluble in water, it dissolves readily in organic solvents. Its vapour, heavier than air, is very irritating to the eyes and mucus membranes. Cyanogen chloride has pungent, biting odour. Normally cyanogen chloride is non persistent.

Detection

Automatic detectors are available which detect attack concentrations of vapour. Draeger™ tubes are also available, as are water testing kits.

Protection

Cyanogen halides are rather poorly absorbed onto charcoal, especially if the charcoal is damp. The cyanide group (which is not ionised) does not react well with the metal salts found in respirator charcoals.

Decontamination

As with hydrogen cyanide, because of its physical properties the agent will not remain for long in its liquid state. Decontamination should not, therefore, be necessary.

Mechanism of Action

Cyanogen chloride acts in two ways. Its systemic effects are similar to those of hydrogen cyanide but it also has local irritant effects on the eyes, upper respiratory tract and lungs as a result of the formation of hydrogen chloride.

Pathology

Cyanogen chloride injures the respiratory tract, resulting in severe inflammatory changes in the bronchioles and congestion and oedema in the lungs. Very low concentrations (e.g. 10-20 mg.min.m⁻³) produce eye irritation and lachrymation.

Signs and Symptoms

The signs and symptoms caused by cyanogen chloride are a combination of those produced by hydrogen cyanide and a lung irritant such as phosgene. Initially, cyanogen chloride stimulates the respiratory centre and then rapidly paralyses it. In high concentrations however, its local irritant action may be so great that dyspnoea is produced. Exposure is followed by an immediate intense irritation of the nose, throat and eyes, with coughing, tightness in the chest and lachrymation. Subsequently, the exposed person may become dizzy and increasingly dyspnoeic. Unconsciousness is followed by failing respiration and death within a few minutes. Convulsions, retching and involuntary defecation may occur. If these effects are not fatal, the signs and symptoms of pulmonary oedema may develop. There may be persistent cough with much frothy sputum, rales in the chest, severe dyspnoea and marked cyanosis.

Treatment

Cyanogen halide poisoning should be treated in the same way as hydrogen cyanide poisoning in respect of its cyanide-like effects. Pulmonary irritation should be treated in the same way as phosgene poisoning.

Course and Prognosis

Recovery from the systemic effects of cyanogen halide poisoning is usually as prompt as in hydrogen cyanide poisoning. However, a higher incidence of residual damage to the central nervous system is likely. Depending on the concentration of cyanogen halide, the pulmonary effects may develop immediately or may be delayed until the systemic effects have subsided. Early prognosis must therefore be guarded.

Further Reading

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