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Is there an ideal pre-hospital drug treatment for acute cyanide poisoning?

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Review

Is there an ideal pre-hospital drug treatment for acute cyanide poisoning?

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Abstract

Introduction

Cyanide, due to its toxicity and prevalence in a variety of industries, is a suitable agent for terrorists or disaffected persons to use as a weapon of terror. New Zealand's National Poisons Centre lists five cyanide antidotes. This review aimed to identify whether there is an ideal pre-hospital drug treatment for acute cyanide poisoning.

Methods

Literature less than 10 years old was selected after a keyword search. The articles were reviewed for specific positive and negative properties of each antidote.

Results

Thirty-nine articles were reviewed of which four were excluded. Results varied, with hydroxocobalamin scoring highly on effectiveness, with limited negative effects. It also demonstrated positive haemodynamic effects, suitability in cases involving trauma, carbon monoxide (CO), smoke inhalation casualties and was safe for pre-hospital use. Sodium nitrite, followed by dicobalt edetate had the next highest scores for efficacy. However, both scored negatively for their effects on blood, causing hypotension and toxicity, and they are unsuitable for trauma, CO or smoke inhalation casualties. Sodium thiosulphate, with a moderate level of efficiency, remained most effective when co-administered with other antidotes. 4-dimethylaminophenol and amyl nitrite rated the lowest, with negative effects similar to sodium nitrite. Adrenaline was tested as an antidote in one study where two novel antidotes both demonstrated promising results.

Conclusion

Hydroxocobalamin had the highest success rate and its safety profile make it the most suitable pre-hospital drug treatment for acute cyanide poisoning.

Keywords

cyanide, hydroxocobalamin, sodium nitrite, dicobalt edetate, 4DMAP, WMD, CBR, CBRNE

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Introduction

Cyanide is a potent metabolic poison. It is prevalent in New Zealand's possum control and precious metal mining industries, among other industrial use (1). Cyanide, due to its toxicity and prevalence in a range of industries, can be a suitable agent for disaffected persons to use as a weapon of terror. Cyanide has been suspected of being used by state actors, such as Saddam Hussein, during the chemical attacks at Halabja and non-state actors in thwarted attacks, on Japan's subway system (2,3). Cyanide acts by binding to cytochrome A3 in the mitochondria preventing aerobic metabolism. Due to the rapid toxic effects of cyanide, pre-hospital administration of antidotes provide the best chance of survival. The main treatments identified by the New Zealand National Poisons Centre are oxygen, amyl nitrite, hydroxocobalamin, sodium nitrite and sodium thiosulphate (4). Amyl nitrite, sodium nitrite and dicobalt edetate are known to cause hypotension, and dicobalt edetate also shows the effects of cobalt poisoning, both of which may exacerbate the condition in hypotensive cyanide poisoned patients.

Hydroxocobalamin is an alternative antidote to the previously mentioned antidotes and has limited adverse effects, none of which exacerbate traumatic injuries. Amyl nitrite is seen as a temporising treatment, if there is a delay in administration of an intravenous antidote. Oxygen is not an antidote, but it is an accepted supportive adjunct (4).

Initial review of literature found most cyanide treatment research drew data from in-hospital treatment. This review aims to identify the most effective pre-hospital drug treatment, emerging drug treatments and if there is an ideal pre-hospital drug treatment for acute cyanide poisoning. A consideration included will be the safety profile of each drug.

Methods

This study was conducted using a review of the recent literature (less than 10 years old). This study was conducted as a research project towards a BHSci Paramedicine in 2013. Only the Scopus medical database was used due to the size of the project. A key word search was used, searching for the words: pre*hospital; cyanide; antidote; antidotes; and treatment. Amyl nitrite was excluded from the search due to its variable uptake and potency, making it unsuitable for empirical treatment. The search, which produced 39 results, was limited to English and to literature published after 2002. New Zealand Poisons Centre guidelines were also reviewed. These provide current guidance for poison treatment in New Zealand. Four results were excluded from the review; three provided no antidote data, one of these could not be accessed to extract data, and the fourth was focused on forensic analysis and not treatment.

A review of these results was carried out for both specific positive and negative effects, these being: physiological effects on the central nervous system (CNS); cardiac effects; effect on blood; haemodynamic stability; toxicity; suitability for use in trauma; suitability for carbon monoxide or smoke inhalation

casualties; safety for administration to non-poisoned casualties; and safety for pre-hospital use. The CNS results were excluded as no data was found. Each element was graded with a value of 1 (positive), -1 (negative), 0.5 (partial effects) or 0 (no datum), to provide a quantifiable value to the results. The results have been summarised by element.

Results

The majority of the 35 articles were retrospective reviews with one human, one beagle and three swine studies. Hydroxocobalamin had the highest reported level of efficacy with 23 positive results, however this may be due to the fact that it is mentioned in more literature (18 times) compared to sodium thiosulphate (three times), sodium nitrite (one time) and adrenaline (one time). Sodium nitrite scored 10 times with dicobalt edetate only scoring five times. Sodium thiosulphate scored five times with some of these points being partial due to the drug having limited effectiveness as a single treatment (5,6); 4-DMAP (4-dimethylaminophenol) scored once only. Amyl nitrite scored zero and of note adrenaline ('epinephrine' is the United States spelling of Australasia's 'adrenaline', for the purposes of this research adrenaline will be used) scored once from a single study (7).

When assessed for cardiac affects, hydroxocobalamin had two positive reports, dicobalt edetate and 4-DMAP both had negative reports. No cardiac effects were noted for the other antidotes (sodium nitrite, sodium thiosulphate, 4-DMAP, amyl nitrite and adrenaline). Hydroxocobalamin was mentioned twice for positive effects on blood. Negative effects were reported for sodium nitrite 14 times, dicobalt edetate once, 4-DMAP once and amyl nitrite once. Sodium thiosulphate and adrenaline had no reported effects on blood. Positive haemodynamic effects were reported with hydroxocobalamin on 14 occasions. Negative effects were noted with sodium nitrite 16 times, 4-DMAP twice, dicobalt edetate, and amyl nitrite both had results once, respectively. Sodium thiosulphate and adrenaline had no reported effects on haemodynamic stability (8).

Hydroxocobalamin was noted as suitable for use in trauma casualties three times. The following antidotes were noted as unsuitable for use in trauma casualties suffering from the effects of cyanide poisoning: sodium nitrite 12 times; amyl nitrite twice; dicobalt edetate once; and 4-DMAP once, respectively. Sodium thiosulphate and adrenaline received no comments regarding suitability in trauma casualties. Hydroxocobalamin was noted eight times as being suitable for use with CO or smoke inhalation casualties. Conversely, negative effects were noted for sodium nitrite 12 times, 4-DMAP twice, dicobalt edetate once, and amyl nitrite once as all were noted as not suitable for use in CO or smoke inhalation cases. There were no comments regarding the suitability of sodium thiosulphate and adrenaline.

Hydroxocobalamin was noted eight times to be safe for administration when cyanide poisoning hadn't occurred. Sodium nitrite and dicobalt edetate were noted to be unsuitable when cyanide poisoning had not occurred twice, and amyl nitrite, once.

There were no comments regarding sodium thiosulphate, 4-DMAP or adrenaline being suitable when cyanide poisoning had not occurred. The only antidotes identified in the literature as safe for pre-hospital use were hydroxocobalamin, noted five times and sodium thiosulphate once, respectively. Six positive

reports revealed hydroxocobalamin had no toxic effects. Toxic effects were noted with sodium nitrite four times, dicobalt edetate once, and amyl nitrite, once. Figure 1 shows these results.

Figure 1. Chart of negative and positive results

Discussion

This review has examined 35 published papers and discussed the key findings. Hydroxocobalamin had twice the reported success rate of sodium nitrite. This was when the drug was administrated either by itself or in conjunction with sodium thiosulphate (5). However, to achieve this level of effectiveness large doses of hydroxocobalamin are required (9-11). Despite the large dosage, hydroxocobalamin had

no reported adverse effects apart from reports of urticarial rashes (12). An added benefit of this drug is that it increases blood pressure, which is likely to be low in cyanide poisoned patients (13). These effects were not judged to be of concern by the literature. Hydroxocobalamin has been administered to healthy individuals with no serious adverse effects (12). Similar research with other antidotes was not noted in the literature reviewed. This may be because human trials of the other antidotes are not likely to receive ethical approval owing to their known toxic or adverse effects.

A noted negative effect of hydroxocobalamin is the interference with some haematological testing methods, which may affect the measurement of carbon monoxide levels in blood (14,15). This is an issue for longer term assessment of the patient but does not affect pre-hospital treatment. With this in mind, hydroxocobalamin appears to be the most suitable pre-hospital drug treatment for acute cyanide poisoning owing to its high level of effectiveness, limited adverse effects and suitability for use in patients affected by smoke or CO inhalation.

Sodium nitrite had the next best results followed by dicobalt edetate and sodium thiosulphate. In several studies, sodium thiosulphate was administered in conjunction with sodium nitrite and dicobalt edetate which increased their efficacy. Conversely sodium thiosulphate was noted by several authors to have limited potency as a sole empirical treatment. Negative effects were noted for both sodium nitrite and dicobalt edetate, with each having adverse haematological, haemodynamic and toxic effects. Both were noted to be unsuitable for administration in smoke inhalation or carbon monoxide poisoned casualties and are not safe for administration when poisoning had not occurred (6,7).

Dicobalt edetate was also noted to be cardio-toxic. With the exception of sodium thiosulphate, none of the other drugs were identified as safe for use in the pre-hospital setting. Sodium thiosulphate was noted to be unsuitable for use in trauma, or where poisoning hadn't occurred, and was associated with some adverse effect (16). For these reasons sodium nitrite and dicobalt edetate appear to be unsuitable for pre-hospital drug treatment of acute cyanide poisoning. Sodium thiosulphate, although safer, has been noted to be unsuitable for use as a sole antidote, however, it provides synergistic treatment when used with hydroxocobalamin, sodium nitrite or dicobalt edetate.

4-DMAP and adrenaline had similar reported levels of efficacy, while amyl nitrite was not noted to be either effective or non-effective due to the variable uptake of this inhaled drug (all other antidotes were intravenous, with the exception of oral novel antidotes). 4-DMAP scored negatively on the majority of measures, possibly because it is an older antidote that appears to have fallen from use. Amyl nitrite was mentioned as a temporising agent until empirical treatment was possible due to the variable uptake of the drug. A common statement was to use amyl nitrite until intravenous access and treatments were readily available (16,17). It suffers similar negative effects to sodium nitrite with adverse effects on blood, haemodynamic stability and potential toxicity. Additionally it is not suitable in trauma, CO and smoke inhalation casualties or when poisoning had not occurred. Adrenaline, although not a cyanide antidote, was mentioned in one study (7) (the extracted data was limited to it being effective).

The study used 45 swine poisoned with potassium cyanide,

then administered hydroxocobalamin, adrenaline or saline as the control. Eleven of the 15 of each of the hydroxocobalamin and adrenaline groups survived compared to 0/15 of the control group. The main variance between the surviving groups was that those treated with hydroxocobalamin had faster recovery, lower lactate levels and required reduced adrenaline administration for hypotension (7). No mention, positive or otherwise, was noted regarding the suitability of either drug for pre-hospital use.

Novel antidotes

One study identified two novel antidotes for cyanide poisoning (18). This study identified two potential pro-drugs of 3-mercaptopyruvate for the treatment of cyanide poisoning with testing being conducted in mouse models. Of particular note was their successful prophylactic use. Due to the limited scope and non-human trials, this is an important development as current treatments are only given post-exposure. These pro-drugs, if able to be used as prophylaxis, could be useful to both security and military services who may be at risk of exposure to impending cyanide release or attack. The combination of the prodrugs of pro-drugs of 3-mercaptopyruvate with adrenaline warrant further research as they provide potential alternative drug treatments.

Limitations of this study

The limitation of this review was that only the Scopus database was used. This was done to limit the data set due to time and size restrictions. Hydroxocobalamin featured more often in research topic headings; 18 times compared to sodium thiosulphate (three times) and sodium nitrite and adrenaline (one each). A data search using the same keywords with a date limitation of a decade earlier (1992-2002) produced only two results: one looked at decontamination, the other patient management during disasters.

Another reason for hydroxocobalamin having prevalence could be the recent approval for use in the United States, and research to confirm its effectiveness and safe use. This in conjunction with the reduction of use of sodium nitrite, as hydroxocobalamin is used as substitute. Further research could be conducted in this area to confirm if this bias is correct or if greater balance is required when studying cyanide antidotes.

Conclusion

New Zealand's National Poisons Centre lists five different cyanide antidotes. This review found hydroxocobalamin to be the most effective antidote with the highest safety profile, making it the most ideal pre-hospital drug treatment for acute cyanide poisoning. Due to the limited scope of this review further research is recommended.

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Conflict of interest

The author declares he has no competing interests. The author of this paper has completed the ICMJE conflict of interest statement.

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