

## **Cyanide Antidotes for Smoke Inhalation: Which should I use and why?**

There will always be the issue of cost when we are discussing the notion of stockpiling any medication. What are the odds of a cyanide terrorist incident producing mass casualties? Probably somewhat limited although real (as in the first world Trade center bombing incident), but as always when we deal with disaster preparedness, we must also consider the consequences of not being properly prepared should the unlikely event actually occur.

Stocking an antidote that has the best risk:benefit ratio should be a consideration. It's plenty easy to say "Let's just stock a bunch of cheap sodium thiosulfate and check that square off and go on to the next issue." Personally, having spent well over 20 years researching cyanide poisoning, smoke inhalation, and all available antidotes and developmental antidotes worldwide both with manufacturers and NGOs such as the International Programme on Chemical Safety (WHO/UNEP/ILO) and as an academic physician and consultant, my belief is that of currently marketed cyanide antidotes in the US, hydroxocobalamin is at least as efficacious as others and has a better adverse effect profile (and this has been shown in the hospital and pre-hospital setting in actual patients, not just in animal studies, as shown in publications from the University of Paris and the Paris Fire Brigade by Baud FJ, Fortin J-L and others).

Several of us have proposed similar studies in the pre-hospital/ED settings in the US, but the funding just hasn't been there. I continue to be somewhat amazed that our panel for the CounterACT program of NIH has managed to successfully recommend funding for two developmental cyanide antidotes: cobinamide and sulfanagen. Should the Phase II and III clinical studies work out as anticipated, I fully expect them to eventually replace the other currently FDA-approved cyanide antidotes in the US. This will likely be some years down the pike. I started researching hydroxocobalamin in 1984 and it took until 2006 for the FDA to approve it.

Yes, all cyanide antidotes are expensive and hydroxocobalamin is more expensive than the old nitrite/thiosulfate kit or thiosulfate alone. The main reason hydroxocobalamin is expensive is that the "cost of goods", what it takes to actually manufacture a pharmaceutical preparation, is very high. There's certainly not a whole lot of profit in selling any antidote. This is one reason why we very seldom get another antidote for any poisoning into clinical availability. However, how much are we as a society willing to spend to keep an HIV/AIDS patient with multiple-drug-resistant TB alive for a few weeks or months compared to a single administration life-saving cyanide antidote dose for an otherwise healthy firefighter or civilian smoke inhalation victim? The final question will always remain: "What's a human life worth?" If it's *me* who's extricated from an enclosed-space fire with smoke present and I meet the criteria, please give me hydroxocobalamin. I'll quite happily pay for it out of my own pocket and I would have a good chance at still being alive to do so. At least until something even more efficacious and safer comes into clinical practice.

To address scientific concerns:

- 1) Inhalation exposure to about 200-500 ppm or so of hydrogen cyanide vapor will cause a rapid "knock-down" after about 2 breaths. We actually did a dry run in the gas chamber at San Quentin prison using a manikin and various sampling devices a number of years ago in conjunction with a lawsuit where the ACLU sued the Warden about inhalational cyanide poisoning being alleged "cruel and unusual punishment". We got to over 14,000 ppm with their old procedure in mere seconds and considering a lung-to-heart-to-brain transit time of 22 seconds, very rapid unconsciousness would have occurred. And there are any number of industrial accidents mostly in facilities that either manufacture cyanide or use large amounts in the production of plastics and polymers. The half-life by inhalation exposure is about 30-60 minutes. The actual intravenous administration studies done in dogs in France and the US used a continuous infusion to mimic inhalation exposure. Obviously, it is safer for the laboratory personnel to

not have the potential for an airborne cyanide release in the lab. What our French colleagues have found for many years and what we are beginning to see here in the US is that smoke inhalation victims with a significant cyanide poisoning component have their best chance of survival when hydroxocobalamin is administered (when clinically indicated only) in the pre-hospital setting. Obviously, until we have a field mechanisms for assessing cyanide exposure, we have to rely on clinical judgment alone. We will have a publication on suggested pre-hospital and ED protocols being published likely in the next two months: O'Brien D, Walsh D, and Hall AH in Pre-hospital and Disaster Medicine. You might want to look it over.

2) There is a widely-quoted study of autopsy data from New Jersey from which the authors concluded that cyanide poisoning in smoke inhalation is uncommon. Several of us have critically reviewed these data and find many points of contention with these conclusions. For example, there is a subset of victims who were still alive on ED arrival, but they were not studied separately. The pre-hospital data from France first showed that without any antidote administration, smoke inhalation victims who died had clinically significant elevated whole blood cyanide levels and those who survived did not. These same data also show that some smoke inhalation victims die with blood carbon monoxide (the French measure pCOs rather than carboxyhemoglobin levels) and cyanide, neither of which would be considered fatal alone. The data I base my opinions on are from surviving smoke inhalation victims, not autopsy data.

My gut feeling is that cyanide poisoning as a part of smoke inhalation is under-diagnosed because it isn't thought about. I can recount numerous occasions when I've been lecturing on the topic and otherwise very astute emergency physicians have commented that they have hardly even used the old Lilly etc. cyanide antidote kit. When I raise the smoke inhalation issue, many seem to think that CO is the whole ballgame, when obviously there can be a great many toxic components of fire smoke depending on what is burning or smoldering and other factors. There are no pathognomonic signs or symptoms of cyanide poisoning. There is an old quote from Sir William Osler that I've always liked. When asked how they made such unusual diagnosis at the Johns Hopkins, Osler replied: "The reason that we make the diagnosis of unusual conditions at the Hopkins is because we *think* of them." For example, in the Wakayama Japan mass foodborne poisoning incident in which about 100 persons were ill and 4 died, the original diagnosis based on analysis of the curry and stomach contents was cyanide poisoning. The curry contained apples and the seeds were included. About 2 weeks later, the survivors' developed pancytopenia and peripheral neuropathies. When I was consulted, I suggested that it might actually be arsenic poisoning, which as it turned out, it was. When I was invited to lecture about this in Japan, I put together two of those generally useless tables listing the common signs and symptoms, and it was interesting to note that except for diarrhea (common in ingestion arsenic poisoning, uncommon in ingestion cyanide poisoning), the two slides were just about the same.

Currently, I have no consulting or contractual relationships with either the hydroxocobalamin manufacturer or the current US distributor. I have had so in the past, and might again in the future. I do not own stock in any of the companies (unless my retirement plan has invested some of the little money I have in them without my knowledge) and I certainly do not receive royalties or commissions on sales. I promote hydroxocobalamin because based on my own research and that of many others, it currently seems to be the best alternative, particularly for smoke inhalation victims who may or may not have a significant cyanide poisoning component.

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