IN-DEPTH REVIEW

The treatment of cyanide poisoning

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Cyanide has gained historical notoriety as a poison used with intent to cause fatality. Its occurrence in industry is confined to a small number of uses in a relatively narrow range of industries, including the manufacture of Perspex and nylon and in electroplating. With proper controls in these settings, episodes of poisoning are extremely rare. However, because of the potential for a fatal outcome, procedures for the treatment of acute poisoning are essential. Antidotes include methaemoglobin generators, direct binding agents and sulphur donors, but there is a lack of international consensus about the treatment of choice. This article reviews the mechanisms and treatment of cyanide intoxication and emphasizes the importance of having agreed local procedures for the emergency treatment of poisoning.

Key words Cyanide; occupational diseases.

Introduction

Poisoning by chemicals at the workplace is an uncommon event nowadays. In the case of cyanide, it is particularly so, and the last accidental (as opposed to homicidal or suicidal) death in the UK was on Teesside in late 1999. However, we have to look back to 1975 to find another such event.

Despite this rarity, cyanide still generates a great deal of interest both for the layman and the professional. Indeed, it is probably perceived as the archetypal ‘poison’, the lethal dose being in the order of only 1 mg/kg. The recognition of its toxicity can be traced back to antiquity, with the consumption of bitter almonds, cherry laurel and cassava being recognized as hazardous pastimes. Hydrocyanic acid was isolated from Prussian blue in 1782, and those with a better classical education than myself will make the connection between ‘cyan’ and blue. In 1786, Scheele, the chemist who was first to isolate the material, fully demonstrated its toxicity by accidentally breaking a vial and dying as a result.

Manufacture and use

Global consumption of cyanide approximates to 1.5 million tonnes annually. It is useful in chemical manufacture where a carbon atom is to be added to a molecule. However, by far the bulk of consumption goes into methyl-methacrylate (which is known as Perspex or Plexiglas when polymerized) and into adiponitrile (a precursor of nylon) manufacture. Other uses are as sodium or potassium salts in the gold extraction and electroplating industries and for the manufacture of methionine or other amino acids in the animal feed industry.

A small but high-profile use is in vermin extermination. The product (Cymag) is used for releasing hydrogen cyanide in the burrows and dens of the target animals. If used improperly there is a real potential for operator exposure.

Manufacture of cyanides in the UK is on Teesside and uses the Andrussaw process:

\[ \text{NH}_3 + \text{CH}_4 + 1.5\text{O}_2 \xrightarrow{1100^\circ \text{C}} \text{HCN} + 3\text{H}_2\text{O} \]

However, another company on Teesside uses the SOHIO process for acrylonitrile manufacture and hydrogen cyanide is a by-product.

\[ \text{CH}_2\text{CHCH}_3 + 3\text{NH}_3 + 3\text{O}_2 \rightarrow 3\text{HCN} + 6\text{H}_2\text{O} \]

An alternative method is the Degussa process:

\[ \text{CH}_4 + \text{NH}_3 \xrightarrow{1200^\circ \text{C}} \text{HCN} + 3\text{H}_2 \]

Manufacture is global, with production in the UK, USA, Europe, Japan and South East Asia.
The material is exported from the manufacturing plant as hydrogen cyanide, solid sodium and potassium salts, liquid sodium cyanide solution and, in the first stages of methyl-methacrylate manufacture, as acetone cyanohydrin.

**Toxicology and clinical effects**

Cyanide exerts its toxicity by the inhibition of cytochrome oxidase causing a cytotoxic hypoxia.

It is toxic to a number of enzyme systems. Mechanisms include combination with essential metal ions, formation of cyanohydrins with carbonyl compounds and the sequestration of sulphur as thiocyanate. However, the main target enzyme is cytochrome C oxidase, the terminal oxidase of the respiratory chain and involves interaction with the ferric ion of cytochrome a3 (Figure 1).

The net effect is the prevention of oxygen uptake at the intracellular tissue level. One of the features of cyanide intoxication is said to be the bright red arterialization of venous blood (because oxygen is not absorbed on passage through tissue). This effect appears to be theoretical only and does not appear to have been recorded in fact.

Cyanide exposure is not limited to the industrial setting: indeed, the greatest potential for exposure is from smoke in household or building fires [1]. Intoxication occurs otherwise from deliberate self-harm or by homicidal intent or through the accidental ingestion of cyanides or other cyanogenic materials.

In fires, cyanide is generated through the combustion of nitrogen-containing compounds (melamine, nylon, etc.) and, in addition, carbon monoxide is generated through the incomplete combustion of carbon-containing compounds. The sequestration of haemoglobin by carbon monoxide as carboxyhaemoglobin presents real problems in the use of cyanide antidotes. I shall return to this issue later.

Cyanide is present naturally in cassava and cherry laurel and the kernels of apricot, cherry, apple and almond seeds. It is said to have the odour of bitter almonds, although only 60% of us (through a genetic mechanism) are able to smell it. However, it is likely that apricot kernels have the highest concentration and at least one case of severe intoxication from this source has been recorded [2]. The ‘natural’ cancer treatment, laetrile, which was popular in the early 1980s, was extracted from apricot kernels and caused some considerable cyanide toxicity.

**Examples of lethal exposures**

1. A.S. was a wealthy lawyer holidaying in Egypt. She was tricked into the ingestion of sodium cyanide. Her partner was convicted of her murder, the conviction being secured largely by his refusal to undertake mouth-to-mouth resuscitation. The case was extensively reported in the (British) press as the ‘Death on the Nile’.

2. The victim was an operator on a hydrogen cyanide manufacturing plant. His duties included taking samples from a reactor containing 82% acetone cyanohydrin. He was seen to enter a room with the sample, emerge a few moments later and collapse. The 100 ml sample was missing, presumed ingested. This dose approximates to 25 times the lethal dose. At the subsequent post-mortem examination, care had to be taken to avoid exposure of the pathology personnel.

3. A third case involved a man who was an operator on an acrylonitrile plant. As above, his duties included the sampling of a hydrogen cyanide reactor vessel.
The task was recognized as a two-man job, the second operator (or ‘buddy’) being present to assist in the event of a problem. The buddy was called away, and it seems that the first operator went ahead with preparing the sampling site whilst awaiting his return. The likelihood is that he opened the sampling valve without first ensuring that the main valve was closed. He was found collapsed, without his breathing apparatus applied. Liquid hydrogen cyanide was splashing from the valve around him.

**Antidotes**

In the field of toxicology, the numbers of materials with specific antidotes are few. The use of acetyl-cysteine in paracetamol poisoning, oximes and atropine in organophosphate exposure and methylene blue in aniline exposure are examples. There are others, but in chemical exposure or drug overdose the most common treatment is supportive only. In the case of cyanide, there is a surfeit of antidotes: regrettably, there is an international lack of consensus. It must be recognized that all of the forthcoming and the position as of July 2003 was one of the excellent text of Marrs [3].

1. Methaemoglobin generators. The use of an oxidizing agent (usually a nitrite) will change the ferrous (2+) ion of haemoglobin to the ferric (3+) ion. The resultant methaemoglobin binds strongly with cyanide as cyanmethaemoglobin. The drugs used are sodium nitrite (i.v.), amyl nitrite (inhaled) and dimethyl aminophenol (i.v. or i.m.).

2. Direct binding agents. These are based on cobalt chemistry and chelate the cyanide ion directly. Dicobalt edetate (Kelocyanor) and hydroxocobalamin (Cyanokit) are both available and both are given i.v.

3. Sulphur donors. The normal route of detoxification is conversion of cyanide to thiocyanate, with the sulphur moiety normally contributed by glutathione. However, sodium thiosulphate will also contribute sulphur and the enzyme rhodanese (a sulphur transferase) is specific to the reaction. It is given i.v.

There are a number of other antidotes, including alternative routes and other sulphur donors. They are beyond the scope of this paper, and the reader is referred to the excellent text of Marrs [3].

All the above drugs are effective. However, there is a general agreement that thiosulphate is too slow in its action and that it should be regarded as a second-line drug only.

Many attempts have been made to identify the antidote that is most effective and to gain international harmony on cyanide treatment. It is fair to say that this has not been forthcoming and the position as of July 2003 was one of lack of consensus. It must be recognized that all of the drugs are effective and by far the most important aspect is for practitioners to agree the preferred antidote with their national authorities and become competent in the use of that drug.

The positions are as follows.

1. In the USA sodium nitrite is the drug of choice. It has a (comparatively) wide margin of safety, but when large doses are given the proportion of methaemoglobin must be monitored.

2. In the UK dicobalt edetate is preferred. It is very rapid in action, but has significant toxicity in its own right. Indeed, before giving the drug one has to be certain that the victim is actually suffering from a cyanide poisoning.

3. In Germany, dimethylaminophenol is recommended. It induces a quick and profound methaemoglobinemia. Monitoring of methaemoglobin is important and reversal with methylene blue must be considered. It has the advantage that it may be given i.m., and thus can be given by paramedical personnel. However, the site of injection has been known to become necrotic and there is concern that absorption will be poor in the acute (peripheral shutdown) stage of intoxication/collapse.

4. It is in France that the newest drug (hydroxocobalamin) is gaining ground. It is the precursor of vitamin B₁₂ and has very little toxicity. It is a very large molecule and only binds cyanide in equimolar fashion. Early preparations were much too dilute to be effective, but a freeze-dried preparation (Cyanokit) is now available. Its only disadvantages appear to be a reported difficulty in getting it into solution and its cost.

The use of this drug in industry was considered at the CEFIC Hydrogen Cyanide Conference in Durham in 1998. The conclusion then was that the advantages did not outweigh the tried and tested procedures in place. More recently, Lam and Lau [4] in Hong Kong and Sauer and Kiem [5] in the USA have called for wider application of the drug.

The issue was revisited at the Hydrogen Cyanide Industry Safety Symposium in Florida, USA, in July 2003. The consensus was that hydroxocobalamin had become the clear leader, being efficacious and non-toxic and, therefore, relatively safe for administration when unsure of cyanide intoxication. A change in formulation had overcome the difficulty of getting it into solution, but cost remained high at $600 per dose. [It should be recorded that cost should not be considered a hindrance given the rarity of cyanide events. However, industry maintains a large number of ‘cyanide kits’ containing these materials and considerable outlay will be required for replacing (and maintaining) these kits.]

It is now incumbent on the industry to seek change on the various national recommendations on the matter.
Nitrites are relatively contraindicated in smoke inhalation, as combustion products will contain carbon monoxide as well as cyanides. Haemoglobin will be bound as carboxyhaemoglobin and the induction of methaemoglobinaemia would further compromise $O_2$ transport. This issue remains open in the USA, but an investigation by Kirk et al. [6] concluded that sodium nitrite administration was relatively safe in smoke inhalation victims.

In ingestion, whether accidental (plant cyanogens, etc.) or with homicidal intent, the dose is inclined to be large and very markedly supralethal. When individuals do survive to emergency care, then gastric lavage will remove any remaining cyanide in the stomach and the administration of activated charcoal will help to prevent any further absorption. Further treatment should be supportive and with the preferred antidote.

One of the most difficult issues for physicians remains whether or not to use an antidote. There are no clear and unequivocal signs or symptoms of cyanide intoxication, particularly in the collapsed and moribund patient. Baud et al. [7] identified plasma lactate as an indicator, but a high index of suspicion and a carefully taken history will guide all medical attendants.

First aid

Cyanide is a very rapidly acting poison and the main chance of survival is through proper and prompt first aid. In industry, accidental exposure is through inhalation and/or skin absorption. The priorities are clear: attendants must ensure their own safety by the use of proper personal protective equipment before going to the victim’s aid. The casualty should then be removed from exposure and fully decontaminated.

We should remember that there is a good endogenous clearing mechanism for cyanide and there are anecdotal accounts of individuals being caught in a hydrogen cyanide gas cloud, falling to the ground and then rapidly gaining consciousness when the cloud has passed over. Where individuals are removed from exposure and prevented from absorbing more of the material, therein lies their best chance of survival.

Further first aid measures include the following.

1. Pure (100%) oxygen. In theory, this should be ineffective. However, there appears to be a strong positive effect and it has the merit of being unlikely to cause harm.

2. Amyl nitrite. This drug is inhaled or an ampoule placed in the lip of the mask when mechanical ventilation is being used. It will generate a limited methaemaglobinaemia (thought to be up to 5%), but enough may be generated to save life.

3. In the collapsed patient, cardiopulmonary resuscitation should be used as appropriate. Mouth-to-mouth ventilation is to be avoided in order to prevent contamination of the attendant. Mechanical means should be used (a Pneupac or Flynn Resuscitator).

Summary

Cyanide is a potent poison that has been known from antiquity. Its toxicology is well characterized and there are a number of antidotes, although opinion on the antidote of choice varies between experts and countries. Survival following cyanide poisoning is possible and particularly so where victims are rapidly removed from further exposure and promptly decontaminated.

References