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Research Article
Hyperbaric Oxygenation Therapy and Gastric Lavage as an Alternative Treatment for Aluminum Phosphide Toxicity in Rats

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Abstract

Background and Objective: Phosphide exposure is one of the most lethal types of poisoning because there is no specific antidote; therefore, the objectives of this study were to analyze the levels of oxidative and mitochondrial damage caused by poisoning and to determine whether gastric lavage with either olive oil or bicarbonate and hyperbaric oxidation therapy improves the recovery from this type of poisoning. **Methodology:** Female Wistar rats (300±30 g) were assigned to 1 of 5 groups. In groups with poisoned rats, 27 mg of aluminum phosphide was administered, after which some of the rats received treatment via gastric lavage (olive oil, 10 mg kg^{-1} or sodium bicarbonate, 1 mEq kg^{-1}) and/or hyperbaric oxygenation therapy. The enzymatic activities of citrate synthase and catalase were measured in cardiac, liver and lung tissue and lactate levels were measured in plasma by spectrophotometry. **Results:** After phosphide administration, the results showed a reduction in the enzymatic activities of catalase, citrate synthase and lactate; however, after combining the gastric lavage of bicarbonate with hyperbaric oxygenation, the catalase and citrate synthase activities increased and the lactate activity returned to normal levels. **Conclusion:** It is concluded that combining hyperbaric oxygenation with gastric lavage exerted a protective effect by reducing the cellular damage and normalizing the enzymatic activities of catalase and lactate.

Key words: Aluminum phosphide, phosphine, poisoning, olive oil, bicarbonate, hyperbaric oxygenation therapy

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Aluminum phosphide (AlP) and zinc phosphide (Zn_3P_2) are used as pesticides in several countries for storing grains as well as to prevent, destroy or control pest infestation[1-3].

Exposure to these substances may be intentional or accidental. These pesticides are the most common method of pest control used in developing countries due to their extremely low price and minimal regulation of their purchase and use. Recent statistics have indicated that teenagers, young adults and the elderly population (≥70 years old) who exhibit symptoms of depression are at higher risk of attempting suicide[3-6].

Pesticides are chemical agents commonly used in suicides. One major difference from organophosphate pesticides is that there is no specific antidote for phosphide poisoning; thus, the mortality rate is high in Mexico and throughout the world, especially in the use of aluminum phosphide[4-6].

The concentration of phosphides in commercial products for fumigation is variable (i.e., between 40 and 70%) depending on the formulation[7]. Once in contact with water, room moisture or a medium rich in hydrogen ions, phosphine gas is released, which is considered to be the primary poison source (Eq. 1). Pure phosphine gas is colorless and odorless, but impurities and stabilizers give it the characteristic odor of rotten fish or garlic[8-10]:

$$AlP+3H^{+}\rightarrow Al^{3+}+PH_{3(g)} \quad (1)$$

When ingested, AlP encounters the acidic gastric secretions in the stomach or moisture from digested food. This triggers the release of phosphine gas, which is absorbed in the system through the mucosa via passive diffusion. As previously described, when the metallic phosphide is hydrolyzed and absorbed as phosphine gas, the resulting chemical acts as a mitochondrial toxin that negatively affects the function of cytochrome c oxidase[11-13].

Anand *et al.*[12] observed that some antioxidant enzymes such as catalase had decreased activity in rats administered AlP. Therefore, when the activities of the respiratory chain and oxidative phosphorylation are blocked, part of the antioxidant system is inhibited. Furthermore, when the levels of antioxidant precursors are reduced, oxidative stress is induced, which increases the production and accumulation of free radicals and results in oxidative damage[2,12-16].

The reported histological changes due to exposure to phosphine gas are diverse the heart experiences vacuolation and cytolysis, at pulmonary level, there is congestion with multiple hemorrhages in a patch-like pattern; the liver presents microvacuolation, congestion and hydropic degeneration in the sinusoids, centrilobular hemorrhage and hepatic necrosis and the stomach exhibits congestion and distension. The most affected organelle is the mitochondrion, which undergoes interstitial edema and a loss in the structural organization as indicated by the lengthening of the mitochondrial crests[12,17].

Measurement of the enzyme citrate synthase is used as a quantitative marker for intact and functional mitochondria, which enables its use as an indicator for the function of mitochondrial protein complexes that participate in the respiratory chain[18,19].

Clinical management for phosphide poisoning is complicated because there is no specific antidote; thus, many diverse protocols focus on predominantly treating systems involved in vital functions; cardiovascular, hemodynamic, respiratory, metabolic, hydroelectrolytic and renal[1,20-23].

In countries with high incidences of AlP poisoning, these protocols focus on the use of immediate gastric lavage to prevent the release and absorption of the gas and implement diverse substances, including potassium permanganate, bicarbonate, activated charcoal and exogenous natural antioxidants such as N-acetylcysteine, vitamin C and melatonin[3,24-31]. Additionally, it has been reported that the use of hyperbaric oxygenation therapy improves survival in individuals with diseases that exert mitochondrial effects because they observed an increase in the biogenesis of these organelles[32]. Additionally, it has been proposed that oil-based substances as coconut oil may reduce oxidative stress-induced cellular and mitochondrial effects and damage. In this study, gastric lavage with olive oil (due to its antioxidant functions) or sodium bicarbonate were used ($NaHCO_3$, due to its antacid effect in the stomach) as buffer to treat plasmatic acidosis. In previous studies the effect of hyperbaric oxygenation therapy with or without gastric lavage of both treatments were compared.

To date, there is no standard treatment for aluminum phosphide poisoning and the treatments currently used have been applied empirically; therefore, the patient's manifestation of symptoms is often insidious and on some occasions, complications at the cardiovascular, respiratory and metabolic level can cause death[3,24,31]. Because of these negative outcomes, the beneficial effects of oily substances, lavage with sodium bicarbonate and hyperbaric oxygenation therapy were compared. These treatments focus on regulating the oxidant/antioxidant state and the reduction of the cellular and mitochondrial damage due to oxidative stress originated by the toxic agent.

It has been previously described that gastric lavage with a saline solution is harmful because the phosphine reacts with the solution resulting in accelerated phosphine gas production and consequent poisoning[32]. For this reason, the use of gastric lavage with bicarbonate is thought to neutralize the effect of this gas. The objective of study was when gastric lavage used in combination with hyperbaric oxygen (which modifies the metabolism and oxidative stress in cells), this regimen could be an excellent treatment for phosphide poisoning experiencing by humans.

MATERIALS AND METHODS

A total of 45 female Wistar rats weighting 300±30 g were distributed into 9 groups of 5 rats per group.

The rats were obtained from the vivarium at the Superior School of Medicine and maintained at room temperature under a normal sleep-wakefulness cycle with food provided *ad libitum*. All the animals were treated in accordance with the Official Mexican Norm 062-ZOO-1999, pertaining to the technical specifications for the breeding, care and use of laboratory animals and the declaration of the World Medical Association on the use of animals for biomedical research.

The lavage, phosphide administration and all related procedures were performed in an extraction hood (laminar flow extraction hood-NOVATECH CE 180 9) by individuals wearing appropriate personal protection.

The DL_{50} for aluminum phosphide was used, which was calculated as 27 mg kg^{-1} and the compound was mixed with 1 cc of double distilled water and administered to the rats via an orogastric tube. The administration of this mixture was completed in less than 10 sec. The gastric lavage was performed with a flexible plastic tube (Tygon®) with a diameter of 1 mm.

Description of the study: There were 9 experimental groups consisting of 5 rats per group.

Group 0: Control rats-no procedure was performed. Samples were collected to obtain the baseline levels for the catalase, citrate synthase and lactate activities

Group 1: Rats were anesthetized with sodium pentobarbital (50 mg kg^{-1}, IP) and then intubated to protect their airway. Gastric lavage was performed with a double distilled water; upon completion of administration, the orogastric tube was removed and the rats were kept under surveillance until the anesthetic effect wore off. Aluminum phosphide was not administered

Group 2: An aluminum phosphide (27 mg kg^{-1}) solution in double distilled water (1 mL) was orally administered through the orogastric tube and then the rats were sedated with pentobarbital sodium (35-45 mg kg^{-1}, IP). The airway was protected with endotracheal intubation and gastric lavage with the saline solution was performed 1 h after administration of AlP

Group 3: The aluminum phosphide (27 mg kg^{-1}) solution in double distilled water was administered via orogastric tube and the rats were then anesthetized and intubated. Gastric lavage was performed with olive oil (10 mL kg^{-1}) through a flexible plastic tube 1 h after administration of AlP

Group 4: The aluminum phosphide (27 mg kg^{-1}) solution in double distilled water was administered via orogastric tube and the rats were then anesthetized and intubated. One hour after AlP administration, gastric lavage was performed with bicarbonate (1 mEq kg^{-1}) through a flexible plastic tube (1 mm diameter)

Group 5: Rats in this group were subjected to a session in a hyperbaric chamber at 2 ATA with no other procedures

Group 6: Aluminum phosphide was administered via orogastric tube at the DL_{50} concentration based on the rats' weight after they were subjected to a session in the hyperbaric chamber at 2 ATA

Group 7: The aluminum phosphide (27 mg kg^{-1}) solution in double distilled water was administered via orogastric tube and the rats were then anesthetized and intubated. Gastric lavage was performed with olive oil (10 mL kg^{-1}) through a flexible plastic tube 1 h after administration of AlP. Immediately after olive oil administration, the rats were subjected to a session in the hyperbaric chamber at 2 ATA

Group 8: The aluminum phosphide (27 mg kg^{-1}) solution in double distilled water was administered via orogastric tube and the rats were then anesthetized and intubated. One hour after AlP administration, gastric lavage was performed with bicarbonate (1 mEq kg^{-1}) through a flexible plastic tube (1 mm diameter) and then the rats were immediately subjected to a session in the hyperbaric chamber at 2 ATA

Sample collection: The rats were observed for 24 h and then they were anesthetized prior to euthanization via decapitation. If the rats died within 24 h, tissue and serum samples were collected at the time of death.

Samples of heart, liver and lung tissue were collected via abdominal longitudinal dissection, the skin and underlying layers were separated until the abdominal tissues were exposed. Once the tissue samples were obtained, they were stored in two Eppendorf tubes at -70°C until further processing to measure catalase and citrate synthase activities. All the samples were homogenized in cold lysis buffer and the mixtures were subjected to sonication in the cold for 15 min followed by centrifugation in the cold at 13,000 rpm. The resulting supernatant was added into a clean Eppendorf tube and was processed to measure the levels of citrate synthase and catalase using Western blotting.

Blood samples were collected to measure serum lactate via exsanguination in rats that were euthanized at 24 h and in rats that died prior to this time point, blood was collected by lancing either the heart or large vessels after abdominal and thoracic dissection. In all the procedures, blood was collected into heparinized syringes to prevent clotting, transferred into Eppendorf tubes and safely incubated for 20 min between 4 and 8°C. Afterwards, the samples were centrifuged to separate the cells and serum, the latter of which was stored in Eppendorf tubes at -20°C until further processing to measure the lactate concentration. For this assay, cold plates were used and 20 µL of thawed serum was mixed with a specific reagent for lactate measurement, after which the samples were added onto ELISA plates and incubated for 5 min at room temperature.

Citrate synthase activity: As an indicator of mitochondrial function, Citrate Synthase (CS) activity was evaluated in adipose tissue samples. Tissue samples (25 mg) were homogenized with a polytron in 250 µL of cold extraction buffer (20 mM Tris-HCl, 140 mM NaCl, 2 mM EDTA and 0.1% sodium dodecyl sulfate) containing protease inhibitors (P2714, Sigma-Aldrich), 5 mM Na_3VO_4 and 3 mM NaF. Homogenates were centrifuged at 10,000Xg for 15 min at 4°C. The supernatants were recovered and used to measure CS activity as the rate of mercaptide ion production based on the conversion of acetyl-CoA and oxaloacetate into CoA-SH. The CoA-SH in the presence of 5,5-dithiobis-2-nitrobenzoic acid (DTNB) produces mercaptide ions. Samples were analyzed in a Beckman DU 730 spectrophotometer (Beckman, Fullerton, CA, USA) at 412 nm. All the samples were tested in duplicate and measured at room temperature.

Catalase activity: Catalase activity was measured using a protein catalase assay kit (Cayman chemicals). Briefly, the tissue was rinsed with a Phosphate-Buffered Saline (PBS) solution (pH 7.4) to remove any red blood cells and clots and then homogenized on ice in 1 mL of cold buffer (50 mM potassium phosphate, pH 7.0, 1 mM EDTA) per gram of tissue. After the lysates were centrifuged at 10,000Xg for 15 min at 4°C, the supernatant was collected for the catalase assay according to the manufacturer's instructions.

Statistical analysis: All values obtained represent the average ±SEM. In all the experiments, n equals the number of rats from which aortic segments and hearts were obtained. The statistical comparisons were made by Two-way ANOVA and a Tukey post hoc test. In all cases, a $p<0.05$ was considered statistically significant.

RESULTS

Upon analysis of developing oxidative stress by catalase activity, which is the most affected enzyme in patients experiencing this type of poisoning (Fig. 1a-c), rats subjected to poisoning showed lower catalase activity in the different tissues compared to the control group. It was interesting to observe that when sodium bicarbonate was administered, the catalase activity was significantly increased in the liver (133 nmol min^{-1} mg^{-1} prot) and pulmonary tissue (221 nmol min^{-1} mg^{-1} prot) compared to he control group (Liver: 300 and lung: 360 nmol min^{-1} mg^{-1} prot). Interestingly, the catalase activity was further increased when the sodium bicarbonate lavage was performed in combination with HPO (heart: 174, liver: 175 and lung 315 nmol min^{-1} mg^{-1} prot) (Fig. 1a-c).

Regarding the measurement of citrate synthase activity, which is used to evaluate the presence of intact and functional mitochondria. Figure 2a (heart: 2.3 nmol min^{-1} mg^{-1} prot control), 2b (liver: 1.6 nmol min^{-1} mg^{-1} prot control) and 2c (lung: 1.2 nmol min^{-1} mg^{-1} prot control) show decreased activity in the groups subjected to aluminum phosphide poisoning (heart: 0.9; liver: 0.6 and lung: 0.36 nmol min^{-1} mg^{-1} prot). Additionally, it can be seen that upon concomitant administration of the sodium bicarbonate gastric lavage and HBO, the citrate synthase activity was normalized in the three tissues (heart: 2.1, liver: 1.1 and lung: 0.9 nmol min^{-1} mg^{-1} prot).

The results for concentration of serum lactate, which indirectly reflect changes in the anaerobic metabolism, showed that there was a significant increase in the serum lactate concentration in the poisoned group (7.5 nmol L^{-1});

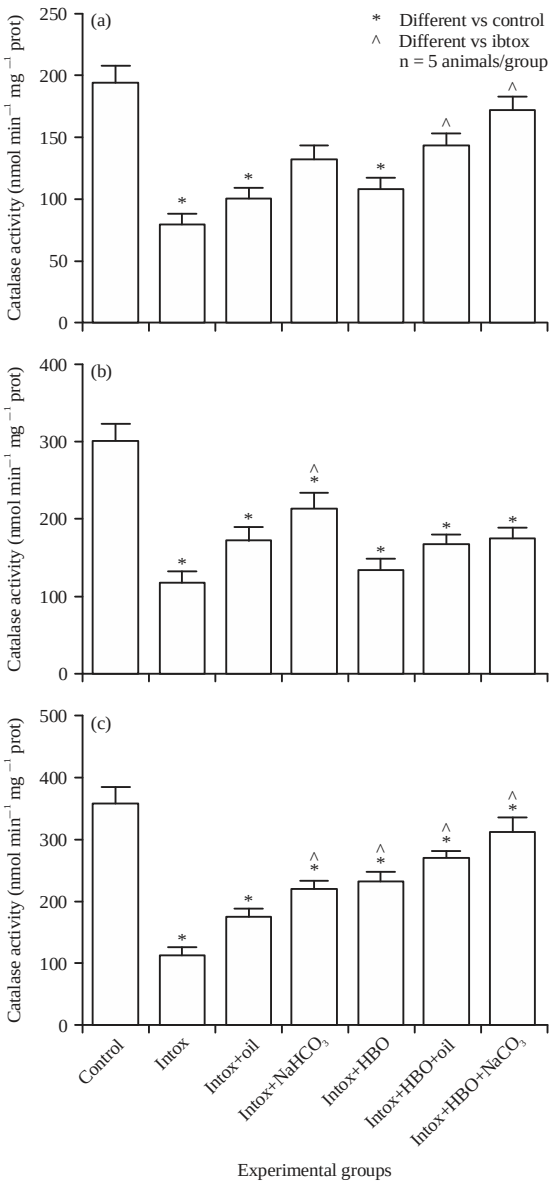

Fig. 1(a-c): Levels of catalase activity in the (a) Heart, (b) Liver and (c) Lung of each experimental group
Each bar represents the Mean±SEM, n = 5, *p≤0.05

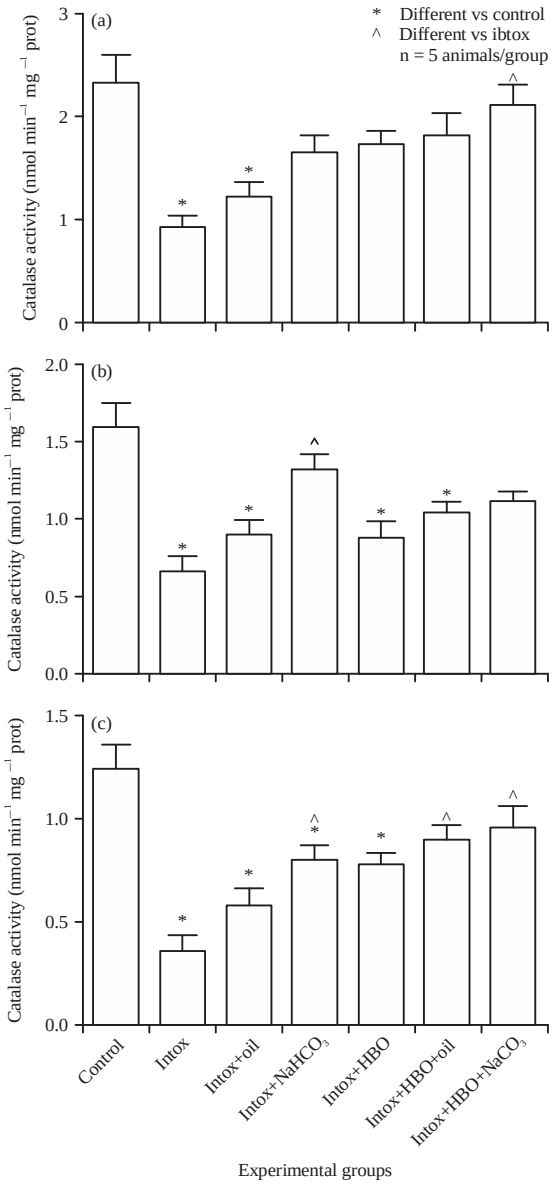

Fig. 2(a-c): Citrate synthase activity in the (a) Heart, (b) Liver and (c) Lung of each experimental group
Each bar represents the Mean±SEM, n = 5, *p≤0.05

however, the group that received sodium bicarbonate gastric lavage and HBO showed a significant reduction of lactate production (4 nmol L^{-1}) (Fig. 3).

DISCUSSION

The results for oxidative stress parameters were 210 nmol min^{-1} mg^{-1} prot in heart, 320 nmol min^{-1} mg^{-1} prot in liver and 400 nmol min^{-1} mg^{-1} in lung, reducing to 77, 120 and 110 nmol min^{-1} mg^{-1} prot, respectively after intoxication. Citrate synthase activity were before intoxication: 2.7 (heart), 1.75 (liver) and 1.4 (lung) nmol min^{-1} mg^{-1} prot and after intoxication was 1 (heart), 0.75 (liver) and 0.5 (lung) nmol min^{-1} mg^{-1} prot. Groups after treatment with hyperbaric oxygenation and gastric lavage showed a normalization of its values.

The results for concentration of serum lactate, showed that there was a significant increase in the serum lactate concentration in the poisoned group (7.5 nmol L^{-1}), however, the group that received sodium bicarbonate gastric lavage and HBO showed a significant reduction of lactate production (4 nmol L^{-1}).

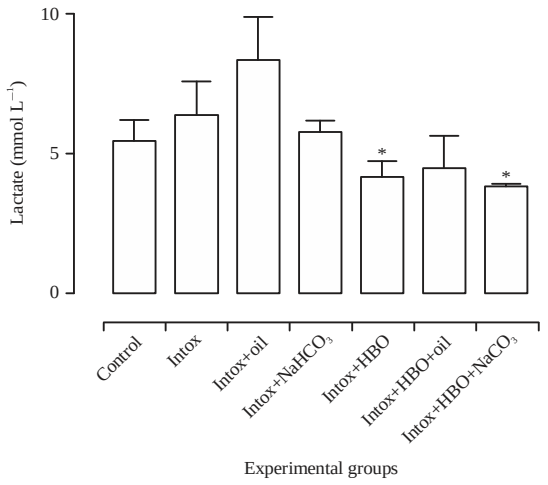

Fig. 3: Lactate activity in serum obtained from each experimental group
Each bar represents the Mean±SEM, n = 5, *p≤0.05

In this study, the results showed that AlP poisoning leads to critical damage due to oxidative stress and mitochondrial lesions and subsequent damage due to hypoperfusion via an anaerobic metabolism. It was observed that the treatments increased the catalase activity, with the pulmonary level exhibiting the most beneficial effect. The site of first contact is the stomach and the gastro-intestinal tract, but the substance is a gas and mainly causes damage at the pulmonary level.

The results showed that the most effective treatments are with $NaHCO_3$ and HBO, which help to reduce the formation of PH_3 gas, prevent its absorption and consequently mitigate cellular damage.

Gastric lavage, which is usually applied in these types of poisonings, in combination with hyperbaric oxygenation therapy was compared in this study. Bicarbonate works by preventing the oxidation of the phosphide to phosphine[21,33,35]. On the other hand, the previous studies observed that 80% of patients treated with $NaHCO_3$ survived AlP poisoning. Oily substances are thought to encapsulate the compounds to prevent contact of the phosphide with the acidic environment and avoid the release of phosphine gas; additionally, the well known antioxidant properties from olive oil is another added benefit that prevents damage from this type of poisoning[27-29,36, 37].

The treatments proposed reduced the lesions in all the tissues, especially in rats treated with bicarbonate and hyperbaric oxygenation therapy, where both therapies helped in regulating the oxidizing state and mitochondrial damage.

Olive oil has been proposed as a therapeutic option because of its chemical and antioxidant properties. In this study, it showed interesting results, although without differences between them, thus, its use may be modified, whether by increasing the dosage of application or increasing the number of treatments to obtain positive effects on the oxidoreduction systems.

Citrate synthase is a marker for mitochondrial content in tissues; low concentrations lead us to believe there is greater mitochondrial damage upon AlP poisoning with negative effects on energy production and all the molecules produced in the mitochondria[38]. The regulation of this enzyme and its genetic transcription is not immediate, but changes are observed 2-3 h after stimulation and may remain for approximately 24 h.

Diverse substances have been used to reduce the damage as well as morbidity and mortality due to exposure to phosphides, Shadnia *et al.*[23] administered oily substances (coconut oil) and bicarbonate (parenteral and nasogastric) to a patient with severe poisoning and observed with appropriate evolution and improvement, which was corroborated by periodical measurement of biochemical parameters. In this study, two treatments usually employed for these types of poisoning were compared but were individually administered in different groups to evaluate each of their functions and to determine which treatment is the most effective. Hyperbaric oxygenation therapy was also included as a treatment modality. It was observed that all 3 treatments reduced the concentration of lactate and normalized the activity of catalase; however, it was the combination of bicarbonate gastric lavage and hyperbaric oxygenation therapy that showed the greatest improvement while increasing the activity after HBO and protecting against cellular damage as evaluated by the levels of citrate synthase.

As described in previous study[39], bicarbonate contributes to maintaining homeostasis and is an element that functions as one of the main buffers for preventing acid base imbalances. It is naturally produced by the kidney. In instances where its function as buffer is affected, bicarbonate should be administered via IV to manage acidemia due to diverse origins, as it is well documented that correcting the cause of the altered metabolic state within the first 24 h is crucial for improvement the patient's condition[39]. Bicarbonate has been administered directly into the stomach via gastric lavage in pediatric patients suffering from iron poisoning, where reduced absorption was observed. In phosphide poisoning, bicarbonate prevents phosphide oxidation and thus the formation of phosphine[9,39-43].

Hyperbaric oxygenation therapy was used by Saidi *et al.*[34] and was shown at an experimental level to increase the lifespan of rats without an apparent mortality reduction.

Additionally, some studies showed increased activity for catalase and a reduction in reactive oxygen species, biomarkers for neurological lesions and lactate levels in patients preconditioned with hyperbaric oxygenation therapy prior to undergoing surgery due to a cardiovascular shunt[43,44]. Other experimental studies showed that the use of a hyperbaric chamber improves survival from diseases involving mitochondrial damage because it increases the biogenesis of these organelles via increasing the expression of regulatory factors in mitochondrial transcription (e.g., NRF1, NRF2, factor PCG-1)[45,46].

CONCLUSION

Gastric lavage with sodium bicarbonate with concomitant hyperbaric oxygenation therapy showed a protective effect in rats poisoned from aluminum phosphide because it normalized the activities of catalase and citrate synthase as well as the lactate levels in the heart, lung and liver.

SIGNIFICANCE STATEMENT

In this study the combination of hyperbaric oxygen therapy and gastric lavage with bicarbonate produced excellent results in protecting against mitochondrial damage and normalizing oxidative stress in rats subjected to aluminium phosphide poisoning.

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