Reminder of important clinical lesson

Occupational cyanide poisoning

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Correspondence to Professor Loïc Amizet, amizet.loic@ch-abbeville.fr**Summary**

Cyanide poisoning has existed for centuries. In most cases, cyanide is combined with other toxic substances; for example with carbon monoxide in fire smoke. Cases of pure cyanide poisoning are rare, and usually due to accidental exposure. Their treatment is based on oxygenation and the infusion of hydroxocobalamin. The seriousness of this type of poisoning calls for a rapid and specific response, which demonstrates the usefulness of non-hospital based medical treatment. The authors report here the case of a man who was the victim of occupational poisoning with sodium cyanide and who was treated at the workplace by fire-fighters and the Service Mobile d'Urgence et Réanimation emergency ambulance service.

BACKGROUND

Cyanide is present throughout industry. More than 600 000 metric tonnes are produced every year worldwide, including 100 000 metric tonnes in the European Union. It has multiple uses, including the manufacture of insecticides and pesticides, the extraction of certain ores in various countries or regions, in the pharmaceutical industry and as a fumigant or synthesis agent in chemistry. Cyanide can take various different forms. In the solid state, cyanide salts release fumes of hydrocyanic (prussic) acid if they come into contact with moisture or even a weak acid. It can also take very volatile liquid forms (nitriles, halogen derivatives), and gaseous forms (hydrocyanic acid, cyanogen), which are present in blast furnace fumes and fire smoke.¹

Cellular toxicity is due to the cyanide ion, which binds itself to the ferric iron in the physiological methaemoglobin fraction of total haemoglobin, and also the mitochondrial enzyme cytochrome oxidase, thus blocking the oxidations controlled by this enzyme, leading to cellular anoxia. The organs that are most sensitive to the cyanide ion are the brain and the retina. The consequences of cyanide poisoning at the cellular level are a blockade of the peripheral use of oxygen, a failure to generate ATP, with a shift to anaerobic glycolysis and the excessive production of lactic acid.

Acute poisoning can result from inhalation, from contact with the skin or by ingestion.²⁻³ The speed at which the symptoms appear depends on the organoleptic properties of the cyanide, on its concentration and on the duration of the exposure. The lethal dose of hydrocyanic acid is 50 to 100 mg by the oral route and 280 ppm by inhalation.

The clinical signs are linked to the anoxic effect of the cyanide ion at cell level. The inhalation or ingestion of cyanide is soon followed by headache, vertigo, confusion, palpitations and hyperventilation. These signs can rapidly progress to a deep coma, hypotension, bradycardia, convulsions and cardiorespiratory arrest.

In the context of severe poisoning, 'primary' respiratory arrest precedes the onset of cardiac arrest, which is followed by the resumption of ventilation and then by final cardiac and respiratory arrest. Loss of consciousness and convulsions are always present. The final cardiorespiratory arrest

occurs within 15 min after inhalation. Due to the rapid onset of these symptoms and their fatal consequences, it is therefore extremely important that the appropriate antidote is administered as soon as cyanide poisoning is suspected or has been confirmed.

In France, the only antidote with a marketing authorisation for use in suspected but not certain (pure cyanide) poisoning is Cyanokit (hydroxocobalamin). After being stabilised and being given the antidote treatment, the patient should be referred to a hyperbaric centre for oxygen therapy. However, this is usually not administered for several hours and must never be allowed to delay the antidote treatment.

CASE PRESENTATION

This case concerns a 41-year-old man, 175 cm tall and weighing 75 kg, whose only previous history was two attacks of nephritic colic and a 23-year history of smoking, with no cardiovascular history and notably no hypertension. He was working for a company carrying out nickel and chrome plating and went down into a tank in the factory in order to clean it with sodium cyanide. This substance is in powder form and is dissolved and used to strip grease from metal parts. Gasification occurs as a result of contact with another substance.

The man was exposed to the toxic agent for about 15 min before he was found unconscious, lying on his back, by his colleagues who got him out of the tank and called the emergency services at 11:52 a.m.

When the fire brigade arrived 6 min after being alerted, the victim could not speak and did not respond to simple commands, but was breathing spontaneously. Four min later, he had a generalised convulsive seizure followed by cardiac arrest, which was reversed after external cardiopulmonary resuscitation for 2 min (consisting of external cardiac massage and ventilation using a manual ventilator with an oxygen flow rate of 12 l/min). The automated external defibrillator failed to shock. Catecholamines were not administered. Initial tests for toxic substances in the air carried out by the fire-fighters detected a cyanide level of over 20 ppm (the highest level registered by the apparatus).

When the SMUR ambulance team arrived, 20 min after he had been discovered, the patient had a Glasgow score of 6, a sinus rhythm of 100 beats per min and a blood pressure of 80/60 mm Hg. His skin was pink, without any marbling. He had another generalised convulsive seizure 23 min after being discovered, which yielded in response to the intravenous injection of 1 mg of clonazepam. The electrocardiogram revealed a sinus rhythm with no impairment of conduction and no repolarisation defect.

In view of his persistent Glasgow score of less than 8, the patient underwent endotracheal intubation with rapid sequence intravenous induction using etomidate and succinylcholine.

Intubation was successful at the first attempt and artificial ventilation was provided with 100% FiO₂ at a frequency of 13/min and a volume of 700 ml. Analgesia and sedation were maintained by midazolam and fentanyl.

Thirty-five min after the patient had been discovered, two bottles of Cyanokit (hydroxocobalamin), that is, 5 grams were administered together with 500 ml of hydroxyethyl amidon and 500 ml of Ringer, before he was transferred to the Resuscitation Department of the Abbeville Hospital (Centre Hospitalier d'Abbeville).

INVESTIGATIONS

On admission 120 min after collapsing, the patient was hypothermic at 35.5°C, his haemodynamics were stable, with a blood pressure of 120/70 mm Hg, a heart rate of 85 beats per min and an oxygen saturation level of 100% under artificial ventilation with 100% FiO₂. The cardiopulmonary examination was normal, and the electrocardiogram revealed a regular sinus rhythm with no impairment of conduction or repolarisation.

Blood gases, determined via the arterial route 120 min after the patient was discovered, and while he was on 100% FiO₂, revealed a pH of 7.18, lactates at 7.6 mEq/l, a PapCO₂ of 45 mm Hg and a PapO₂ of 380 mm Hg, with bicarbonates at 15 mmol/l and HbCO at 1.1%.

Venous blood tests, carried out 85 min after administering the Cyanokit (hydroxocobalamin), found the following values: white blood cell 26 500 giga/l, blood sugar 39 mmol/l, serum glutamic oxaloacetic transaminase 34 U/l, serum glutamic pyruvic transaminase 23 U/l, total bilirubin 4.4 µmol/l, conjugated bilirubin 1.0 µmol/l, γ-glutamyltransferase 42 U/l, PT 61%, urea 8.0 mmol/l, creatinine 105 µmol/l, myoglobin 2081 ng/ml (normal <72 ng/ml). A blood alcohol test was negative (0 g/l), as were tests for toxic substances.

Upon transfer to the Hyperbaric Centre at Lille, the patient was haemodynamically stable and hypothermic with a temperature of 34°C. The chest x-ray did not reveal any parenchymatous focus. Laboratory tests showed hyperleukocytosis with a count of 18 500/ml, a C-reactive protein level of 68 mg/l, creatinine of 134 µmol/l, urea of 8.8 mmol/l, elevated troponin, peaking at 0.88 ng/ml, creatine kinase of 1250 IU/l, a balanced blood electrolyte reading, normal liver function tests and a thiocyanate determination below the poisoning level, after receiving treatment with Cyanokit (hydroxocobalamin).

TREATMENT

On admission to the Resuscitation Department, sedation was continued with midazolam and sulphentanyl, and

hydration by physiological saline. In view of the severity of the poisoning, it was decided to infuse a 2.5 g bottle of Cyanokit (hydroxocobalamin), that is, a cumulative dose of 7.5 grams since the beginning of treatment. The urinary catheter installed 15 min after his admission evacuated 1000 ml of 'port-coloured' red urine.

The patient was transferred to the Hyperbaric Centre at the Lille CHU University Hospital to receive further specialist care. Treatment included continued sedation, and hydration by physiological saline.

The patient underwent a session of hyperbaric oxygen therapy at a pressure of 2.5 atmospheres absolute lasting 90 min, 210 min after collapsing.² A further 2.5 grams of Cyanokit (hydroxocobalamin) was administered that is, the patient had now been given a total dose of 10 grams of Cyanokit (hydroxocobalamin).

OUTCOME AND FOLLOW-UP

The patient was extubated 30 h after collapsing, 22 h after the last therapy session during which he had received a combination of the injection of hydroxocobalamin and hyperbaric oxygen therapy. His progress was essentially marked by rhabdomyolysis, which was rapidly reversed. The patient returned home a week later, and returned to work normally 2 weeks after the accident.

DISCUSSION

The care of victims of cyanide poisoning is initially symptomatic. Cyanide poisoning involves cell anoxia. Initial treatment is therefore based on high flow oxygen therapy, or even controlled ventilation due to the risk of the onset of apnoea with 100% FiO₂, and a high tidal volume as ventilatory compensation for the severe lactic acidosis, for as long as this persists. Treatment also includes the correction of any haemodynamic problems by filling and inotropic and vasoconstrictor catecholamines, the management of a convulsive state with benzodiazepines, and alkalinisation in cases of severe metabolic acidosis that do not respond to treatment and are so severe that high doses of catecholamines do not improve the haemodynamics. In many countries, including France, the specific treatment for cyanide poisoning is based on high doses of Cyanokit (hydroxocobalamin), a naturally occurring form of vitamin B12. This reacts with the cyanide ion, which replaces a hydroxyl group with a cyano group to form cyanocobalamin, a stable covalent complex, which is excreted mainly in the urine in unchanged form, turning the urine wine red in colour ('Bordeaux'). One molecule of hydroxocobalamin binds one molecule of cyanide, which means that high doses of hydroxocobalamin have to be used. The dosage is 70 mg/kg, that is, about 5 grams for an adult (ie, two 2.5 g bottles) infused over a period of 30 min. Depending on the severity of the patient's clinical condition, this can be administered once or repeated twice, as a slower infusion administered over a period of 30 min to 2 h.³⁻⁵ The other antidote treatments are amyl nitrite, sodium nitrite and sodium thiosulphate, all of which can be used either alone or concomitantly (Cyanide Antidote Package, also known as the Lilly Kit or Taylor Kit). Amyl nitrite administered by inhalation results in the formation of methaemoglobin, which combines with the cyanide to produce cyanmethaemoglobin, the basic therapeutic agent in methaemoglobinising substances. Sodium nitrite is administered

by injection and acts in the same way as amyl nitrite. Sodium thiosulphate has very low toxicity and is administered by intravenous route at a dose of 12.5 grams over 10 min. Sodium thiosulphate converts the cyanide into thiocyanate by means of a hepatic enzyme, Lang's rhodanese. Thiocyanate is atoxic and is excreted in the urine in unchanged form. The use of amyl nitrite and of sodium nitrite is limited due to their contraindications and side effects, so it is essential to be certain that pure cyanide poisoning has occurred. In a context of mixed poisoning (fire smoke inhalation) carbon monoxide leads to the formation of carboxyhaemoglobin, the effects of which are cumulative with those of methaemoglobin, thus exacerbating the hypoxaemia. Similarly, the production of methaemoglobin can worsen underlying ischaemic heart disease.

Hydroxocobalamin is commonly used as an antidote to cyanide poisoning, and if administered quickly and combined with hyperbaric oxygen therapy, can result in complete recovery of the subject, as shown in this case.⁶ The case presented here emphasises that rapid administration of antidote increases the likelihood of survival and antidotes should be available on site.

Learning points

- ▶ The prognosis of serious cyanide poisoning is closely linked to how quickly antidote treatment is provided and resuscitation measures are undertaken to treat or prevent cardiorespiratory and/or neurologic decompensation.
- ▶ Emergency care provided on site by a medicalised team can save valuable time before hospital treatment is started and antidotes should be available on site to increase the likelihood of survival.
- ▶ The patient should be referred to a centre with polyvalent resuscitation facilities, if possible a centre providing hyperbaric oxygen therapy, the indication for which can then be assessed on a case-by-case basis.

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