Cyanide poisoning: pathophysiology and treatment recommendations

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INTRODUCTION

This paper aims to assess and compare currently available antidotes for cyanide poisoning. Such evaluation, however, is difficult. Thus, extrapolation from the results of animal studies has potential pitfalls, as significant inter-species differences in response may exist, and these experiments often involve administration of toxin and antidote almost simultaneously, rather than incorporating a more realistic time delay before initiation of treatment. Direct inference from human case reports is also problematic; either because of uncertainties over the exposure levels involved (and hence the likely outcome without treatment), or because of difficulties in identifying the specific contribution of a particular antidote within the overall treatment regimen. Certainly an effort to compare the relative efficacy of cyanide antidotes produces equivocal findings, with no single regimen clearly standing out. Indeed, factors such as the risks of antidote toxicity to various individuals and other practical issues, may be more important considerations. There is therefore no single treatment regimen which is best for all situations. Besides individual risk factors for antidote toxicity, the nature of the exposure and hence its likely severity, the evolving clinical features and the number of persons involved and their proximity to hospital facilities, all need to be considered. Clinically mild poisoning may be treated by rest, oxygen and amyl nitrite. Intravenous antidotes are indicated for moderate poisoning. Where the diagnosis is uncertain, sodium thiosulphate may be the first choice. With severe poisoning, an additional agent is required. Given the various risks with methaemoglobin formers or with unselective use of kelocyanor, hydroxocobalamin may be preferred from a purely risk-benefit perspective. However the former alternatives will likely remain important.

Key words: Cyanide poisoning; oxygen and amyl nitrite; pathophysiology; treatment recommendations.

MECHANISM OF POISONING

Hydrogen cyanide was first isolated from Prussian blue dye in 1786, and cyanide was extracted from bitter almonds around 1800, although the poisonous properties of these had been recognized since antiquity. Today there are a range of cyanide compounds encountered in such industries as electroplating, metal cleaning, gold extraction, and as rodenticides, fumigants or as raw materials including in the plastics industry. Many are rapidly absorbed through the skin as well as the respiratory and gastrointestinal tracts. Inhalation of airborne concentrations in excess of 100 ppm can be fatal within an hour, and concentrations above 300 ppm are generally fatal within several minutes.

Investigation into antidotes, including studies of both cobalt compounds and nitrates, had begun by the late nineteenth century. Research emphases have varied from one country to the next, which has influenced the pattern of clinical use and experience in different nations, and their current licensing arrangements, which tend to favour some antidotes over others. For this reason alone it is not practical to recommend universal use of a single antidote regimen unless it is clearly superior.

The primary effect of cyanide poisoning is impairment of oxidative phosphorylation, a process whereby oxygen is utilized for the production of essential cellular energy sources in the form of ATP (adenosine triphosphate). A necessary part of this process is transfer of electrons from NADH (nicotinamide adenine dinucleotide, supplied via the Kreb's Cycle) to oxygen, via a series of electron carriers. This is catalyzed by the cytochrome oxidase enzyme system in the mitochondria, and the impairment arises from the inhibition by cyanide of cytochrome oxidase a. This in turn arises from the high
binding affinity of cyanide to the ferric ion found in the haem moiety of the oxidized form of this enzyme. The resulting chemical combination results in loss of the structural integrity and, hence, effectiveness of the enzyme. As a result tissue utilization of oxygen is inhibited with rapid impairment of vital functions. Other metabolic processes continue and the rate of glycolysis is increased markedly; however the pyruvate so produced can no longer be utilized via the impaired Kreb's Cycle, and is reduced to lactate, resulting in a metabolic acidosis. Thus it has been shown that cyanide significantly decreases brain ATP and increases brain lactate levels.3

The cytochrome oxidase a3 complex is not the only enzyme affected,1 and other mechanisms are considered significant, particularly in severe poisoning. Thus it is postulated that pulmonary arteriolar and/or coronary artery vasoconstriction can occur, decreasing cardiac output, and in extreme cases resulting in cardiac shock.7 It is possible that the release of biogenic amines may also contribute. Pulmonary oedema has also been observed. It is thought that this is more related to left ventricular failure than capillary endothelial damage or neurogenic causes.3 However the precise mechanisms behind the circulatory changes remain speculative.

SIGNS AND SYMPTOMS

The symptoms of mild poisoning include headache, nausea, metallic taste, drowsiness, dizziness, anxiety, mucous membrane irritation and hyperpnoea. Later frank dyspnoea, bradycardia, hypotension, arrhythmias and periods of cyanosis and unconsciousness develop. In severe cases, progressive coma, convulsions and cardiovascular collapse with shock and pulmonary oedema can occur, with a fatal outcome.

MECHANISMS OF TREATMENT

Cyanide antidotes have been classified into three main groups according to their primary mechanism of action: sulphur detoxification, methaemoglobin formation and direct combination.

Sulphur detoxification

The most important naturally occurring cyanide detoxifying mechanism involves the addition of a sulphur atom to form the much less toxic thiocyanate ion. The two most significant enzymes in this process are mitochondrial rhodanese (thiosulphate-cyanide sulphur transferase) and B-mercaptopyruvate sulphur transferase.8 Various synthetic compounds have been used as sources of additional sulphur to facilitate this natural process. The most frequently used has been sodium thiosulphate, although this does not readily penetrate the mitochondrial membrane within which the rhodanese system operates,18 and is hence not ideal from a theoretical basis. A novel antidotal approach in animal studies has been the administration of exogenous rhodanese as well as a sulphur-donating compound,9 so that the whole reaction can take place readily within the blood, reducing the need for thiosulphate access into the mitochondria. However this has not progressed beyond the experimental stage. Similarly the use of B-mercaptopyruvates or similar sulphur donors, interacting with sulphur transferase enzyme systems which are not intra-mitochondrial, has not progressed to the clinical stage.

Methaemoglobin formation

Various methaemoglobin formers have been tested as antidotes since it was observed that cyanide interacts with met-Hb. In the conversion of oxy-Hb to met-Hb, the iron atoms in the haem groups are oxidized from the ferrous (2+) to the ferric (3+) state and it is the high affinity between cyanide and iron in the trivalent ferric state that is exploited. Methaemoglobin formation provides a large circulating source of ferric ion to counteract the critical cyanide binding to the ferric ion of cytochrome oxidase a3. While the binding affinity of cyanide to metHb is less than that to cytochrome oxidase, the production of large amounts of the alternative substrate can counteract this situation to some extent, with a significant fraction of cyanide combining to form cyanmethaemoglobin. This in turn slowly releases cyanide which diffuses out of the red cells in a gradual fashion producing plasma levels that can be more readily coped with by hepatic rhodanese and other sulphur detoxification enzyme systems. It has been customary to provide exogenous sources of sulphur to facilitate the process and this forms the basis of the classical regimen supported by Chen and Rose9 and others, of intravenous sodium nitrite and sodium thiosulphate.

Methaemoglobin-generating chemicals have been divided into three groups: directly and indirectly acting compounds (the latter requiring metabolic activation), and those requiring the presence of oxygen.11 While the nitrates are direct-acting, sodium nitrite is a relatively slow metHb former relative to 4-dimethylaminophenol (DMAP).12 It is largely for this reason that it has been superseded in Germany and other countries by DMAP (which falls into the third group). However there is evidence that the effect of nitrates is only partially related to met-Hb. Thus there is good evidence for some therapeutic effect before any significant metHb formation could have occurred, and indeed in one experimental study, when such formation was prevented by methylene blue, sodium nitrite still conferred protection.13,14 Further, the effects of nitrates on circulatory haemodynamics may offer an explanation.15 With cyanide, effects on the cardiovascular system can include systemic hypotension in association with a sharp increase in central venous pressure, while, following amyl nitrite treatment in experimental studies, the raised CVP reversed rapidly along with improvement in arterial pressure.16 This has been attributed to the greater vasodilating effect of nitrates on the venous side than on the arterial resistance vessels.
Direct combination

Cobalt compounds have received by far the greatest attention as direct combiners with cyanide, with effects noted before the turn of the century and since confirmed by several workers. Significant toxicity was observed with various cobalt salts, however, so that compounds such as dicobalt edetate (cobalt EDTA) containing cobalt in a chelated form, were also investigated in the hope of their being less toxic. Evans compared a cobalt salt (the acetate), di cobalt edetate, hydroxocobalamin and cobinamide, largely in mice and rabbits. He concluded that 1 mole of cobalt as a salt could combine with 6 moles of cyanide to form a relatively non-toxic anion, while di cobalt edetate combines at a molar ratio of 2 only. One therefore might expect that equimolar doses of the edetate should be less toxic (and efficacious) than cobalt salts. However this question does not appear to be resolved completely. Certainly toxicity with Kelocyanor (the commercial form of di cobalt edetate) can occur; this may be related in part to the fact that this preparation contains some additional free cobalt. As regards efficacy, Paulet claimed that di cobalt edetate was more effective in dogs than various cobalt salts, and indeed, more effective than sodium nitrite either alone or in combination with thiocyanate.

Hydroxocobalamin (Vitamin B12a) was later investigated as a potentially less toxic source of cobalt. It binds cyanide strongly to form cyanocobalamin or Vitamin B12. In animal studies it was found to be a rapidly acting antidote and clinical studies have suggested few toxic effects. The antidotal effect is enhanced by thiocyanate.

ADVANTAGES AND DISADVANTAGES OF TREATMENTS

Evaluation and comparison of antidotes, with regard to relative efficacy and toxicity, is not straightforward. Results from animal studies must be interpreted cautiously, giving consideration to possible inter-species differences plus the particular route and timing of antidote administration relative to that of the toxin. Prophylactic or contemporaneous use gives no idea of the time after exposure within which treatment can still be effectively initiated. On the other hand interpretation of human case reports can also be difficult because of uncertainties over the dose ingested or the exposure levels involved, and hence the likely clinical course in the absence of antidotal treatment. Thus it has been pointed out that in the review by Chen and Rose of 48 cases suggesting a high effectiveness of the ‘classical’ therapy combination, in very few were blood cyanide levels or other indices of severity documented. Even where such indices are available, it is difficult to distinguish between the roles played by different elements of the treatment regimen, and to define the contribution of a specific antidote. (Indeed, there is good evidence that antidotes are not always essential for a satisfactory outcome even in the presence of severe poisoning).

Nevertheless attempts have been made at comparison within the limits of the data available. Paulet found that Kelocyanor was more effective than sodium nitrite alone or in combination with thiocyanate. This is not surprising given its relatively quick reaction with cyanide compared with the slower, indirect effect of metHb formation by nitrites, although the latter may act in other ways as well. However some studies have suggested that the more rapid metHb former, DMAP, could be more effective than Kelocyanor. A firm conclusion regarding comparative efficacy appears difficult to make, certainly from the human data alone. While Kelocyanor may be slightly more effective than the nitrites, it may be less so than DMAP, and the effectiveness of all the antidotes is enhanced by thiocyanate. Partly due to these uncertainties, toxicity considerations are important in any evaluation.

The major concern with nitrites and DMAP is excessive metHb production. This is a particular risk in young children, with serious complications and death being described especially in those more susceptible due to metHb reductase deficiency. MetHb levels over about 40% pose significant risk. It is established that cyanide toxicity, as well as carbon monoxide (and smoke particulates) can be a risk for fire victims and the possibility of combined toxicity or even synergy should not be overlooked. It is preferable, however, that any cyanide component should not be treated with metHb formers, as significant carboxyHb may already be present, reducing oxyHb levels and conferring increased sensitivity to such agents. Further, a degree of ‘baseline’ methaemoglobinemia has been described in smoke inhalation victims, reinforcing the argument for other types of antidotes for any cyanide component in this situation. A further difficulty is that while the level of methaemoglobin can be measured, the test does not in fact detect cyanmethaemoglobin and hence does not provide an accurate guide to the amount of oxyhaemoglobin. Hypotension has also been cited as a hazard with nitrites, although the cardiovascular effects of nitrites can be beneficial and the hazard relates more to excessive speed of administration. DMAP does not have the disadvantage of nitrites in posing a risk of hypotension. However it also does not share their beneficial vasodilatory properties, and given its more rapid production of metHb, may pose a greater risk for those especially susceptible to this effect which can be unpredictable in its degree. Haemolysis is a rare complication from nitrites and is also a risk with DMAP, patients with glucose-6-phosphate-dehydrogenase deficiency being most susceptible.

Toxicity is a major concern with Kelocyanor. Adverse effects include possible anaphylactic reactions which may manifest as urticaria, angioedema affecting the face and neck and also occasionally the larynx, dyspnoea and hypotension. Cardiac arrhythmias and convulsions have also been described. The cobalt and cyanide interaction involves mutual inactivation so that the combination is less toxic than either on their own. Thus cobalt toxicity per se should be much less of a risk in cases where cyanide poisoning genuinely exists. This has led to recommendations that Kelocyanor should only be used in
well-established cases and not in equivocal cases where exposure seems just a possibility. This requires clinical experience and strict criteria for the diagnosis, as anxious patients involved in ‘scares’ over possible exposures may exhibit signs and symptoms resembling mild or early poisoning. Administration of Kelocyanor in such cases would not be warranted and is more likely to result in toxicity. While good judgement has generally resulted in few adverse effects in industrial settings, inappropriate use with adverse consequences remains a possibility.

Furthermore, toxic reactions have been described even in cases of unequivocal cyanide poisoning. The toxicity is considerably reduced by co-administration of glucose (mechanism uncertain), which is thus incorporated into the formulation. However the recommendation not to use in doubtful or mild cases still stands.

The relatively low toxicity of hydroxocobalamin combined with its rapid action are major advantages of its use. However a practical inconvenience is that large volumes of the commercial preparation are required to deliver a sufficient dosage, due to its high molecular weight plus the fact that it can only combine with cyanide on a one-to-one molar basis. Thus detoxification of 1 mmol cyanide (or 65 mg KCN) requires 1406 mg hydroxocobalamin, while in most countries it is only available in formulations of 1–2 mg. In other countries it is available as a reconstitutable powder but still requires large volumes of solution best given as an IV infusion, making its use outside a hospital environment rather impractical. It has been used principally in France, often in combination with thiosulphate, for several years. While clinical experience elsewhere has been limited, this combination is gaining increasing support, principally because of its apparent lower toxicity and fewer at-risk situations than with the other major alternatives. The most common adverse effect is a harmless orange-red discoloration of the skin, mucous membranes and urine. However some issues remain to be addressed, such as its relative cost and apparent toxicity in animal studies.

The findings from cyanide antidote comparison exercises are arguably equivocal rather than clear-cut, and this appears to be reflected in the recommendations of the IPCS/CEC Committee set up for their evaluation. Thus the two metHb generating compounds discussed above are presented as alternatives, as are the two cobalt compounds. This may be partly due to practical considerations such as the varied clinical experiences and licensing arrangements in different countries. The layout of the overview in this publication however may present some risk of misinterpretation.

**FACTORS IN THE CHOICE OF ANTIDOTE**

The IPCS/CEC Committee identified several factors which should influence the choice of antidote (if any) to use in cyanide poisoning. These include: (1) the nature of the cyanide compound and the exposure circumstances; (2) the severity of poisoning; (3) the presence of certain risk factors for antidote toxicity; (4) the number of patients involved and (5) proximity to hospital facilities.

This implies that there is no single best antidote for all situations. Thus nitrites or other metHb formers cannot be recommended for fire victims, young children or those with certain enzyme (e.g., G6PD) deficiencies which increase susceptibility. On the other hand Kelocyanor is not recommended for equivocal or mild cases.

**Mild poisoning**

Where symptoms suggest mild poisoning, rest and oxygen treatment may be all that is required. Any deterioration is an indication for amyl nitrite treatment (0.2–0.4 ml via Ambu bag) and arrangement for transfer to hospital. Symptoms may be somewhat delayed with some compounds (e.g., acetonitrile) which only release cyanide on metabolism and judgement is required on if and when to transfer. While amyl nitrite has been found (at least in inhalation and self-administration) to produce only very modest metHb levels (up to 7%) which are insufficient to bind a potentially lethal dose of cyanide, there is increasing evidence that the cardiovascular effects of nitrites are their most important mechanism of action.

**Moderate poisoning**

For more moderate poisoning where symptoms may include brief periods of unconsciousness, convulsions or cyanosis, intravenous antidotes are also indicated. Clearly these are most easily administered within a hospital setting, ideally an intensive care unit, where overall management will be most effective. Sodium thiosulphate may be the first choice, particularly if the diagnosis is uncertain.

**Severe poisoning**

In severe poisoning with deep coma, dilated non-reacting pupils and worsening cardiorespiratory function, an additional intravenous antidote should be administered. Methaemoglobin formers can be hazardous in some circumstances, and kelocyanor can be a risk particularly when cyanide poisoning is an incorrect diagnosis. From a strictly risk-benefit point of view, hydroxocobalamin is arguably the best alternative. However due to its relative cost and some practical difficulties with administration, it is probable that nitrites and kelocyanor will retain a role, particularly for physicians familiar with them.

Recommended dosage regimens for available antidotes are listed in Table 1. Repeat dosing may be indicated in the case of a poor response. Recommendations are the same dose for thiosulphate or Kelocyanor, or half the initial dose of sodium nitrite after a 30 min interval. However it is strongly advised to review the diagnosis and monitor for toxicity before repeat-dosing with Kelocyanor or sodium nitrite.

**SUPPORTIVE TREATMENT**

What has emerged is the importance of oxygen treatment and the need for ongoing clinical and biochemical monitoring. There is now experimental evidence that
**Table 1. Recommended cyanide antidote dosage regimens**

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Dose and Administration</th>
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<tr>
<td>Sodium thiosulphate</td>
<td>50 ml of 25% solution (12.5 g) IV over 10 min</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>10 ml of 3% solution (300 mg) IV over 5–20 min</td>
</tr>
<tr>
<td>4-DMAP</td>
<td>5 ml of 5% solution (250 mg) IV over 1 min</td>
</tr>
<tr>
<td>Dicobalt edetate</td>
<td>20 ml of 1.5% solution (300 mg) IV over 1 min</td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>10 ml of 40% solution (4 g) IV over 20 min</td>
</tr>
</tbody>
</table>

*Recommended initial doses may be somewhat higher in children, e.g., sodium thiosulphate: 300–500 mg/kg; sodium nitrite: 4–10 mg/kg.*

Oxygen has specific antidotal activity. It can accelerate the reactivation of cytochrome oxidase and may have other modes of action. Artificial ventilation with 100% oxygen is recommended, though for no longer than 12–24 hours at this concentration. Monitoring of arterial blood gases, fluid and electrolyte balance, level of consciousness and circulatory status including CVP measurements are essential in addition to intensive support of respiratory function. Blood cyanide estimations are useful as an added guide to management. However, the majority of cyanide in the bloodstream resides in the red cells (even in the absence of metHb formation) so the test may not accurately reflect plasma levels of free cyanide which probably correlates better with symptoms. Nonetheless the IPCS/CEC review suggests that mild poisoning is often associated with blood concentrations below 2 mg/l while the most severe cases usually have levels above 3 mg/l and such levels may be a useful adjunct in monitoring the clinical course.

**SUMMARY**

Cyanide poisoning in the workplace has historically resulted in an emotional first aid response. The purpose of this article is to make clear that with proper judgement, based on evaluation of the clinical state of the victim and the circumstances of their exposure, a range of treatment procedures can be provided.

With mild presentations, oxygen and amyl nitrite are the treatment of choice. With moderate to severe cases, oxygen and amyl nitrite together with any necessary immediate first aid resuscitative measures are indicated, followed by prompt transfer to an intensive care unit.

When cyanide is used as part of a work process in an isolated worksite, it should be expected that health personnel (doctor, nurse or first-aider) be trained to administer intravenous treatments if required, based on the criteria discussed.

**REFERENCES**