

Aluminum Phosphide Poisoning, Mechanism of Action and Treatment: a Literature Review

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Abstract

Aluminum phosphide (AIP) is an important fumigant, a commendable and very effective outdoor and indoor insecticide. AIP, locally named “rice tablet”, is widely used to protect rice. As soon as taking a very small amount of an AIP tablet, phosphine vaporizes due to the exposure to the air and affects different kinds of organs. Although, in most cases, clinical history can help making the final diagnosis, analytical tests such as gas chromatographic method in post-mortem specimens and survivors have been developed to measure the level of phosphine and to distinguish between ZnP and AIP poisoning.

AIP poisoning management should be started quickly. In addition to supportive therapy, various antioxidant agents, as candidate protective factors, such as N-acetylcysteine (NAC), melatonin, glutathione, magnesium, β -carotene, and vitamin C and E have also been recommended to decrease oxidative damage and cardiotoxicity due to the limited antioxidant defense systems.

The present study highlights the fact that Antioxidant therapy in severe ALP poisoning confers different survival benefits. This literature review showed that the administration of antioxidant therapy in addition to the supportive treatment may decrease the mortality rate and could be considered in the treatment of acute AIP poisoning in combination with other therapeutic protocols.

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Introduction

Aluminum phosphide (AIP) is an important fumigant, a commendable and very effective outdoor and indoor insecticide (registered in the USA) and rodenticide, widely purchased and used since the 1940s (1, 2). AIP is easily available as pellets or a tablet formulated and sold in porous bags in solid form, under trade names such as Phostoxin,

Quickphos Phosphume Phostek, Bhostoxin, Quickphos, Alphos, and Celphos (can release 1 g PH₃). It is used in developing countries like India and Iran in suicide attempts (3). AIP is available in pesticide markets as a low-priced grain rodenticide (4).

High potential properties are the reason for the importance of its availability. The properties are near ideal toxicity species, not affecting the viability of the seeds, leaving little residue on food grains, being cheap and highly formulation (5). Moisture in the air combined with aluminum phosphide, produces phosphine gas, the main active toxin (6, 7).

Albeit AIP is the prevalent substance used in suicide attempts in some suburban and rural parts of Iran and Northern India, there are some reports from Turkey, France, and Germany, showing its use as the usual mode of suicide (8-11). AIP, locally named "rice tablet", is widely used to protect rice in factories (11). The most cases of exposure include suicidal ingestion or accidental exposure, especially through food products by farmers (12) and skin exposure that rarely induce severe systemic toxicity (6).

The Chemistry of AIP

AIP is generally available in solid form (pellets or tablets) placed in blister packs, usually synthesized as dark brown/gray

or yellow crystals that contain 44% aluminum carbonate and 56% AIP (6, 13). Any 3 g tablet disseminates 1 g of phosphine with significant toxicity occurring during the reaction of stomach hydrochloric acid and phosphine gas (14).

It has been illustrated that PEL (Permissible Exposure Limit) for fatal dose (70 kg adult in 30 min) is 0.3 ppm over an 8 h period, and 400–600 ppm (10 mg/Kg AIP) is the range that has been reported for lethal dose (15).

Absorption of phosphine gas, with odorless and colorless properties, is rapid through mucosal and skin contact, inhalation and ingestion due to the formation of diphosphines (16, 17). After ingestion, which is the most common way of exposure, a small quantity of zinc phosphide attains to the kidneys and liver and is hydrolyzed stillly in the tissues (18). Zinc phosphide is synthesized by combination of phosphorus and zinc (19). In table 1, characteristics of commonly available metal phosphides are shown.

Table 1. Properties of commonly available metal phosphides

No	Metal phosphide	Chemical formula	Source	Lethal dose (LD50)	Physical form
1 ^a	Aluminium phosphide	AIP	Fumigant /insecticide/rodenticide	20 mg/kg	Dark gray or yellow crystals
2 ^b	Zinc phosphide	Zn ₃ P ₂	Insecticide/rodenticide	4-5 gr	Gray-black/Gray crystals powder
3 ^a	Magnesium phosphide	Mg ₃ P ₂	Fumigant/insecticide /rodenticide	10.4 mg/kg	Green or yellow crystals
4 ^a	Calcium phosphide	Ca ₃ P ₂	Rodenticide	8.7 mg/kg	Brown or red crystalline powder or gray lumps

^a European Food Safety Authority Scientific Reports (2008). Available at <http://www.efsa.europa.eu/> (accessed on 17.06.11).

^b Vij, K. (2008). Textbook of Forensic Medicine and Toxicology-Principles and Practice, 4th edition, Elsevier-A Division of Reed Elsevier India Private Limited, New Delhi.

Epidemiology

An epidemiological research demonstrated various kinds of reports on the young agricultural worker population and also some cases with the purpose of suicide in urban and rural Asian

areas (20). Approximately, over 300,000 deaths are reported all over the world every year as the result of pesticide poisoning (21, 22). Frequent reports related to hospital admission records

from young adult population reflect only a fraction of its real incidence (23).

Shadnia et al. reported 471 AIP poisonings in Tehran until 2009 of whom 31% died (22). According to a research in Germany, between 1983-2003, inhalation toxicity related to gas releasing because of inadequate self-protection affected poisoned people through its effects on GI (gastrointestinal) and respiratory systems (24).

According to the National Poisons Information Service (NPIS), unwanted exposure has been reported especially in the UK, which shows accidental exposure to phosphine gas in agricultural locations (25). The most frequent symptoms reported immediately after completing fumigation activities in the workplace are dyspnea, chest tightness, cardiac arrhythmias and headache (26).

Mechanism of action

It has been demonstrated that about 0.5 g is the lethal dose of AIP (10). Oral ingestion is the quickest way of absorption. ALP gas releases as soon as different kinds of phosphide salts react with stomach contents especially hydrochloric acid (27).

After tissue absorption, the cytochrome C oxidase enzyme and mitochondrial electron transport chain are blocked (16).

Phosphine mainly binds to cytochrome oxidase (especially in mitochondrial electron transport chain of lung and heart cells) (28), changing the valences of the hemoglobin (especially hem component), which ultimately leads to protein denaturation, cell membranes death in different organs and lipid peroxidation (29). Some studies show the reduction of serum cholinesterase related to high phosphine concentration (13). Disrupted ionic barrier, protein denaturation, cell death, damaged nucleic acid, and finally cell death occur (30). AIP also reduces glutathione as a substantial antioxidant defense agent (25). Authors indicated that the changes in levels of malonyldialdehyde (MDA), superoxide dismutase (SOD), and catalase have a direct role in mortality by AIP (14). According to human and animal studies, Phosphine has an important role in denaturation of oxyhemoglobin which can induce oxidative damage of cellular life especially in the lung, brain and liver (27). Proposed mechanisms for phosphine toxicity have been shown in Figure_1.

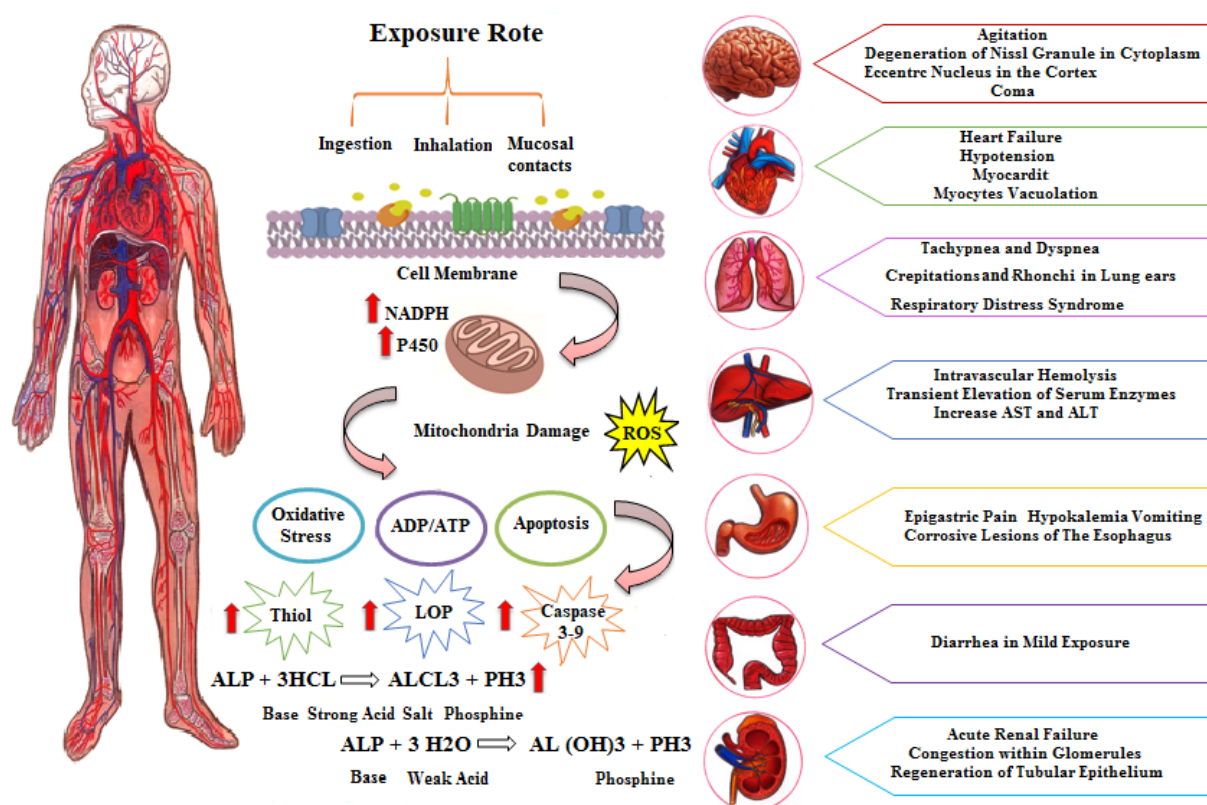


Figure1. Proposed mechanisms of phosphine toxicity

Clinical manifestations/diagnosis

As soon as taking a very small amount of an AIP tablet, phosphine vaporizes due to the exposure to the air and affects different kinds of organs (31).

The main organs affected by the first exposure are heart, gastrointestinal tract, lungs, and kidneys and related symptoms are nausea, pulmonary edema, cyanosis, abdominal pain, palpitation, epigastric pain, refractory hypotension, shock, metabolic acidosis, and cardiac arrhythmias, which are related to myocardium injury reported in some cases (28, 32, 33). The preliminary symptoms including vomiting, nausea, agitation, epigastric pain (3), and leucopenia are significant indices in reported AIP poisoning cases (34). Clinical tests are used according to clinical symptoms and laboratory assessment. Based on the results, increased level of serum glutamic pyruvic

transaminase (SGPT) and glutamic oxaloacetic transaminase (SGOT) induced metabolic acidosis indicate moderate to severe AIP toxicity and show liver cells damage (14).

A recent controversial research indicated that continuous damage to the liver due to AIP poisoning is able to induce hepatotoxicity (35). The main findings in this regard were fatty liver changes, destruction of the hepatocyte nuclei, centrilobular necrosis, and central vein congestion (36). Manifestation of hepatotoxicity usually develops after 72 h of AIP intoxication (8). It has been also found that death could happen due to hepatocellular toxicity and acute fulminant hepatic failure, which has been reported in some acute intoxication cases in several researches (14).

Pancreatitis, hepatitis, acute tubular necrosis, acute adrenocortical insufficiency, and disseminated intravascular

coagulation are common during AIP poisoning. Post-mortem reports of AIP toxicity show cardiac toxicity, acute tubular necrosis, respiratory alkalosis, and intravascular coagulation (4, 10).

Furthermore, Jain S and colleagues showed various ECG changes following ALP poisoning (37). Common ECG changes and cardiovascular complications like PR and QRS interval prolongation, ST segment elevation which leads to decreasing systemic venous pressure (severe hypotension), complete heart block to ectopic pacemaking, irreversible myocardial hurt, and atrial fibrillation have been reported in various studies as well (38, 39). In the first 3 to 6 hours after poisoning, there are ST-T changes and sinus tachycardia that are followed by conduction disturbances and also continuous arrhythmias in 6-12 hours after poisoning (26, 36).

Anteroinferior wall ischemia with RBBB (right bundle branch block), wave flattening simulating myocardial ischemia, and complete RBBB have been reported in different cases, which were related to myocardial injury (38, 40).

The most significant gastrointestinal indication of AIP ingestion are hematemesis, vomiting, fistula, esophageal strictures and epigastric pain, which lead to upper gastrointestinal bleeding (8, 32, 33). Destruction of stomach and esophagus tissues and slugged mucosa have been reported in different endoscopy reports (32).

According to previous studies, dysphagia can be a common late condition after increasing slugged mucosa during ALP poisoning (41). There are some evidences of necrotic and thinned out stomach wall and mucosa in the fundus wall of the stomach (32). There are reports of spontaneous inflammation and stomach wall burns occurring during oral poisoning by AIP (42, 43). Primary or secondary to vomiting, hypokalemia can

occur because of water and electrolytes disorders. Respiratory alkalosis, acute renal failure, metabolic acidosis, and wide variety in calcium, phosphate, magnesium, cortisol and citrate levels have been observed. Different changes in blood glucose levels are seen, too (44).

Silver nitrate test, as an important, simple, and sensitive spot test is used for investigating the poisoning with rice pills. Fresh silver nitrate solution paper helps to detect exhaled PH_3 gas. In this method, sample color changes to black. There are some advanced biochemical analyses in which gastric aspiration sample or blood sample is used to detect phosphine (45). The most valid way in diagnosis of ALP poisoning is detecting phosphine gas in samples (43). Even though, clinical history can help to make the final diagnosis in most times (46). Ion chromatographic methods are utilized to characterize phosphine in the bio-samples (46). Analytical tests such as gas chromatographic method in post-mortem specimens and survivors were developed to measure the level of phosphine and to distinguish between ZnP and AIP poisoning (12).

Tissue morphology following AIP exposure

There are different researches about morphological changes of tissues following AIP exposure and poisoning. In AIP toxicity, target organs are liver, brain, kidneys, heart and lungs. Moreover, microscopic analysis shows different levels of edema, inflammation and congestion in body organs (36).

In our review, the main histopathological findings in the lung tissue were congestion, interstitial edema, hemorrhage, variable degrees of alveoli collapse, alveolar thickening (40), and emphysema (47). In the brain, the most frequent morphological changes include neuronal degeneration, cerebral edema, infiltration in cerebellar tissue (round cells into

the molecular layer), and cytoplasmic degeneration in nissl granules (35, 40). Generally, in AIP poisoning histopathology, hypoxic damage to brain neurons with deep shrunken nuclei and eosinophilic cytoplasm have been reported (48).

morphology study of liver sample in ALP poisoning has showed vacuolar degeneration in hepatocytes cells, central venous congestion, mononuclear infiltration (40), sinusoidal dilatation, and centrilobular hemorrhagic necrosis (48), and as a result, massive necrosis in the liver (47). In a study on thirty-eight cases of confirmed fatal phosphine poisoning, the frequent morphological findings of liver sample were sinusoidal congestion and vacuolization in cytoplasmic liver cell. The intense sinusoidal congestion caused clumping of red blood cells (7). Nevertheless, frequent histopathologic diagnosis are portal edema, centrilobular necrosis, nuclear fragmentation, clusters of polymorph nuclear leukocytes in sinusoids, sub capsular hemorrhage, and macro vesicular steatosis (7). Sinusoidal cluster of polymorph nuclear leukocytes, hepatocytes nuclear and sinusoidal congestion were reported in the mentioned study (7). Subsequent to liver damage, the plasma level of renin raises and also cortisol decreases at the upper level in intense AIP poisoning (49).

In microscopic examination, changes in the kidneys included renal medulla, glomeruli and intraparenchymal congestion, and swelling of epithelial cells in the proximal convoluted tubules area (48). Additionally, in a case report, AIP poisoning in a 19-year-old depressed male farm worker, presented histologic abnormalities in myocardium such as contraction band necrosis, edema and hemorrhage, early coagulative necrosis, and pyknosis of cardiac myocyte nuclei (50).

Management of poisoning

AIP poisoning management should be started quickly. At first, the complete history must be taken and clinical examination should be done as soon as possible (51). management of intoxication is mainly supportive including fluid resuscitation, inotropic support, and mechanical ventilation (52). However, no definitive treatment have been introduced and most treatment strategies have not been completely successful and acceptable; some treatment strategies are mentioned below (53).

Gastrointestinal decontamination

After AIP ingestion, the different gastrointestinal manifestations like nausea, diarrhea, vomiting, abdominal tenderness and then abdominal and epigastric pain were reported (14, 54).

Despite occurring vomiting as frequently reported symptom in patients, gastric lavage with a 1/5000 potassium permanganate solution causes removal and/or oxidization of unabsorbed poison. However, care shall be taken to prevent aspiration during gastric lavage. For neutralization of hydrochloric acid and afterward reducing the release of phosphine, a 2% bicarbonate solution may also be used (52, 53). The level of bicarbonate less than 15 mEq/L requires sodium bicarbonate in a minimum dose of 50–100 mEq intravenously every 8 h until the bicarbonate level rises to 18–20 mEq/L. (53). In different patients, sodium bicarbonate may be required up to 300–500 ml or more (14). Moreover, consumption of H₂ receptor antagonists and proton pump inhibitors may reduce the gastric acidity and inhibit further releasing of PH₃ gas after AIP ingestion. A pH under 7.1 is an

important and risky condition, which is related to abnormal changes in heart rhythms (14).

Other treatments that have been recommended include administration of sorbitol solution as cathartic and liquid paraffin and vegetable oils as inhibitors of phosphine released from the AIP. A recent research on ALP poisoning indicated that, coconut oil has positive clinical effects in managing acute phosphine poisoning in humans even 6 h after poisoning (55). The mechanism of coconut oil and other lipids in the gastrointestinal tract is unclear. Coconut oil prevents the absorption of PH₃ gas through causing a protective layer around the mucosa of stomach as well as diluting HCl in the stomach and reducing phosphide breakdown (48). A previous study showed that gastric lavage with sweet almond oil significantly reduced the mortality of rats poisoned with AIP and lowered the level of plasma cholinesterase (56). However, this effect has not been confirmed in humans. In another study, wide gastric lavage combined with admixture of coconut oil and sodium bicarbonate solution has been recommended (57).

Management of cardiac manifestations

Severe metabolic acidosis and refractory hypotension are early signs of AIP poisoning. As soon as poisoning, 2 h after ingestion, these signs, firstly lead to shock and tissue perfusion failure owing to cardiogenic shock and peripheral circulatory failure (58). Acute myocardial infarctions and various kinds of cardiac arrhythmias are important cardiovascular complications which should be considered (55). post-mortem reports showed that the cardiac toxicity of AIP poisoning includes profound heart failure, heart congestion, hemodynamic instability, separation of myocardial fibers by edema, non-specific

focal necrosis, eosinophil or neutrophil infiltration and vacuolation of myocytes (51).

In many patients, cardiogenic shock has been reported as important cause of death in poisoned patients (58). Hence, blood pressure and ECG checking and cardiac monitoring are the most important functions to keep the patient alive (38). To control the central venous pressure (CVP) or pulmonary artery wedge pressure (PAWP), early resuscitation with fluid therapy and vasoactive agents should be done (59). Some reports have recommended 2–3 liters of normal saline (within the first 8–12 h) and guided or rapid infusion of saline (3–6 liters) in the initial 3 h to compensate the lost water and keep the CVP around 12–14 cm of water (60).

Drugs such as norepinephrine, dopamine, phenylephrine, and dobutamine can be used to treat hypotension and refractory shock, while anti-arrhythmic agents should be administered to improve cardiac arrhythmias (59). Trimetazidine, as an anti-ischemic drug, has proved to be impressive in discontinuing ventricular ectopic beats and reducing oxygen consumption by switching myocytes metabolism to glucose from fatty acids (61). Recent studies suggest that intra-aortic balloon pump (IABP) is an impressive treatment of AIP poisoning by supporting the heart mechanically, especially in refractory shock induced by toxic myocarditis (62).

Recent evidences suggest that according to the hypothesis that digoxin application is useful in AIP-poisoned cardiogenic shock through increased myocardial contractility and blood pressure, it can be used to stabilize the left ventricular heart failure (38, 63). Our review showed a successful treatment of AIP poisoning in a case with undetectable blood pressure and a severe left ventricular systolic dysfunction. Thus, dopamine (10 µg/kg/min) and digoxin (0.5 mg) were administered every 6 h

during the first toxicity days and digoxin administration was continued with 0.25 mg per day on the following days (55). Studies show that at least 5 days after supporting, the ECG parameters became ordinary (63, 64).

Airway protection

Changes in the cardiovascular and respiratory systems can lead to death (65). Involvement of the respiratory system may result in dyspnea, which may progress toward type I or II respiratory failure. Tachypnea, dyspnea, edema, congestion, atelectasis, capillary vasodilation, crepitation, and alveolar wall thickening are the pulmonary complications and common signs of AIP intoxication (66). Adult respiratory distress syndrome (ARDS) which happen after ALP poisoning has been reported in different studies (67). When ARDS occurs, hilar or perihilar congestion is shown in chest X-ray (67). ARDS and other types of pulmonary edema are prevalent in adults, accompanied by protein-rich or hemorrhagic pleural effusions. In Chugh et al study, all patients were in shock at admission and experienced increased ARDS within 6 hours. The exhalation of PH₃ gas that can be verified with positive silver nitrate paper test, was the possible noxious triggering factor in new researches (67).

There are two kinds of acute poisoning due to AIP: the ingestion of AIP tablet or powder and inhalation of phosphine gas (35). In inhalation poisoning cases, the patient must be transferred to a well-ventilated space or fresh air. Also, contaminated clothes should be removed, and skin and eyes should be washed with tap water as soon as possible (25).

In Lauterbach et al. study on the epidemiology of AIP poisoning in Germany between 1983 and 2003, of 188 reported cases, 65 % were accidental, mostly by inhalation because of inappropriate self-protection from the released gas. This study

demonstrated that the prevalence of AIP inhalation poisoning is high (24). Data show that lung injury affects patients and they may need endotracheal intubation and mechanical ventilation (58). On the other hand, according to some studies, hyperbaric oxygenation improved the survival time in an animal model of AIP poisoning. However, its efficacy in humans needs more research (67).

Antioxidant therapy

In addition to supportive therapy, various antioxidant agents, as candidate protective factors, such as N-acetylcysteine (NAC), melatonin, glutathione, magnesium, β-carotene, and vitamin C and E have also been recommended to decrease oxidative damage and cardiotoxicity due to limited antioxidant defense systems. Moreover, recent studies show that magnesium sulfate, melatonin, NAC and coconut oil play significant role in AIP poisoned patients and help to reduce the reactive oxygen species (ROS) as outcomes of phosphine toxicity (16). In a clinical trial on acute AIP poisoning, it had been demonstrated that supportive treatment helps patients to decrease adverse effects of AIP. In the mentioned study, patients received supportive treatment such as vitamin E (400 mg/BD/IM), that reduced malondialdehyde (MDA) and total antioxidant capacity of plasma level. The results also show that, Vitamin E as an important antioxidant along with other supportive treatments could have an important therapeutic effect in acute AIP poisoning. Further studies have been recommended in the mentioned study to confirm the effects of administration of vitamin C and methylene blue on outcome of patients with AIP intoxication (68).

Melatonin

Melatonin is one of the antioxidant agents with an amphiphilic structure that has the ability to affect all cellular and intracellular compartments, and also has the highest concentration in mitochondria (69). Melatonin, potentially, protects mitochondria against oxidative stress. Moreover, many studies have claimed that melatonin could be more advantageous than classic antioxidants like vitamins C and E (70).

The mitochondrion, a key organelle, is the main intracellular source of ATP production and reactive oxygen species (ROS) that affect the respiratory chain. ROS is located in the inner mitochondrial membrane in all mammalian cells. Mitochondria form about 45% of the myocardial volume and produces cardiomyocyte energy (69).

Animal studies demonstrated that AIP decreases the activity of respiratory chain and cellular ATP levels, whilst melatonin is able to neutralize the AIP effects on the respiratory chain. Moreover, melatonin plays an important role in ROS scavenging (53, 69). Thus, the effect of melatonin on mitochondrial function shows that it is a perfect option to ameliorate AIP-induced cardiotoxicity associated with mitochondrial dysfunction. Probably, it amend the clinical advent of further AIP exposure (71).

Recent studies have illustrated that AIP increases cellular toxicity via inhibiting the activity of antioxidant enzymes especially SOD, GPX, and catalase and decreasing cellular antioxidant defense (20, 72). Other researchers have shown contradictory results. They believe that AIP enhances SOD activity and increases H₂O₂ levels leading to cell damages in membranes including protein denaturation or lipid peroxidation (LPO) (3, 35). It has been indicated that melatonin facilitates

gene expression of catalase and GPX and SOD contributes to glutathione (GSH) recycling resulting in enhancement of cellular antioxidant defense (73). A recent study demonstrated that melatonin treatment at doses of 40 and 50 mg/kg following AIP treatment could reduce LPO and ROS levels. Additionally, melatonin administration enhanced GPX and SOD activities in an animal model (74).

Another function of melatonin in AIP intoxication is its effect on blood pressure. It has been shown that melatonin could compensate the low blood pressure of AIP poisoning in animal studies, whereas it had no effect on blood pressure at its basal levels in healthy controls (74). It has been suggested that melatonin has some effects on vasoconstriction and vessel permeability and leukocyte adhesion while it has the possibility to elevate capillary perfusion. Furthermore, it seems that melatonin can correct ECG abnormalities caused by AIP toxicity, for instance, it can alleviate QRS widening and prolonged QTc (75).

N-acetylcysteine

N-acetylcysteine (NAC) is another antioxidant that may be used in AIP intoxication due to the characteristic of NAC as a precursor of L-cysteine and GSH. NAC can be administered in various ways, especially orally and intravenously (48). Oral administration of NAC is rapid and NAC is quickly metabolized to cysteine as an important precursor of intracellular GSH synthesis. As a result, NAC acts as an antioxidant by increasing GSH level and decreasing oxidative stress and inflammation (52).

Different researches on this issue have noted the significant role of NAC (as an antioxidant) in AIP poisoning along with a reduction in oxidative stress (52). In an experimental model, the

administration of NAC before exposure to AIP in addition to post-treatment improved the survival time and stabilized the heart rate and blood pressure in rats through reducing oxidative stress in tissue (76). Tehrani et al. reported that NAC administration in high dose leads to amelioration of the oxidative stress and has significant survival benefit (52). In contrast, in a prospective intervention study, Bhalla et al. indicated that antioxidant therapy, especially the use of NAC in severe AIP intoxication, did not confer any survival benefit (77).

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Conclusion

In conclusion, according to the mentioned mechanisms of Action and treatment strategies, antioxidant therapy in severe ALP poisoning confers different survival benefits. The present review study showed that antioxidant therapy in addition to supportive treatment decreases the mortality rate and could be considered in the treatment of acute AIP poisoning; so, it could be considered in the treatment of acute AIP poisoning in combination with other therapeutic protocols. Considering the importance of AIP poisoning, further attention to treatment factors can improve treatment and save more lives.

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