

REVIEW

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ACUTE CYANIDE POISONING: CLINICAL SPECTRUM, DIAGNOSIS, AND TREATMENT

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Cyanide poisoning presents in many forms. Industrial intoxications occur due to extensive use of cyanide compounds as reaction products. Smoke inhalation, a polyintoxication, is most often responsible for domestic cyanide poisonings. Suicidal poisonings are rare. Cyanogenic compounds may produce acute or subacute toxicity. Signs of cyanide poisoning include headache, vertigo, agitation, confusion, coma, convulsions and death. Definitive laboratory confirmation is generally delayed. Elevated plasma lactate, associated with cardiovascular collapse, should suggest cyanide intoxication. Immediate treatment includes 100% oxygen, assisted ventilation, decontamination, correction of acidosis and blood pressure support. Antidotes include oxygen, hydroxocobalamin, di-cobalt EDTA and methaemoglobin-inducers. Hydroxocobalamin is an attractive antidote due to its rapid cyanide binding and its lack of serious side-effects, even in the absence of cyanide intoxication. Sodium thiosulphate acts more slowly than other antidotes and is indicated in subacute cyanogen poisoning and as an adjunct to acute cyanide poisoning. Initial evaluation of antidotal efficacy is based on correction of hypotension and lactic acidosis; the final analysis rests on the degree of permanent central nervous system injury.

Key terms:
antidotal efficacy, cyanide antidotes, cyanogens, hydrogen cyanide, hydroxocobalamin, methaemoglobin, nitriles, thiosulphate

Acute cyanide poisoning is not as rare as was once believed. Formerly recognized only as a dramatic form of suicide and the source of occasional industrial intoxications, cyanide is now known to be an important component in the smoke produced when a multitude of natural and synthetic compounds, including silk,

wool, nylon, polyurethane, melamine, polyacrylonitrile and polyamide plastics, are burned (1-3). Depending on temperature and oxygen conditions, virtually every structural fire has the potential to produce substantial amounts of airborne cyanide, and thus lead to cyanide poisoning.

The potential for industrial intoxications should not be minimized either. Due to their chemical reactivity, cyanides and cyanogens are utilized in laboratories as reagents, and in many industries for the fabrication of other products, such as plastics, and in electroplating, mining, photography, and precious metal reclamation. Cyanides and cyanogens serve as fumigants for warehouses, ships, and other buildings. While improvements in industrial hygiene should diminish the likelihood of significant cyanide exposure in most developed nations, the potential for untoward incidents continues to exist.

Finally, suicidal cyanide poisoning, while rare, requires rapid diagnosis and treatment if positive outcomes are to be achieved. It is thus incumbent on physicians and other health care providers to renew their awareness of this potentially deadly toxin.

PATHOPHYSIOLOGY

The pathophysiology of cyanide poisoning is based primarily on cyanide capacity to inhibit oxidative phosphorylation by attachment to the ferric iron of the haem moiety of mitochondrial cytochrome oxidase. Though oxygen remains present, it cannot be utilized, resulting in cellular hypoxia. Thus, the most oxygen sensitive tissues, the brain and heart, are rapidly affected.

While interruption of oxidative phosphorylation is unquestionably a key mechanism for cyanide toxicity, it is known that a host of other enzyme systems are inhibited by cyanide, including glutamate decarboxylase, xanthine oxidase, superoxide dismutase, nitrite reductase and others (4). As nitric oxide synthase is, like cytochrome oxidase, a haem-based molecule, it is not unreasonable to suspect that it too is inhibited by cyanide. As the pivotal role of nitric oxide in the control of vascular tone and as a neurotransmitter becomes increasingly apparent, knowledge regarding the occurrence of inhibition of nitric oxide synthase becomes essential. Such effects are currently under study. Fortunately, cyanide binding of haem proteins is reversible. Thus, with rapid supportive therapy and the use of cyanide antidotes, cyanide poisoning may be successfully treated.

SPECTRUM OF ACUTE CYANIDE POISONING

Cyanide is present in a number of forms, including hydrocyanic acid, soluble and relatively insoluble cyanide salts, and cyanogens. The form of cyanide to

which one is exposed is of great importance in the rapidity of symptom onset and, to some extent, the gravity of these intoxications.

Hydrogen cyanide

Hydrogen cyanide has been responsible for literally millions of human deaths. As mentioned, it is now appreciated that cyanide plays an important role in death from smoke inhalation. Along with carbon monoxide and other compounds, cyanide forms part of the composition of gases responsible each year for more poisoning deaths than any other compound. Although these smoke inhalation deaths are often classified as "carbon monoxide poisoning", it is clear that a polyintoxication is at work.

Intentional cyanide poisoning was at the core of one of the darkest eras in the history of mankind. After viewing its efficacy as a raticide when constructing the death camp at Auschwitz, Commandant Rudolph Hoess instituted the use of hydrogen cyanide for mass exterminations (5). Cyclon B (cyanide) was to have been the Nazis' "final solution", and was used throughout the holocaust.

Hydrogen cyanide, generated by the mixture of a strong mineral acid with a cyanide salt, remains to this day a means of official extermination, being used in legal executions in the United States.

Industrial poisonings with hydrogen cyanide are often collective. Not uncommonly, as one unprotected worker collapses, others come to the rescue only to be overcome by this invisible toxin. If concentrations are adequate, death may be virtually instantaneous.

Soluble salts

The soluble salts of cyanide (sodium, potassium, calcium, and ammonium cyanides) are responsible for rapidly evolving intoxications. These salts dissolve easily in liquids under physiological conditions. The intoxication by ingestion of cyanide salts results not only in absorption of the cyanide ion by the intestine, but in the release and subsequent inhalation of hydrogen cyanide gas generated in the acid milieu of the stomach. It should be underscored that the pKa's of cyanide salts are relatively high: ~9, so that even water contact (pH 5-7) may result in a deadly release of cyanide gas (6).

Low solubility salts

The poorly soluble salts of cyanide (mercury cyanide and oxycyanide, copper, silver and gold cyanides) may be responsible for intoxications after massive ingestion or when they come in contact with strong mineral acids. The mercury salts of cyanide may also induce mercury intoxication (7, 8).

Cyanogens

The halogenated cyanide derivatives, cyanogen chloride and cyanogen bromide, are often used in fumigation. In addition to being capable of inducing cyanide poisoning, they are potent pulmonary irritants and may result in pulmonary oedema.

Sodium nitroprusside, used therapeutically in the treatment of angina and in the control of blood pressure, may result in cyanide poisoning when administered at high doses or over a long period of time (9).

The nitriles (R-CN) are ubiquitously utilized as solvents (acetonitrile), as intermediates in chemical synthesis (butyronitrile, propionitrile), and extensively in the manufacture of plastics (acrylonitrile). The toxicity of nitriles is, in part, a function of their capacity to liberate cyanide *in vivo* by hepatic metabolism (10, 11). They may have additional toxicity as well. The metabolism of the aliphatic nitriles (acetonitrile, acrylonitrile, propionitrile and butonitrile) to cyanide occurs over a period of several hours. Tragic poisonings in infants have occurred due to ingestion of acetonitrile packaged for the removal of artificial finger nails (12).

The hexaferrocyanates (Prussian blue and Prussian red), the isocyanates, and thiocyanates are stable compounds and are not cyanogenic.

CLINICAL PRESENTATION AND DIAGNOSIS

The delay between cyanide exposure and the onset of symptoms depends on the type of cyanide responsible, the route of entry, and the dose. This may vary from a few seconds, in the case of inhalation of a strong concentration of hydrogen cyanide, to several minutes after ingestion of cyanide salts, to many hours after skin absorption of acetonitrile.

The inhalation of hydrogen cyanide is immediately followed by headache, vertigo, agitation and confusion. Following this, dyspnoea and hyperpnoea ensue, consistent with stimulation of the central respiratory centre and presence of a severe metabolic lactic acidosis, shortly followed by loss of consciousness and convulsions. Cardiovascular collapse and cardiorespiratory arrest may rapidly intervene. Due to the diminished consumption of oxygen, the patient's external appearance may be misleadingly reassuring, with a persistent "rosy" skin colour even during cardiac arrest, rather than the typical cyanosis seen with other aetiologies of cardiovascular collapse. Furthermore, the collapse is frequently associated with a normal heart rate. Thus, one must thus keep a watchful eye on the arterial blood pressure from the outset of the discovery of these patients.

Table 1 reveals the experience of the Toxicological Intensive Care Unit at Fernand Widal Hospital among 36 cases of inhalation or ingestion of cyanide or cyanogens, excluding smoke inhalation. It is noteworthy that none of the signs are uniform, lactic acidosis being the most consistent finding. The "classic" odour of bitter almonds is often lacking, can only be detected by a minority of examiners

when present, and in the case of smoke inhalation may be masked by the smell of soot.

Table 1 *Clinical symptoms among 36 cyanide intoxications* admitted to the Toxicological Intensive Care Unit at Fernand Widal Hospital*

Symptom	n	% of total
Asymptomatic	8	22
Cardiovascular collapse	10	28
Coma	13	36
Convulsions	6	17
Metabolic acidosis	18	50
Post-anoxic coma and death	5	14
Psychomotor retardation	6	17
Respiratory arrest	8	22

* Intoxications by ingestion or inhalation, excluding smoke inhalation victims.

Smoke inhalation is responsible for a systemic polyintoxication, notably by carbon monoxide and hydrocyanic acid (2, 13-15). Multiple factors contribute to the asphyxia of fire victims (16):

- the decrease in partial pressure of oxygen in the atmosphere provoked by combustion;
- the diminution of oxygen-carbon dioxide exchange in the pulmonary arterioles related to the broncho-alveolar injury induced by the associated irritant gases (nitroxides, HCl, formaldehyde, etc.);
- diminution of oxygen transport by carbon monoxide; and
- blockade of cellular utilization of oxygen by cyanide.

In sum, this ensemble of oxygen deprivation by simple and complex (chemical) asphyxia results in symptomatology that is common to exposures by the individual components: headache, confusion, tachypnoea, vertigo, syncope, coma, convulsions, cardiac rhythm disturbances and death. Thus, it is not possible to anticipate the toxic gases as cause on the basis of clinical signs.

Cyanide intoxication should be suspected in a fire victim in the following circumstances:

- the setting of fire in an enclosed space;
- the presence of soot in the mouth and sputum (indicating proximity to the burning material);
- the presence of altered consciousness or higher functions;
- the existence of arterial hypotension; and
- plasma lactate ≥ 10 mmol/L (in the absence of burns $\geq 15\%$ total body surface area).

While persistent coma presents no diagnostic dilemma, it is much more difficult to identify transitory loss of consciousness. The impairment in these patients is often subtle. Asking a patient exposed to a melange of asphyxiants

if he or she has lost consciousness seems somewhat akin to asking an alcoholic if he or she has had too much to drink. Thus, one must interrogate rescuers and family members, and carefully elicit from the patient signs of anoxic encephalopathy, manifested by slowing of thought processes, mental confusion, or incoherent agitation. A frequent presentation is that of a conscious, agitated, non-cooperative, confused patient. Among 138 smoke inhalation victims treated in our hospital who presented with soot in the mouth or sputum, the association of these neurological signs (n=89) (loss of consciousness or alteration of superior functions, even if transient), was very sensitive (98%) for significant cyanide intoxication (blood concentration $\geq 40 \mu\text{mol/L}$), though the predictive value of a positive test was low (44%) (Table 2). Conversely, the absence of these signs permits the exclusion of a diagnosis of grave cyanide intoxication (negative predictive value 98%).

Table 2 Clinical criteria predictive of cyanide intoxication in 138 smoke inhalation victims out of 467 admitted

Neurological disturbances*	Blood cyanide $\geq 40 \mu\text{mol/L}$	Blood cyanide $< 40 \mu\text{mol/L}$
Present	39	50
Absent	1	48

* Neurological disturbance was defined as loss of consciousness or disturbance or alteration of superior functions (change in behaviour, psychomotor retardation)

Sensitivity = 98%; Specificity = 49%; Positive predictive value = 44%; Negative predictive value = 98%

Looking further at the 89 patients with neurological disturbance, the association of an arterial blood pressure less than 100 mm Hg at the time of discovery of the victim, in the absence of evident trauma (fall or jump from height, blast injury or extensive burns), was very suggestive of cyanide intoxication, with a specificity of 85%, and a positive predictive value of 72% (17).

LABORATORY STUDIES

Lactic acidosis is the biochemical translation of the inhibition of mitochondrial oxidative phosphorylation. It is the most reliable laboratory finding of cyanide intoxication generally available within the first hour after exposure. In a patient suspected of cyanide intoxication, the discovery of a major lactic acidosis associated with one or more of the other symptoms in Table 1 should evoke the diagnosis of cyanide intoxication and should be treated as such. Elevated lactic acidosis has an important diagnostic value because quantification of blood cyanide and of its metabolite, thiocyanate, are not typically available urgently. There exists

a significant correlation between the plasma concentration of lactate and that of cyanide. In the case of known "pure" cyanide exposure, a lactic acidemia greater than or equal to 7 mol/L should evoke the diagnosis of grave cyanide intoxication, defined by a blood concentration greater than or equal to 40 $\mu\text{mol/L}$ (18). In smoke inhalation victims, the corresponding value for plasma lactate is 10 mmol/L (15). In the case of impossibility to obtain a plasma lactate concentration, an elevated anion gap may serve as a surrogate.

This elevated lactic acidemia coexists with the abolition of the arterial-venous oxygenation gradient, entrained by the blockade of oxidative phosphorylation by cyanide. A narrowing of this gradient will support the diagnosis of cyanide intoxication and can be obtained by simultaneous sampling of venous and arterial blood gases on admission of the patient.

LABORATORY DETERMINATION OF CYANIDE

The detection of cyanide in the gastric liquid may be realized *in vitro* by use of the Lee-Jones test, which involves placing 4-5 drops of 20% NaOH and a few crystals of FeSO_4 in 5 ml of gastric aspirate. This is boiled, cooled, then 8-10 drops of 10% HCl are added. A green-blue colour is positive for ferrocyanide formation. This reaction, however, is only useful within the first hour after ingestion of cyanides and is falsely positive in the presence of benzodiazepines, phenothiazines, barbiturates, and tricyclic antidepressants, limiting severely its reliability (19).

The quantification of blood cyanide may be accomplished by either gas chromatography or by a colorimetric method. A rapid accurate technique using derivative spectrophotometry has been recently described in our laboratory (20). In the blood, cyanide concentrates in the erythrocytes to such an extent that the dosage is almost always performed on whole blood and virtually never on plasma. The diagnostic importance of early blood specimens, taken at the scene of the fire when the intravenous line is established and before any antidotal treatment should be emphasized. The blood should ideally be collected in heparinized tubes with minimal headspace and refrigerated at 4 °C on arrival at the hospital. Given the poor conservation of cyanide in collected blood, laboratory analysis should be accomplished as rapidly as possible.

A concentration of whole blood cyanide $\geq 40 \mu\text{mol/L}$ is considered toxic. A concentration $\geq 100 \mu\text{mol/L}$ is considered potentially lethal, though there is not a known concentration beyond which death is constant.

In fire victims, the correlation between the blood concentration of cyanide and that of carbon monoxide is statistically significant, but very weak (15, 21), so that cyanide concentration cannot be reliably predicted on the basis of the measure of carboxyhaemoglobin. Moreover, there exists at least an additive relationship of toxicity between carbon monoxide and cyanide, which explains why a certain number of victims succumb at infralethal concentrations for the two

gases (15). This underscores the importance of determining the presence not only of carbon monoxide exposure, but that of cyanide in smoke inhalation victims.

The quantification of blood or urine thiocyanates gives a retrospective estimation of the importance of cyanide intoxication but is of little value in the acute treatment of patients.

EVOLUTION OF TOXICITY

The early phase of intoxication by cyanide may be marked by repeated convulsions. It should be noted that cyanide is an inhibitor of glutamate decarboxylase, an enzyme which produces gamma-aminobutyric acid, an inhibitory neurotransmitter. Rhabdomyolysis is frequent, even in the absence of convulsions, and may result in renal insufficiency. Cyanide is a cause of pulmonary oedema by direct pulmonary injury or of cardiogenic origin. Cyanide possesses a powerful depressant effect on myocardial contractility (22). Consequently, vascular fluid repletion in the presence of cardiovascular collapse should be judicious.

The prognostic factors of this intoxication are not well described. In our experience, the prognosis of these intoxications where verbal contact persists is excellent. The prognosis of comatose forms is much less favourable, except in the case of fire victims. Cyanide intoxication may terminate in post-anoxic chronic coma. A syndrome of neurological sequelae after a symptom-free interval has also been described after cyanide intoxication.

TREATMENT

The treatment of these intoxications begins with extraction of the victim from the site of toxic exposure by appropriately protected trained rescuers, external decontamination in the case of skin contact (particularly in the case of HCN and nitriles) and the immediate institution of supportive symptomatic therapy adapted to the condition of the victim. Aggressive airway support with intubation and 100% oxygen, correction of acidosis with sodium bicarbonate, support of blood pressure with fluids and pressors must precede any attempt at antidotal therapy. These early gestures may be lifesaving (23). It is not currently possible to say that the cyanide antidotes are lifesaving, by themselves. Nonetheless, it may be said that antidotes, and in particular hydroxocobalamin have simplified considerably the resuscitation of these patients.

SPECIFIC TREATMENTS

Oxygen is the foundation of antidotal treatment. Its utilization is *a priori* illogical taking into account what is known about the pathophysiology of the intoxication. However, both experimentally (24, 25) and clinically (26), oxygen therapy is efficacious. This paradoxical action may be explained by several mechanisms: the reactivation of cytochrome oxidase should be more rapid in the presence of high concentrations of oxygen and augmentation of the partial pressure might activate other routes of oxidation insensitive to cyanide. Normobaric oxygen therapy should be undertaken as soon as possible (27). Hyperbaric oxygen therapy has also been proposed (26) but its role remains controversial, animal studies showing mixed results (28, 29).

Methaemoglobin inducers, including amyl nitrite, sodium nitrite, and 4-dimethylaminophenol act (primarily?) by transforming the ferrous iron of haemoglobin into ferric iron. The methaemoglobin formed may then compete with cytochrome oxidase for the cyanide ion. Cyanide is transferred to the ferric iron of methaemoglobin, becoming cyanmethaemoglobin, which is less toxic and may be subsequently detoxified by rhodanese to thiocyanate and methaemoglobin. To be efficacious, some authors have suggested that these agents should induce a methaemoglobinaemia on the order of 20-40% (30, 31), though Way has suggested that mechanisms other than methaemoglobin induction may be as important in the antidotal action of these agents (32). Vasodilatation has been proposed as one of the possible therapeutic effects of nitrites. However, this same vasodilatations, sometimes severe, may result in severe hypotension (31) or even induce cardiovascular collapse (33). This effect may be even more severe in the absence of cyanide poisoning, making the certainty of diagnosis practically a requisite for their administration. Furthermore, these agents diminish the capacity of oxygen transport in direct proportion to the amount of methaemoglobin formed. In the course of experimental intoxications by the combination of carbon monoxide and cyanide, these products increase significantly the mortality of the animals treated (34). Given their side-effects, it has been suggested that their use be abandoned (15, 35), particularly in the setting of cyanide intoxication by smoke inhalation.

Two further points must be articulated regarding the use of methaemoglobin inducers and evaluation of their efficacy. Even though the necessity of methaemoglobin induction has been questioned by Way (32) and others, there remain recommendations in the recent literature (6) to quantify methaemoglobin formation after nitrite administration, prior to administering a second dose, in order to avoid excess nitrite therapy. While the presence of high concentrations of methaemoglobin should certainly dissuade the physician from giving additional nitrites, the converse is absolutely not true. Ignorance of this fact may lead to disaster. Neither the classic Evelyn-Malloy method of methaemoglobin determination nor the current CO-oxymetric methods can detect cyanmethaemoglobin (36). In fact, the Evelyn-Malloy method of methaemoglobin determination is a differential one, based on the elimination of the characteristic 630 nm band of methaemoglobin

by addition (*in vitro*) of potassium cyanide (36). Thus, if methaemoglobin has been formed and has efficiently bound cyanide (*in vivo*), the circulating cyanmethaemoglobin will not be detected. This cyanmethaemoglobin nonetheless is present and, depending on its ratio to oxyhaemoglobin, deprives the body of a percentage of its oxygen-carrying capacity. Administration of additional nitrite could potentially result in fatal methaemoglobinaemia with "sublethal" measured methaemoglobin concentrations!

The second point has to do with post-treatment cyanide concentrations. Cyanide which attaches to methaemoglobin during treatment remains inside the red blood cell *in vivo*. The standard methods for blood cyanide determination (37, 38) and the new method of Laforge (20) all utilize a strong mineral acid to release cyanide from the red blood cells *in vitro* as HCN, which is then trapped by a molecule (chloramine-T, hydroxocobalamin, others) detectable by chromatography or spectrophotometry. Thus, any unbound cyanide (from vascular and extravascular sources) is released on adding the strong acid and subsequently measured. We recently demonstrated this in the rat, where blood concentrations of cyanide taken immediately following termination of an intravenous cyanide infusion ("peak concentrations") were compared with a second measurement in the same animal following intravenous therapy with sodium nitrite or hydroxocobalamin. In the nitrite treated animals, the concentration of cyanide often more than doubles, whereas in the hydroxocobalamin group, the cyanide decreases (this because the cyanocobalamin formed is stable in the *in vitro* acid media) (Borron, S., personal observation). Thus, if nitrites are utilized to treat cyanide poisoning, neither the post-treatment methaemoglobin concentrations nor blood cyanide concentrations are reliable or safe for determining the need for additional therapy.

Sodium thiosulphate is the natural substrate of rhodanese, or sulphur thio-transferase. This enzyme, in the presence of thiosulphate, transforms cyanide into less toxic thiocyanate, which may be eliminated in the urine. This is an effective sure treatment, but its action is slow, and thus cannot be used as a first line cyanide antidote. It may be administered with impunity in suspected intoxication, in association with another antidote (34). Thiosulphate is administered at a dose of 8-16 grams intravenously over 24 hours. In the United States, recommendation is for 12.5 grams of thiosulphate to be administered over several minutes in adults, a dose which may be repeated after thirty minutes to one hour, if indicated. Thiosulphate appears to be ideal in the prolonged intoxications provoked by exposure to nitriles, where ongoing metabolism to cyanide requires continuing renewal of rhodanese stores. Because of the antithyroid activity of thiocyanates, a thyroid function panel should be obtained within several weeks following recovery of the patient.

Dicobalt EDTA, like hydroxocobalamin, is a cobalt compound. Cobalt possesses a very high affinity for cyanide. The experimental efficacy of dicobalt EDTA is remarkable. Each molecule is capable of complexing two cyanide ions. However, dicobalt EDTA has deleterious cardiovascular side-effects and is often poorly tolerated (vomiting, diarrhoea, headache) (39). These effects are enhanced in patients not intoxicated by cyanide, which serves as a relative contraindication when the diagnosis

Table 3 Clinical reports of the use of high dose hydroxocobalamin in human cyanide poisoning (Modified from ref. 45)

Reference	Toxin	Observation No.	Blood cyanide $\mu\text{mol/L}$	HOCO* dose grams	Other antidotes	Outcome
Yacoub (1974)	KCN 1g	1	1797	4**	EDTA	Recovery
Jouglard (1974)	KCN 1.5 g	1	ND	7**	SThio	Sequelae
Bourrellet (1971)	NaCN	1	ND	0.2**	EDTA	Recovery
Bismuth (1984)		1	77	4**	EDTA	Death
		2	291	4**	EDTA	Chronic coma
		3	257	4**	EDTA	Recovery
Racle (1976)	KCN 50mg	1	ND	8**	-	Recovery
Motin (1970)	KCN 1g	1	ND	4**	EDTA-Nitrite-SThio***	Recovery
Lutier (1971)	KCN 1g	1	ND	4**	EDTA	Recovery
	KCN 1g	2	ND	4**	EDTA-Nitrite-	Recovery
	KCN	3	ND	4**	SThio***	Recovery
Danel (cited by Brouard 1987)	CN	1	ND	4**	-	Recovery
	CN	2	ND	4**	-	Recovery
	CN	3	ND	4**	-	Recovery
	CN	4	ND	4**	-	Recovery
Dougherty (1990)	NaCN 0.2 g	1	400	4**	-	Recovery
Tassan (1990)	KCN 2.5 g	1	494	4**	-	Recovery
Tartière (1992)	KCN	1	125	5	-	Recovery

* Hydroxocobalamin

** This preparation of hydroxocobalamin comes from Anphar-Roland premixed with 8 grams sodium thiosulphate

*** Hydroxocobalamin was given when the other antidotes had failed

EDTA - Dicolbalt ethylenediaminetetraacetic acid

Sthio - Sodium thiosulphate

ND - Not determined

of cyanide poisoning is uncertain. It is delivered as an intravenous bolus of 300 mg, which may be repeated. Its administration is followed by that of hypertonic glucose, on the basis of hypoglycaemia noted in experimental studies.

Hydroxocobalamin, experimentally and clinically, is an efficacious antidote of cyanide. Its antidotal action vis à vis the negative inotropic effect of cyanide appears without delay (40). Table 3 summarizes the published observations of which we are aware regarding the use of hydroxocobalamin, most often in association with other antidotes. Of all the cyanide antidotes, hydroxocobalamin is the best tolerated experimentally (39) and clinically (41). In a prospective study of 50 fire victims, clinical side-effects were observed neither in patients intoxicated by cyanide, nor in non-intoxicated patients (41), thus establishing an excellent tolerance of high doses of hydroxocobalamin in these victims of smoke inhalation. In spite of the fact that anaphylactic shock is a known potential side-effect of hydroxocobalamin, we have never observed such an event, even during the administration of very high doses, ranging from 5 to 15 grams. Hydroxocobalamin provokes constantly a strong red coloration of the urine for approximately 5-7 days following its administration in patients with normal renal function. This coloration might be confused with intravascular haemolysis or severe rhabdomyolysis. It also interferes with determination of glucose. Likewise, hydroxocobalamin leaves a dark

red tint to the vein through which the antidote is infused. This side-effect is not painful, is not accompanied by any cutaneous lesions, and is reversible.

THERAPEUTIC INDICATIONS

The therapy indicated depends on the clinical gravity of the patient and on the nature of the cyanide or cyanogen as cause. Oxygen rests as the foundation of this treatment (27).

According to clinical gravity: Intoxications by hydrocyanic acid are often collective. Frightened unintoxicated patients are mixed in among the truly intoxicated patients. In the face of coherent anxious agitation, no treatment other than oxygen is necessary. These troubles are most often related to fear rather than to intoxication.

Patients presenting with evident dyspnoea, consistent with lactic acidosis, receive without delay a dose of 5 grams of hydroxocobalamin intravenously over 15-30 minutes (70 mg/kg for the child). These patients often have a discrete drop in blood pressure and signs of encephalopathy before antidotal treatment.

For patients found comatose, convulsing, or in cardiovascular collapse, intubation and assisted ventilation with 100% oxygen should be undertaken without delay. An initial dose of 5 grams of hydroxocobalamin is followed by an additional dose infused over 2-4 hours. The symptomatic intensive care of these intoxications is non-specific.

According to the nature of the cyanide-containing product: During an intoxication by ingestion of cyanide salts, aimed at suicide, the quantities of cyanide ingested may exceed the capacity of neutralization of 10 grams of hydroxocobalamin. Furthermore, the absorption is prolonged, probably on the basis of the haemodynamic status of the patient with diminished intestinal perfusion. In these cases, a continuous infusion of sodium thiosulphate is added to the hydroxocobalamin therapy. Gastric emptying by lavage is undertaken as soon as the haemodynamic status of the patient permits it. This may be followed by whole bowel lavage, using high molecular weight polyethylene glycol solutions in order to decrease the transit time of the remaining cyanide in the digestive tube.

In the case of intoxication by nitriles, when seen early and in the absence of symptoms, priority should be given to decontamination of the gut, in the case of ingestion, or of the skin, in the case of cutaneous contact. These products are absorbed percutaneously and by inhalation. In the face of frank symptoms of cyanide intoxication, hydroxocobalamin should be instituted without delay. One dose of 5 grams is generally sufficient. This is accompanied by a dose of 8 grams of sodium thiosulphate intravenously per day. In a case of intoxication by acetonitrile, persistently elevated blood cyanide concentrations required the administration of 8 grams daily of sodium thiosulphate over a course of eight days (Baud, FJ., personal observation).

CRITERIA FOR THE EVALUATION OF THE EFFICACY OF ANTIDOTAL TREATMENT

The appropriate ranks of these criteria are, in the order: clinical, biochemical, and analytical.

Clinical

The amelioration of the haemodynamic state with hydroxocobalamin and supportive treatment is often spectacular. In contrast to supportive treatment alone, the addition of an adequate dose of hydroxocobalamin often permits rapid weaning of catecholamines, when these have been necessary in the initial management.

Biochemical

In pure cyanide poisoning, the rapid normalization of lactic acidemia is a witness to the efficacy of the antidotal therapy. With specific therapy, in the absence of catecholamines, there is a significant correlation between the blood cyanide concentration and the corresponding plasma lactate concentration during the entire course of poisoning. In smoke inhalation, some degree of lactic acidosis may persist, even after blood cyanide concentrations are no longer measurable (42).

Analytical

It is possible to perform a rapid measurement of the plasma concentration of hydroxocobalamin and cyanocobalamin by derivative spectrophotometry (43) or by HPLC (44). These quantitative tests, realized in real time, should permit the adaptation of the antidotal therapy according to the severity of the cyanide concentration.

CONCLUSION

The diversification of our environment, professional as well as domestic, has augmented the likelihood of our exposure to cyanide and to cyanogenic products. Although often of severe gravity, the possibility of recovery from such an intoxication should not be underestimated. The symptomatic treatment is facilitated by the use of a first-line antidote which is efficacious and devoid of deleterious secondary effects. In our experience, hydroxocobalamin most completely fills these demands.

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Sažetak**AKUTNO OTROVANJE CIJANIDIMA: KLINIČKA SLIKA, DIJAGNOZA I LIJEČENJE**

Otrovanje cijanidima može nastati na različite načine. Profesionalna otrovanja uzrokovana su širokom uporabom cijanidnih spojeva u kemijskoj sintezi. Udisanje dima u požarima najčešći je uzrok otrovanja cijanidima u kućnom okolišu. Otrovanja u svrhu samoubojstava su rijetka. Cijanogeni spojevi mogu uzrokovati akutna ili subakutna otrovanja. Znakovi otrovanja su glavobolja, vrtoglavica, nemir, smetenost, koma, konvulzije i smrt. Konačna laboratorijska potvrda uzroka otrovanja često dolazi sa zakašnjenjem. Povišenje laktata u plazmi praćeno zatajenjem srca i krvotoka upućuje na moguće otrovanje cijanidima. Hitno liječenje uključuje kisik, umjetno disanje, mjere dekontaminacije, suzbijanje acidoze i održavanje krvotoka. Kao antidoti rabe se kisik, hidroksikobalamin, dikobalt-EDTA i lijekovi koji dovode do methemoglobinemije. Hidroksikobalamin je antidot izbora zbog sposobnosti brzog vezanja cijanida, s malo ozbiljnih nuspojava čak i ako otrovanje nije uzrokovano cijanidima. Natrijev tiosulfat djeluje sporije od drugih antidota i indiciran je u subakutnim slučajevima otrovanja te kao pomoćni lijek za akutna otrovanja cijanidima. Početna procjena djelotvornosti antidota temelji se na sposobnosti suzbijanja hipotenzije i laktičke acidoze, dok se konačna ocjena temelji na procjeni stupnja trajnog oštećenja središnjeg živčanog sustava.

Ključne riječi:

antidoti cijanida, cijanogeni, djelotvornost antidota, hidroksikobalamin, methemoglobin, nitrili, tiosulfati, vodikov cijanid

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