Published in final edited form as:

Clin Toxicol (Phila). 2014 June ; 52(5): 566. doi:10.3109/15563650.2014.923906.

Are H₂S-trapping compounds pertinent to the treatment of sulfide poisoning?

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Dear Sir

We have read with interest the study of Brenner *et al.* (1) on the effects of the Vitamin B12 analog cobinamide on H₂S toxicity. In this study, the effects of various vitamin B12 analogs were compared using, as the main outcome, the duration of NaHS infusion that can be maintained *after* administering the antidote until death occurred – or up to a maximum of 270 mg.

Although Cobalt compounds belong to a category of antidotes, such as methemoglobin, which do complex H₂S (2, 3), it is essential to consider their potential clinical benefit in the light of the kinetics and fate of the various pools of sulfides *during* and *following* H₂S exposure (4). *During* an infusion of NaHS, a large part of hydrogen sulfide is immediately oxidized in the blood or eliminated by the lungs. What is left equilibrates into 2 main pools: 1- a small “compartment” of free/soluble or exchangeable sulfides, i.e. gaseous H₂S and its sulfhydryl anion HS⁻ (4), 2- a large and complex pool of sulfides, which is combined with the cysteine residues of many proteins or with metallo-proteins. Only the free/soluble H₂S can be trapped by cobalt compounds. This is why during a continuous infusion of NaHS, any vitamin B12 analog already present in the blood will combine free sulfide as it enters the blood stream. This will reduce the amount of free H₂S and the rate at which it would have otherwise diffused into the cells and eventually combined with the cytochrome c oxidase (akin to the interaction between ferric compounds and soluble sulfide).

However, the pool of free/exchangeable sulfides remains present in the blood only if H₂S infusion is maintained (4). As soon as H₂S exposure ceases, when for instance a victim is withdrawn from a source of intoxication to be treated by first responders, free H₂S drops to undetectable levels within less than a minute (4). This exceptionally rapid disappearance of H₂S can be accounted for by the ability of mitochondria to oxidize large amounts of sulfide at a very high rate (4, 5). Little benefit is thus to be expected from compounds interacting with the pool of exchangeable sulfide, since all free H₂S would have vanished well before any antidote can be administered. Incidentally, the large pool of combined H₂S, which is not “accessible” to trapping, also decreases rapidly (4).

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Due to the unique behavior of H₂S (4), the challenge for treating H₂S poisoning is to find an antidote capable of diffusing very rapidly into cells, restoring ATP production, and counteracting or preventing the toxic and post toxic/anoxic injuries to the brain, the heart and the lungs, even *in the absence of free sulfide*.

Acknowledgments

This work was supported by the CounterACT Program, National Institutes of Health Office of the Director (NIH OD), and the National Institute of Neurological Disorders and Stroke (NINDS), Grant Number 1R21NS080788-01.

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