Hydroxycobalamin, hyperbaric oxygen and cyanide poisoning

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From initial analysis of the literature [1-5] and the first HBO Committee Reports [6], cyanide intoxication (CNHI) appeared in the list of potential indications for hyperbaric oxygen (HBO_2) therapy. Some references were found years later [7-11]. The therapeutic mechanism was not obvious, and many physicians did not consider HBO_2 in the treatment of CNHI as a reliable or consistent indication. Further, there was a general assumption that this very serious intoxication is rarely seen in emergency units of general hospitals, mainly because this poisoning is usually very serious, even fatal, in the majority ofcases, thus with very few chances for survival. Additionally, there was no clinical or analytical base for a clear diagnosis of CNHI because no easy, rapid, and inexpensive analytical test is available even today that permits detection of the existence of CNH in the blood of victims in which a suspicion of CNHI exists.

In 1991 an article published by Baud *et al.* [12] and a clinical approach appeared in 1995 [13] defending the assertion that cyanide can be formed when fire occurs in a closed environment, with combustion of nitrogen-based materials at very elevated temperatures. Houeto *et al.* [14], Baud [15] and other authors [16-20] continued this research, establishing clinical conditions in which patients rescued from these types of fires and who were suffering from smoke inhalation syndrome could be poisoned by CNHI – provided they are in a very serious condition with systolic hypotension, evidence of metabolic acidosis, and soot surrounding the nose and/or mouth is observed. It is obvious that these patients would be suffering at the same time from a joint intoxication by carbon monoxide (CO). Signs and symptoms of carbon monoxide poisoning (CMP) and a possible CNHI will be overlapping.

At the end of the 1990s several meetings were organized in Europe to announce a new system to diagnose CNHI in patients rescued from fires, as well as the introduction of a new drug which would be a valid antidote for cyanide in cases of serious poisonings. This diagnostic method was a reassembling of Baud's criteria; and the new antidote for CNHI was high doses of hydroxycobalamin (HCM), the pharmaceutical form of the B12 vitamin. The irruption of the pharmaceutical industry, this time in the field of toxicology, succeeded in widely advertising the administration of very high doses of HCM in all patients in whom CNHI was suspected.

Due to the fact that it was presented as safe, effective and easily administered in an emergency, the indication of HCM was spontaneously enhanced in some countries and, in the years that followed, given to almost all patients rescued from fires. As the antidotal dose of HCM is about 500 times higher than the old preparations of the B12 vitamin, a new product, ready to be given endovenously, was presented and quickly introduced, not only in emergency units of general hospitals, but in ambulances and mobile advance life support units.

Surprisingly, the absence of any controlled human study proving the efficacy of the drug in the practice, plus not a single descriptive analysis of a large series of patients treated on an empiric basis receiving HCM endovenously, were not an obstacle for the large diffusion of the new antidote. Neither the relatively high price of any preparation (higher than $1,500US), as well as the existence of reports of pharmacological interactions [21-30] and adverse effects [31-33] – including old descriptions of very serious anaphylactic reactions [34-37] – seemed to have no effect on its wide use. It seems obvious that an unbiased approach to this therapy should take into account these considerations.

In the last 30 years CRIS-UTH, the Hyperbaric Therapy Unit of Barcelona, has achieved a relatively large experience in the treatment of inhaled intoxications, mainly from carbon monoxide, that at the beginning of 2011 totals upward of 3,400 cases. A prospective protocol was designed in the 1980s and the data computerized. The analysis of these data is reliable, and introducing the same criterion for the diagnosis of CNHI described by Houeto, Baud, *et al.* was not difficult. The results were really interesting. The basis for this conviction is the same used by different authors

to support the administration of HCM in the treatment of CNHI. If this method has been considered valid to accept administration of megadoses of HCM in these patients, there should not be any reason to refuse the validity of the same method to accept a double origin of the poisoning in these patients.

The result was that among the 3,400 cases of CMP received in CRIS-UTH, 94 patients had suffered from CNHI simultaneously with a CMP [38]; 64 of them were in very serious condition, accomplishing all of Baud's criteria. All these patients were in very critical condition and had received HBO_2 during at least 60 minutes at 3ATA, plus compression and decompression procedures. Twelve of them had been intubated and received HBO_2 through mechanical ventilation. All patients survived, and 92% of them experienced complete recovery in the short term. None of these patients had received HCM, but all of them had undergone HBO_2 only. No patient developed the typical delayed neurological deterioration some weeks after discharge. Of the two patients who did not receive HBO_2 but only high doses of HCM, both developed a very serious late neurological syndrome. The first case was communicated in June 2003 to the Congress of the Spanish Society of Urgencies and Emergencies (SEMES).

There is a good theoretical and laboratory basis to accept HCM as a valid antidote, but no direct effect is known over brain hypoxia. There is no clinical evidence on the validity of HCM in the treatment CNHI – only several very enthusiastic opinions of clinicians from hospitals not having a hyperbaric facility who have finally found a treatment they can apply without the need to transfer patients to another center.

Only one clinical research project performed in real CNH-poisoned cases – not in smoking volunteers – communicated a favorable outcome in 67% of the patients from a series of 69 who received HCM [39]. Borron *et al.* considered the administration of HCM as the only reason for such satisfactory results, in spite of the fact that 57 of their patients (82.1%) had received HBO_2 as well – which, surprisingly, is not mentioned in the abstract of the paper. This study was supported by EMD Pharmaceuticals, an affiliate of Merck KGaA.

After these few convincing reports, many unbiased and objective clinicians familiar with urgencies in clinical practice and applying the principles of evidence-based medicine were surprised by the high diffusion of this new therapy that seems to be a valid antidote for cyanide. However, no effect is known about the cellular hypoxia that is the actual reason for the death of the untreated patients. And these doubtful considerations have remained for years without an answer. Because of this, the role of HCM alone in the treatment of CNHI still remains to be proven.

Fortunately, this issue of the *Undersea and Hyperbaric Medicine Journal* publishes a very good experimental paper that can be very helpful in providing an answer to this dilemma. It is one of the few good papers focusing on the comparative effect of HBO_2 and HCM therapy in cyanide intoxication. It is an experimental study from which very interesting conclusions can be obtained, both from the point of view of research in basic science and on the clinical approach to a valid therapy. Both departing points, those of the researcher and the clinician, are not always going in the same direction.

The title of the paper, which follows this commentary, is "Hydroxycobolamin or hyperbaric oxygen therapy attenuate surges in brain interstitial glucose and lactate in cyanide-intoxicated rats." After its reading, there seems to be no doubt that both therapies – HBO_2 or HCM – equally attenuate brain interstitial glucose and lactate in CNH-intoxicated rats, which was the main objective of the research. The conclusions are consistent, and there is no need to emphasize other differences between both therapies. This is a purely research-based approach coming from basic sciences, and these are the main conclusions provided by the authors in an interesting and suggestive paper.

However, a more detailed reading of the paper permits some very important observations of crucial interest:

- ". . . HBO_2 treatment showed a fast improvement in respiration and disappearance of cyanosis";
- ". . . HBO_2, but not normobaric oxygen, was shown to improve mitochondrial oxidative processes during CN poisoning";
- ". . . HBO_2, but not normobaric oxygen therapy, has been shown to be beneficial in ameliorating pathological events associated with central nervous system injuries";
- ". . . HBO_2 therapy, but not normobaric oxygen breathing, has been shown to increase the bioavailability of nitrous oxide."

This paper clearly proves very important differences in the efficacy of HBO_2 alone over HCM plus normobaric oxygen, as the paper clearly describes. This can establish a very important departure for HBO_2 and a dominant

position in the therapy of CNH poisoning in human clinical cases. This is a clear advantage and should be a very important conclusion from the clinician's point of view.

Once more, it can be concluded that reading the abstract of a good article is not enough to extract the maximal value of a paper. Frequently these differences are not clearly focused in the limited number of words implicit to an abstract. The whole paper must always be read. Those reading only the abstract of the Borron *et al*. paper [39] will believe that HCM is the only agent responsible for the favorable outcome of the patients, when the great majority of survivors had been treated with HBO_2 as well. And how many colleagues in the world had clearly understood, after having read the abstract of the superb paper by Weaver *et al.* about CMP, published in 1990 [40], that no significant differences were observed among patients who received one to two HBO_2 treatments when compared to those receiving five HBO_2 sessions? This important conclusion was not included in the abstract, and those not reading the entire paper (the majority of the readers) are not aware of that.

Certainly the *UHM Journal* is focused on both clinical and basic sciences. But the clinical use of HBO_2 strongly needs evidence and important proofs on the efficacy of HBO_2 over some drug therapies that are dominant in the medical world, sometimes in spite of being supported by less evidence than some solid HBO_2 indications.

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REFERENCES

1. Ivanov K. Effect of elevated oxygen pressure on animals poisoned with potassium Cyanide. Pharmacol Toxicol 1959; 22:476-9.

2. Savateev NV, Tonkopii VD, Frolov SF. Vliianie kisloroda pri normal'nom i povyshennom dovlenii na techenie otravlenii tsianidami. Farmakol Toksikol (Moscow) 1969; 32(3): 328-30.

3. Carden E. Hyperbaric oxygen in cyanide poisoning. Anaesthesia 1970; 25(3):442-3.

4. Way JL, End E, Sheehy MH, De MP, Feitknecht UF, Bachand R, Gibbon SL, Burrows GE. Effect of oxygen on cyanide intoxication. IV. Hyperbaric oxygen. Toxicol Appl Pharmacol 1972 July;22(3):415-21.

5. Larcan A, Laprevote Heully MC, Lambert H, Jacson R. Les indications de l'oxygenotherapie hyperbare en reanimation medico chirurgicale. Ann Med Nancy 1974; 13:963-94.

6. Kindwall E. Carbon monoxide poisoning and cyanide poisoning. In: Davis & Hunt, ed. Hyperbaric Oxygen Therapy. Underesea Medical Society, Inc., Bethesda 1977; 177-90.

7. Takano T, Miyazaki Y, Nashimoto I, Kobayashi K. Effect of hyperbaric oxygen on cyanide intoxication: in situ changes in intracellular oxidation reduction. Undersea Biomed Res. 1980; 7:191-97.

8. Trapp W, Lepawsky M. 100 % survival in five life-threatening acute cyanide poisoning victims treated by a therapeutic spectrum including HBO. HBO Review. 1983;4:252.

9. Hart GB, Strauss MB, Lennon PA, Whitcraft DD. Treatment of smoke inhalation by hyperbaric oxygen. J Emerg Med. 1985; 3:211-15.

10. Davis F, Ewer T. Acute cyanide poisoning: case report of the use of hyperbaric oxygen. J Hyp Med. 1988; 3:103-6.

11. Zagami A, Bulla G, Vaccaro G, Di Bono G, Blasco M, Marroni A. Pure cyanide poisoning treated with hyperbaric oxygen a report of 2 cases. In: Bitterman N, Ed. EUBS 89, Procedings of the 15th Annual Meeting of the EUBS, Eilat. 1989; 280.

12. Baud FJ, Barriot P, Toffis V, Riou B, Vicaut E, Lecarpentier Y et al. Elevated blood cyanide concentrations in victims of smoke inhalation. N Eng J Med 1991; 325(25): 1761-6.

13. Houeto P, Hoffman JR, Imbert M, Levillain P, Baud FJ. Relation of blood cyanide to plasma cyanocobalamin concentration after a fixed dose of hydroxocobalamin in cyanide poisoning. Lancet 1995; 346(8975):605-8.

14. Houeto P, Borron SW, Sandouk P, Imbert M, Levillain P, Baud FJ. Pharmacokinetics of hydroxocobalamin in smoke inhalation victims. J Toxicol Clin Toxicol 1996; 34(4):397-404.

15. Baud FJ, Bavoux E, Astier A, Hoffman JR. Relation between plasma lactate and blood cyanide concentrations in acute cyanide poisoning. Brit Med J 1996; 312(7022):26-7.

16. Hantson P, Benaissa L, Baud F. Intoxication par les fumées d'incendie. Presse Med 1999 ; 28(35) : 1949-54.

17. Mannaioni G, Vannacci A, Marzocca C, Zorn AM, Peruzzi S, Moroni F. Acute cyanide intoxication treated with a combination of hydroxycobalamin, sodium nitrite, and sodium thiosulfate. J Toxicol.Clin Toxicol. 2002; 40(2):181-3.

18. Keim ME. Terrorism involving cyanide: the prospect of improving preparedness in the prehospital setting. Prehospital. Disaster.Med 2006; 21(2 Suppl 2):s56-s60.

19. Geller RJ, Barthold C, Saiers JA, Hall AH. Pediatric cyanide poisoning: causes, manifestations, management, and unmet needs. Pediatrics 2006; 118(5):2146-58.

20. Dart RC. Hydroxocobalamin for acute cyanide poisoning: new data from preclinical and clinical studies; new results from the prehospital emergency setting. Clin Toxicol.(Phila) 2006; 44 Suppl 1:1-3.

21. Gourlain H, Caliez C, Laforge M, Buneaux F, Levillain P. Study of the mechanisms involved in hydroxocobalamin interference with determination of some biochemical parameters. Ann Biol Clin (Paris) 1994;52(2):121-4.

22. Erdman AR. Is hydroxocobalamin safe and effective for smoke inhalation? Searching for guidance in the haze. Ann Emerg Med 2007; 49(6):814-6.

23. Curry SC, Connor DA, Raschke RA. Effect of the cyanide antidote hydroxocobalamin on commonly ordered serum chemistry studies. Ann Emerg Med 1994; 24(1):65-7

24. Vest P, Renaudeau C, Tellal S, Ragot C, Renard C. Interference of hydroxocobalamine treatment on commun biochemical determinations. Ann Biol Clin (Paris) 2002; 60(1):57-64.

25. Sutter M, Tereshchenko N, Rafii R, Daubert GP. Hemodialysis complications of hydroxocobalamin: a case report. J Med Toxicol. 2010; 6:165-67.

26. Beckerman N, Leikin SM, Aitchinson R, Yen M, Wills BK. Laboratory interferences with the newer cyanide antidote: hydroxocobalamin. Semin Diagn Pathol. 2009; 26:49-52.

27. Heitzman J, Shen Q, Cazares J, Illoh O. Transfusion medicine illustrated: hydroxocobalamin-colored plasma. Transfusion. 2009; 49:2555-56.

28. Pamidi PV, DeAbreu M, Kim D, Mansouri S. Hydroxocobalamin and cyanocobalamin interference on co-oximetry based hemoglobin measurements. Clin Chim Acta. 2009; 401:63-67.

29. Denninghoff K, Walter FG, Langa AJ, He Y, Chipman RA. Spectrophotometry of hydroxocobalamin and hemoglobin reveals production of an unanticipated methemoglobin variant. Clin Toxicol (Phila). 2008; 46:545-50.

30. Lee J, Mukai D, Kreuter K, Mahon S, Tromberg B, Brenner M. Potential interference by hydroxocobalamin on cooximetry hemoglobin measurements during cyanide and smoke inhalation treatments. Ann Emerg Med. 2007; 49:802-5.

31. James J, Warin RP. Sensitivity to cianocobalamina and hydroxicobalamin. Brit Med J 1971; 2(5756):262.

32. Woodliff HJ. Allergic reaction to cyanocobalamin injection. Med.J.Aust 1986; 144:223.

33. Vidal C, Lorenzo A. Anaphylactoid reaction to hydroxycobalamin with tolerance of cyanocobalamin. Postgrad Med J, 1998; 74(877):702.

34. Branco-Ferreira M. Anaphylactic readtion to hydroxycobalamin. Allergy 1997; 52(1):118-9.

35. Hovding G. Anaphylactic reaction after injection of vitamin B12. Brit Med 1968; 3(5610):102.

36. Auzépy P, Veissieres JF, Deparis M. Choc anaphylactique du à l'hydroxocobalamine. Nouv Presse Med 1974; 3:152.

37. Ugwu CN, Gibbins FJ. Anaphylactic reaction to vitamin B12 apearing after several years of treatment. Age Ageing 1981; 10:196-7.

38. Desola J, Sala J. Joint intoxication by cyanide plus carbon monoxide. Review of 90 cases. UHMS Annual Scientific Meeting, St. Pete Beach, Florida , June 3-5, 2010. Poster no. E18.

39. Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C. Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. Ann Emerg Med 2007; 49(6):794-801.

40. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, Orme JF, Jr., Thomas FO, Morris AH. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002; 347(14):1057-67.

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