EDITORIAL

Hydroxocobalamin as first-line antidote to treat cyanide poisoning in fire smoke inhalation: an additional step for efficacy evidence

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Smoke inhalation represents the major circumstance of cyanide poisoning in the developed countries, accounting for several thousand deaths each year. Smoke is a mixture of various chemicals including irritant gases and cell asphyxiants such as carbon monoxide and hydrogen cyanide. Cyanide toxicity results from its attachment to the ferric form of several vital cellular enzymes including the mitochondrial cytochrome oxidase. Therefore, in smoke inhalation victims, elevation of plasma lactate concentration ≥ 10 mmol/L was shown to be a sensitive and specific biomarker of cyanide intoxication defined by blood cyanide concentration ≥40 µmol/L[1]. As success in the treatment of cyanide poisoning is time-critical, lactate measurement easily performed by pre-hospital medical services or fire-fighters using portable analyzers, is currently used to assess cyanide poisoning and indicate antidote administration.

Although licensed and frequently used in France since the 70s, hydroxocobalamin was only recently approved as cyanide antidote by the US Food and Drug Administration (Dec 2006) and the European authorities (Nov 2007). Hydroxocobalamin covalently binds cyanide, forming a stable non-toxic compound, cyanocobalamin, which is excreted in urine. Experimental studies support the assumption that hydroxocobalamin is beneficial in cyanide poisoning[2]. However, human efficacy data remains limited to anecdotal reports, case series, and uncontrolled studies[3]. Recently, Borron and coworkers reported a 67%-survival rate among 42 cyanide poisoned patients treated with hydroxocobalamin[4]. Fortin and coworkers reported a 42%-survival rate among 72 smoke inhalation victims following hydroxocobalamin infusion with significant improvement in blood pressure and neurological status, while 12 among 38 patients found in cardiac arrest on the scene returned to a spontaneous circulation during pre-hospital care[5]. Consistently, Borron and coworkers reported a 67%-survival rate among 69 smoke inhalation victims treated with hydroxocobalamin on the scene, further admitted to a specialized intensive care unit, and confirmed a posteriori to have had cyanide poisoning[6]. As all these data were obtained from limited observational case-series, definitive efficacy assessment still awaits prospective randomised trials, although adequate placebo-controlled trials appear ethically difficult to conduct in humans[7]. On the other hand, while evidence for hydroxocobalamin efficacy remains sparse, safety data appears solid. Hydroxocobalamin is lacking in adverse effects when compared to other available antidotes[3-7]: this is essential in life-threatening fire smoke victims suffering from hypotension and hypoxemia.

In the present issue, EMERGENCIAS publishes an interesting clinical study investigating hydroxocobalamin ability to reverse cyanide-induced lactate elevation in fire smoke inhalation[8]. The authors designed a prospective observational study comparing plasma lactate concentrations before and after 70-mg/kg hydroxocobalamin administration in twenty-eight patients. They reported a significant decrease in lactate concen-

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trations: 10.2 ± 2.2 mmol/L on the scene versus 6.7 ± 2.1 mmol/L on hospital admission, 31.9 ± 9.1 min after hydroxocobalamin infusion. This significant decrease was similarly observed in the subset of twelve patients with a significant cyanide poisoning defined by lactate concentrations ≥ 10 mmol/L as previously reported[1].

Lactate elevation in cyanide poisoning is not specifically related to its direct mitochondrial effects and may be induced by various conditions including cardiovascular failure, seizures, apnea, catecholamine rush or administration, and associated toxicants[9]. By excluding patients with severe burns and significant hypotension (< 80 mmHg), the authors wished to limit such bias.

Based on the cyanide toxicity threshold defined by the Medical Association of Madrid, the Samur-Protection Civil services used to administer hydroxocobalamin to fire victims with lactate ≥ 7.5 mmol/L. This is a prudent and safe guideline, as the very concept of toxic cyanide concentration remains itself poorly defined. However, in Corral Torres's work[8], no description of the patient's clinical status was reported, except the mean initial systolic blood pressure. The patient's neurological and respiratory status would have been of a great interest for cyanide toxicity assessment. On the fire scene, cyanide poisoning should be immediately suspected based on a characteristic toxidrome including: i)- soot in the face, mouth, nose or expectorations; ii)- neurological impairment, both signs having an excellent negative predictive value[1]; and iii)- the presence of any abnormal respiratory or cardiovascular pattern, since neurological symptoms could be also attributed to carbon monoxide poisoning. Lactate measurement is confirmatory of cyanide intoxication. A threshold for cyanide toxicity was assessed as 10 mmol/L in smoke inhalation[1] and 8 mmol/L in acute cyanide poisoning[10]. In the present work, the authors included patients with 7-10 mmol/L considered as moderately poisoned, although probably non-toxic concentrations of cyanide (i.e. < 40 µmol/L) would have been assessed if measured. Similarly, patients with cardiovascular instability were excluded, although probably corresponding to the most severely poisoned patients who would have mostly needed the antidote. However, despite these criticisms, the study remains highly interesting. As previously reported[1,10], lactate elevation may occur without obvious cardiovascular failure in cyanide poisoned patients exhibiting systolic blood pressure within the normal range. However, despite apparently normal hemodynamic conditions based on the only measurement of blood pressure in such supposed cyanide-intoxicated patients, cyanide-induced cardiovascular dysfunction should be considered as the most important factor in the development of lactic acidosis in cyanide poisoning[1,10].

Another important concern in this study is the absence of a control group as a decline in lactate concentrations could be achieved spontaneously, under oxygen or following aggressive out-of-hospital management. The observed 33.8%-decrease within a 32 min-period of time after hydroxocobalamin infusion should be compared with the 3.2h-median early half-life of plasma lactate reported in five severely cyanide-poisoned patients treated with this antidote[10]. Interestingly, such a rapid pharmacodynamic effect was also reported regarding the systolic blood pressure recovery within an average time of 30.6 min in hemodynamically unstable smoke inhalation victims receiving hydroxocobalamin[5]. Like other efficacy studies, this study is lacking of controlled data demonstrating that hydroxocobalamin can reverse or attenuate cyanide toxicity. Evidence-based medicine force us to acknowledge that uncontrolled data alone do not prove effectiveness[7]. However, based on the published safety as well as the progressively growing efficacy data, its is reasonable to consider to date that empiric hydroxocobalamin, an easy-to-administer cyanide antidote with a favourable risk/benefit ratio, should be recommended as the first-line antidote in smoke fire inhalation. Thanks to Emergencias to add one more stone to the pyramid of evidence that may help embrace hydroxocobalamin with more confidence in the future.

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