Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: informahealthcare.com/journals/iemt20

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To cite this article: Omid Mehrpour, Natalie Neumann & Patrick Ng (2019) Is cytochrome oxidase inhibition the primary mechanism in aluminum phosphide poisoning?, Expert Opinion on Drug Metabolism & Toxicology, 15:8, 613-614, DOI: 10.1080/17425255.2019.1645833

To link to this article: https://doi.org/10.1080/17425255.2019.1645833

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
2019, VOL. 15, NO. 8, 613–614
https://doi.org/10.1080/17425255.2019.1645833

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EDITORIAL

Is cytochrome oxidase inhibition the primary mechanism in aluminum phosphide poisoning?

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ARTICLE HISTORY Received 27 March 2019; Accepted 16 July 2019

KEYWORDS Aluminum phosphide; cytochrome c oxidase; mechanism; poisoning

Aluminum phosphide (AlP) has common applications as rodenticides and grain fumigants in Asian countries. It has a very high mortality rate [1–3]. Overall mortality related to AlP reported from 30% to 100% [1–3]. The cause of which is a cardiogenic shock [4]; it also induces severe metabolic acidosis and refractory hypotension [5]. Although it is a significant concern in many countries, the pathophysiological mechanisms have not been clearly explained in humans. However, several articles suggest that it can inhibit cytochrome c oxidase activity in severely poisoned patients [1,5–8]. Oxidative stress is another suggested mechanism [1,8].

Moreover, complexation of calcium and magnesium is another suggested mechanism of toxicity induced by AlP. Both hypomagnesemia and hypermagnesemia are reported in AlP poisoning [9,10].

In a previous study, Anand et al. evaluated mitochondrial electron transport chain complexes, oxidative stress, and catalase markers in patients with severe AlP poisoning. They concluded that AlP not only inhibits cytochrome c oxidase but also affects other enzymes, resulting in severe energy insufficiency and increased production of reactive oxygen species, which can synergistically cause tissue damage [8]. Moreover, Dua et al. found that the interaction of AlP with redox chain components causes the impairment of the electron transfer along the respiratory chain [11].

In fact, in the literature, inhibition of cytochrome c oxidase is a suggested mechanism for the toxicity of AlP. Cytochrome oxidase, which is recognized as an iron-containing enzyme, is necessary for oxidative phosphorylation and, therefore, aerobic energy generation. This enzyme acts in the mitochondrial electron transport chain, converting catabolic glucose products into adenosine triphosphate (ATP).

There are some major concerns in this area:

There are some similarities between AlP, cyanide, hydrogen sulfide, and azide because all of these toxins induce cellular hypoxia through inhibition of cytochrome oxidase and electron transport chain. In cyanide, hydrogen sulfide, and azide poisoning, oxygen cannot be used despite adequate oxygen supply; therefore, ATP molecules cannot be generated. Unincorporated hydrogen ions accumulate, leading to metabolic acidosis. Because of failure in aerobic energy metabolism, hyperlactatemia may ensue, especially in cyanide poisoning [12]. In general, the mechanisms of hyperlactatemia are cellular hypoxia due to hypoperfusion, hyperstimulation of Na^+/K^+–ATPase, increased pyruvate and lactate because of rise in anaerobic glycolysis, lactate clearance decline, seizures inducing muscle hyperactivity, and electron transfer and oxidative phosphorylation impairment. Baud et al. recently revealed that hyperlactatemia as the single factor has an ability to predict cyanide poisoning [13]. Moreover, they found that the level of blood cyanide meaningfully associated with the blood lactate increasing. Interestingly in cases with lactic acidosis, the median serum creatinine phosphokinase activity was not significantly different from that in control patients [13].

There are very few articles evaluating lactate levels in cases of AlP poisoning. Erfantalab et al. investigated the trend of lactate in this poisoning; they found that there is a short time hyperlactatemia at the initial phase of poisoning, although the trend was descending, and it returned to the normal range at the end of the first day of admission [14]. In addition, because of reduced oxygen utilization in tissues, high venous oxygen saturation is usually reported in these cases of poisoning.

Although the suggested mechanism of AlP poisoning is very similar to the abovementioned poisoning, elevated venous oxygen saturation is rarely reported following AlP poisoning. Moreover, hyperlactatemia may be seen in all of these poisoning, but the trend is different between them.

In addition, one of the consequences of cellular energy depletion is rhabdomyolysis. However, this is rarely reported following AlP poisoning. Besides, coma is a major finding induced by inhibitors of cytochrome oxidase, including cyanide, hydrogen sulfide, and carbon monoxide but was not reported in AlP poisoning. In fact, patients may remain conscious until the late stage. Coma may happen as a result of anoxia due to refractory shock, not due to the neurotoxicity of AlP [15].

If cytochrome c oxidase inhibition is a major factor in AlP toxicity, rhabdomyolysis, high venous oxygen saturation, and coma in poisoned patients may be expected. However, this finding is rarely reported. Although we should be aware that AlP occurs far less frequently and often in developing countries that may not evaluate for or report arterial blood gas/venous blood gas mismatch and rhabdomyolysis.

In conclusion, there are few pieces of evidence against the role of cytochrome c oxidase inhibition in the literature. Also, it seems

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that some aspects of AlP poisoning are not evaluated. So, we strongly encourage researchers to evaluate the other mechanisms in this lethal poisoning. The knowledge of a complex mechanism of acute toxicity of AlP is important and necessary to reach a precise diagnosis of poisoning and to develop adequate treatment of acute poisoning with AlP. We encourage researchers to evaluate the exact mechanism of AlP-induced toxicity.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Proudfoot AT. Aluminium and zinc phosphide poisoning. Clin Toxicol (Phila). 2009;47(2):89–100.
2. Mehrpour O, Asadi S, Yaghoubi MA, et al. Cardiogenic shock due to aluminum phosphide poisoning treated with intra-aortic balloon pump: a report of two cases. Cardiovasc Toxicol. 2019 Apr 4.
3. Hena Z, McCabe ME, Perez MM, et al. Aluminum phosphide poisoning: successful recovery of multiorgan failure in a pediatric patient. Int J Pediatr Adolesc Med. 2018 Dec;5(4):155–158.
4. Farzaneh E, Ghobadi H, Akbarifard M, et al. Prognostic factors in acute aluminium phosphide poisoning: a risk-prediction nomogram approach. Basic Clin Pharmacol Toxicol. 2018 Sep;123(3):347–355.
5. Hassanian-Moghaddam H, Zamani N, Rahimi M, et al. Successful treatment of aluminium phosphide poisoning by extracorporeal membrane oxygenation. Basic Clin Pharmacol Toxicol. 2016;118:243–246.
6. Bansal M, Bansal V. Pediatric ECMO for toxin exposure: a case report. J Pediatr Crit Care. 2017;4(2):96–100.
7. Singh S, Bhalla A, Verma SK, et al. Cytochrome c oxidase inhibition in 26 aluminum phosphide poisoned patients. Clin Toxicol (Phila). 2006;44:155–158.
8. Anand R, Sharma DR, Verma D, et al. Mitochondrial electron transport chain complexes, catalase and markers of oxidative stress in platelets of patients with severe aluminum phosphide poisoning. Hum Exp Toxicol. 2013 Aug;32(8):807–816.
• **Documented the role of cytochrome c oxidase as the current suggested mechanism for AlP toxicity.**
9. Chugh SN, Jaggal KL, Sharma A, et al. Magnesium levels in acute cardiotoxicity due to aluminium phosphide poisoning. Indian J Med Res. 1991 Dec;94:437–439.
10. Gupta S, Ahlawat SK. Aluminum phosphide poisoning – a review. J Toxicol Clin Toxicol. 1995;33(1):19–24.
11. Dua R, Gill KD. Effect of aluminium phosphide exposure on kinetic properties of cytochrome oxidase and mitochondrial energy metabolism in rat brain. Biochim Biophys Acta. 2004 Sep 6;1674(1):4–11.
12. Cooper CE, Brown GC. The inhibition of mitochondrial cytochrome oxidase by the gases carbon monoxide, nitric oxide, hydrogen cyanide and hydrogen sulfide: chemical mechanism and physiological significance. J Bioenerg Biomembr. 2008 Oct;40(5):533–539.
• **Documented the reduced oxygen utilization in cyanide, azide, hydrogen sulfide, and azide toxicity.**
13. Baud FJ, Haidar MK, Jouffroy R, et al. Determinants of lactic acidosis in acute cyanide poisonings. Crit Care Med. 2018 Jun;46(6):e523–e529.
14. Erfantalab P, Soltaninejad K, Shadnia S, et al. Trend of blood lactate level in acute aluminum phosphide poisoning. World J Emerg Med. 2017;8(2):116–120.
15. Mehrpour O, Jafarzadeh M, Abdollahi M. A systematic review of aluminium phosphide poisoning. Arh Hig Rada Toksikol. 2012 Mar;63(1):61–73.