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Review Article

Protective role of coenzyme Q10 as a means of alleviating the toxicity of aluminum phosphide: An evidence-based review

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ABSTRACT

Aluminum phosphide, which is known as rice tablet in Iran, is being used in an increasing number of cases of self-poisoning, and such cases have a high mortality rate. This poisoning has become an important problem in various developing countries. There is no specific antidote, and supportive care usually fails to restore cardiac systolic function and to resolve the patient's severe hypotension. The main mechanism of action of aluminum phosphide is believed to be an inhibition of cytochrome *c* oxidase in mitochondria followed by a stoppage of cellular metabolism. Currently, scientific attention is exploring modifying the functioning of mitochondria using various novel therapeutic agents. One such agent is coenzyme Q10, which has an important role in the mitochondrial electron transport chain. It is hydrophobic in nature acting as an antioxidant with the ability to scavenge oxygen-derived free radicals. As a result of these properties, coenzyme Q10 has a crucial role to play in reducing cellular oxidative stress. Moreover, there is evidence suggesting that coenzyme Q10 is able to enhance cardiac systolic function in heart failure patients. Based on the above, we propose that treating patients suffering from aluminum phosphide poisoning with coenzyme Q10 may be able to mitigate mitochondrial dysfunction and improve heart contractility. This novel therapeutic intervention enables this by removing oxygen-derived free radicals from the mitochondria and modifying mitochondrial functioning. We believe that this treatment has potential as an effective adjunct to supportive care in cases of aluminum phosphide poisoning and should also help to alleviate tissue injury.

1. Introduction

1.1. Aluminum phosphide poisoning

Aluminum phosphide, which is known as rice tablet in Iran, is being used in an increasing number of cases of self-poisoning, and these have a high mortality rate. Furthermore, self-poisoning using aluminum phosphide is becoming an important problem in a number of developing countries [1]. After ingestion, when the aluminum phosphide comes in contact with the acidic contents of the stomach, phosphine gas (PH_3) is released from the aluminum's weak bonds and is then quickly absorbed through the gastric mucosa [1,2]. The primary symptoms of aluminum phosphide poisoning include retrosternal burning and vomiting, which are followed by severe metabolic acidosis and cardiovascular incompetence [1]. Aluminum phosphide poisoning has a high mortality rate because there is a major depression of cardiac functioning and, consequently, the presence of refractory hypotension [3]. There is no specific antidote to aluminum phosphide poisoning, and old-fashioned gastrointestinal decontamination methods such as potassium permanganate (1:10,000 solution) and activated charcoal are not helpful. Medical toxicologists are only able to support the functioning of the patient's vital organs; nevertheless, supportive care usually fails to restore cardiac systolic function and to resolve the patient's severe hypotension [3–6]. The main mechanism of

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action of the phosphine produced from the aluminum phosphide is believed to be an inhibition of cytochrome *c* oxidase in the mitochondria, which reduces ATP (adenosine triphosphate) production and promotes oxidative stress [7,8].

Mitochondria are the main source of intracellular free radicals, are able to transport electrons, and are involved in oxidative phosphorylation as well as being part of the mechanisms that control intracellular calcium homeostasis [9]. Singh et al [10] demonstrated that aluminum phosphide causes a 45% reduction in cytochrome *c* oxidase activity in humans. Dua and Gill [7] demonstrated a 21–49% and 21–28% decrease in the activity of complex I and complex II, respectively, using an animal model [7]. Furthermore, inhibition of the electron transport chain will result in overproduction by the mitochondria of reactive oxygen species. Hence, in cases of aluminum phosphide poisoning, it would seem that improving mitochondrial functioning and cellular bioenergetics in general should be an effective way to combat the multiorgan dysfunction associated with this deadly method of poisoning.

1.2. Coenzyme Q10 shows specific characteristics

Coenzyme Q10 (CoQ10) is a biological antioxidant that is able to induce depolarization of mitochondria and of the electron transport chain that accepts electrons from complexes I and II and transfers them to complex III [11]. It also is involved in adjusting ATP production and decreasing free radical generation [12]. In animal models, CoQ10 has been shown to have protective properties against toxin-induced oxidative stress [13]. There is also evidence that CoQ10 can play a role in increasing energy production at the mitochondrial level to a degree that is sufficient to bring about a recovery in the contractility of the human myocardium [14].

We propose that CoQ10 might be useful as a potential cellular defense against oxidative damage after aluminum phosphide poisoning. We believe that in the presence of phosphine induced cell toxicity, CoQ10 will be able to increase cytochrome *c* oxidase activity; this, in turn, should help to restore mitochondrial activity and ATP production, as well as improve systolic cardiac contractility. It is our belief that CoQ10 should be able to not only alleviate oxidative stress at the level of the mitochondria and consequently increase cell survival, but is also likely to help to resolve the multiorgan dysfunction present in patients with aluminum phosphide poisoning.

2. Evaluation of this therapeutic option

Despite some recent uncertainty [3], most clinical toxicologists believe that cytochrome *c* oxidase in mitochondria is the target for phosphine's toxic effects [8,10]. This is supported by *in vitro* experiments that have examined cytochrome *c* oxidase inhibition by phosphine [7]. These studies suggest that, at the cellular level, the reactivation of cytochrome *c* oxidase in the mitochondria might act as an antidote *in vivo* in cases of aluminum phosphide and thus enhance cell survival.

Coenzyme Q (2,3-dimethoxy-5-methyl-6-polyprenylbenzoquinone) plays a key role in the mitochondrial respiratory chain. CoQ10, the predominant form of CoQ in humans, consists of a polar quinoid head group attached to 10 hydrophobic isoprenoid tail units. The oxidized ubiquinone (UQ) form and the reduced ubiquinol (UQH2) form are the foremost redox forms of CoQ [15]. Each cell synthesizes CoQ itself, and the major resources of CoQ10 within the body's tissues are found in the mitochondria of the myocytes and myocardiocytes [16,17]. During an oxidative assault, UQH2 is destroyed by an oxidation chain reaction that propagates by itself, and ubisemiquinone radical generation becomes a self-perpetuating reaction. This means that when mitochondria are exposed to oxidants such as phosphine, this will increase superoxide production as well as decrease the CoQ content of the mitochondria [15].

Kwong et al [18] have reported that there is an increase in total CoQ content across all tissue homogenates after CoQ supplementation. Moreover, concentrations of CoQ were found to be significantly higher in the mitochondria of various tissues, particularly in myocytes and myocardiocytes. They also mentioned that, although CoQ has antioxidant as well as oxidant properties, CoQ supplementation does not seem to promote the mitochondrial generation of oxidants but does seem to reduce oxidative stress by acting as an antioxidant rather than a pro-oxidant. They then suggested that these findings support the hypothesis that CoQ supplementation may alleviate oxidative stress in certain organs [18]. Comparatively, the protein carbonyl content in mitochondria is known to act as a marker of oxidative damage to cellular proteins, and this measure of oxidative damage is decreased when CoQ activity is active scavenging radicals in mitochondria [18–21]. Following the administration of CoQ10, there seems to be a general uptake by all tissues. However, some specific organs show superior uptake, and a higher concentration of CoQ10 is found in the mitochondria of these tissues; in fact, the regulation of CoQ tissue contents is autarchic [17,18].

As mentioned above, replacement of CoQ10 is able to effectively reactivate the mitochondrial electron respiratory chain and alleviate oxidative stress. Furthermore, it has been demonstrated that the employment of high doses of CoQ10 is safe and well tolerated [22]. After the reactivation of mitochondrial ATP production, we would expect an improvement in organ functioning. Interestingly, several studies have confirmed improvements in cardiac systolic function among patients with heart failure after a short-term treatment with CoQ10 and replenishment of the cardiac CoQ10 [23–26]. Another possible benefit of CoQ10 replenishment might be a restoration of the balance between energy demand and supply, as well as a reduction in reactive oxygen production at the cellular level, which in turn would ameliorate metabolic acidosis.

3. CoQ10 in clinical applications

CoQ10 is not approved by the Food and Drug Administration for medical use and is traded in the marketplace as a dietary supplement. The known adverse effects associated with CoQ10 intake are gastrointestinal upset, headache, and skin rash [27]. As mentioned above, it would seem that administration of a CoQ10 supplement has a beneficial effect on systolic function in heart failure patients. However, a recent Cochrane Collaboration meta-analysis found that the available dataset is inconclusive, and there is no definite evidence to confirm its efficacy [28]. In their study, Pringsheim et al [29] concluded that there is good evidence to support the prescription of CoQ10 as a prophylactic medication when treating patients with migraine headaches. Other studies have indicated that CoQ10 may benefit patients with sperm abnormalities, statin-induced myopathy, Huntington's disease, and Parkinson's disease; these studies have not yet been supported by evidence from clinical trials [30–33].

4. CoQ10 in evidence-based studies

Mortensen et al [34], in a randomized double-blind clinical trial, evaluated the effect of CoQ10 on morbidity and mortality among chronic heart failure patients. Their study showed that the long-term treatment of these patients with CoQ10 was well tolerated and that, in comparison to treatment with a placebo, there was a decrease in cardiovascular mortality and a significant improvement in the patients' New York Heart Association (NYHA) functional class [34]. Pourmoghaddas et al [35] evaluated the effect of atorvastatin alone and a combination of CoQ10 and atorvastatin as a standard treatment for congestive heart failure. This study showed that after 4 months, treatment with a combination of atorvastatin and CoQ10 increased the patients' ejection fraction and improved their NYHA functional class compared to the group of patients who were treated with atorvastatin alone. Berman et al [36], in their double-blind, placebo-controlled, randomized study, assessed the effect of CoQ10 on patients with end-stage heart failure awaiting cardiac transplantation. They concluded that the administration of CoQ10 to these heart transplant candidates for 3 months led to a significant improvement in their 6-minute walk test together with decreases in dyspnea, NYHA functional class, nocturia, and fatigue compared to the placebo-treated patients [36].

5. Conclusion

In spite of advances in critical care and in clinical toxicologists' efforts to eliminate symptoms of aluminum phosphide poisoning, consumption of this chemical still results in high mortality. This presents as increased rates of death from aluminum phosphide poisoning in many developing countries. In such circumstances, a novel treatment method for aluminum phosphide poisoning would be very valuable indeed. The safety of CoQ10, its ability to revive cellular energy production, the fact that it can act as a scavenger of free radicals, and its ability to improve cardiac systolic functioning are generally well accepted. Based on these findings, we suggest that for patients who are suffering from aluminum phosphide poisoning, CoQ10 is likely to act, at least to some extent, as an antidote to the poison. We believe that treatment with CoQ10 might become an efficient adjunct to supportive care when treating cases of aluminum phosphide poisoning because it will help to alleviate the tissue injury caused by the uptake of phosphine.

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