Heliyon 9 (2023) e22165

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

The therapeutic effect of a novel parenteral formulation of dihydroxyacetone in aluminum phosphide-intoxicated patients

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ARTICLE INFO

Keywords:
Aluminum phosphide
Clinical toxicology
Pharmacotherapy
Phosphine
Suicide

ABSTRACT

Background and objectives: Aluminum phosphide (AlP), known as "rice tablet," is widely used as an effective pesticide. However, AlP poisoning is a common cause of mortality in many countries, such as Iran. Unfortunately, there is no specific antidote for AlP toxicity to date. AlP releases phosphine gas when it is exposed to moisture or acid. Phosphine is a potent mitochondrial toxin that could significantly inhibit cellular energy metabolism. AlP poisoning is an emergency condition that needs instant and effective intervention. Dihydroxyacetone (DHA) is a simple saccharide used for several pharmacological as well as cosmetic purposes. Previously, we found that DHA could significantly prevent mitochondrial impairment induced by toxic agents such as cyanide and phosphine in various *in vitro* and *in vivo* experimental models.

Methods: Hospitalized patients (n = 111) were evaluated for eligibility criteria. Among these patients, n = 35 cases were excluded due to incomplete data (n = 11) and suspicion of poisoning with poisons other than AlP (n = 24). Meanwhile, n = 76 cases with confirmed AlP poisoning were included in the study. AlP-poisoned patients who did not receive DHA (n = 18) were used as the control group.

Patients (n = 58) received at least one dose of DHA (500 ml of 5 % DHA solution w/v, i.v.) as an adjuvant therapy in addition to the routine treatment of AlP poisoning. Arterial blood gas (ABG), blood pH, bicarbonate levels, and other vital signs and biochemical measurements were monitored. Moreover, the mortality rate and hospitalization time were evaluated in DHA-treated and AlP-poisoned patients without DHA administration. Several biomarkers were assessed before (upon hospitalization) and after DHA treatment. The routine tests for AlP-poisoned patients in this study were the measurement of electrolytes (K^+ and Na^+), WBC, RBC, hemoglobin, INR, carbonate (HCO_3), blood pH, $PaCO_2$, and PaO_2 and SGPT, SGOT, BUN, Cr.

Results: Upon patients' admission, significant decreases in blood pH (acidosis), blood PaO_2, and HCO_3 levels were the hallmarks of AlP poisoning. It was found that DHA significantly alleviated

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https://doi.org/10.1016/j.heliyon.2023.e22165
Received 26 July 2023; Received in revised form 17 October 2023; Accepted 6 November 2023
Available online 10 November 2023

biomarkers of AlP poisoning and tremendously enhanced patients' survival rate (65.52 % in DHA-treated *vs* 33.34 % in the control group) compared to patients treated based on hospital routine AlP poisoning protocols (no DHA). No significant adverse effects were evident in DHA-treated patients in the current study.

Interpretation and conclusions: These data suggest that parenteral DHA is a novel and effective antidote against AlP poisoning to be used as an adjuvant in addition to routine supportive treatment.

Trial registration: IR.SUMS.REC.1394.102.

1. Introduction

Aluminum phosphide (AlP) is an effective pesticide for preserving stored grain, especially rice, from weevil damage [1]. AlP is known as the "rice tablet" in Iran and is widely used in Iran and some other countries, such as India, Thailand, Pakistan, *etc*., to protect stored grains. However, acute and lethal toxicity is a common complication associated with AlP [1,2]. There is a concerning record of suicidal attempts using AlP in Iran [1,3–7]. Unfortunately, there is no efficient therapeutic intervention against AlP poisoning so far, and the mortality rate of this compound is very high (up to 80 %) [8,9]. The current treatment for AlP poisoning includes just supportive treatments, including I.V. administration of sodium bicarbonate, magnesium sulfate, some antioxidants, oral administration of different oils or paraffin, and decontamination with activated charcoal [10,11].

AlP releases a significant amount of phosphine gas (PH_3) upon interacting with moisture or acids (*e.g.*, gastric HCl) [12]. Mechanistically, phosphine robustly impairs cellular energy metabolism. PH_3 inhibits the cytochrome *c* oxidase complex and impairs mitochondrial ATP production after entering the cell and mitochondria [12,13]. PH_3 also affects many other mitochondrial indices, leading to energy crises in different tissues [14]. The PH_3-induced energy crisis is perilous for high energy-demanding organs such as the heart and brain [9,15,16]. However, many other complications and multi-organ failure could also occur in AlP toxicity, resulting in patient death [9,11,17].

AlP poisoning is an emergency state that requires immediate and rigorous therapeutic intervention. Death usually occurs between 2 and 24 h post-ingestion of AlP or zinc phosphide [18,19]. In addition to supportive care, previous studies suggested that the administration of olive/castor/coconut oils and antioxidant molecules such as N-acetyl cysteine, melatonin, vitamin C, and vitamin E are effective in the treatment of phosphine poisoning and significantly decreased AlP toxicity-associated complications [20–27]. These interventions should be considered along with rigorous monitoring of vital signs, blood biochemistry, and brain/heart function. However, there is still a high mortality rate despite the treatment of AlP poisoning based on the mentioned routine protocols. The mortality rate of patients largely depends on many factors, including the amount of AlP ingested, time of admission to the hospital, concurrent poisoning with other agents, and the quality of therapeutic strategies and hospital care. As PH_3 inhibits mitochondrial ATP production, the mitochondria-related cell functions could rapidly deteriorate, and the function of high energy-demand organs such as the heart and brain are damaged. Therefore, a rapid restoration of mitochondrial function and energy metabolism in these organs is necessary. The current protocols for treating AlP poisoning, which are primarily supportive care and administration of some antioxidants, lack such an effect on mitochondria. Therefore, a safe molecule that can rapidly bind PH_3, although reversibly, in the blood and the cell could decrease the entry of PH_3 into the cell and mitochondria and greatly decrease toxic and fatal effects of AlP poisoning.

Dihydroxyacetone (1, 3-dihydroxypropanone; DHA) is a simple saccharide freely soluble in water. DHA has been previously investigated for its pharmacological and cosmetic effects. It is used for skin tanning, increasing exercise capacity in athletes and the elderly, reducing weight, and mitigating the complications of fatty liver disease [28–33]. It was also recommended for the treatment of hemorrhagic shock as an injectable form [34]. Previously, we found that DHA is an effective antidote against the toxicity induced by lethal mitochondrial toxin cyanide in both *in vitro* and *in vivo* experiments [35–37]. It was found that DHA significantly improved mitochondrial function and prevented cellular ATP depletion during cyanide exposure by reversibly binding to CN^- [35–37]. Later, in other *in vitro* and *in vivo* studies, we also found that DHA significantly prevented the toxicity induced by phosphine [38–40]. It was found that DHA significantly prevented PH_3 cytotoxicity in cultured HePG2 cells and significantly decreased the mortality of phosphine-poisoned mice by binding to PH_3 [38–40]. Since DHA is produced in the body in the glycolysis pathway and is a very safe compound with an LD_{50} of more than 8 g/kg in mice [34], the current study was designed to evaluate the effect of DHA in AlP-poisoned human cases.

In a recent animal study, it has been reported that oral DHA administration significantly decreased cardiovascular complications of AlP toxicity in rats [41]. However, as AlP poisoning is an emergency state that rapidly deteriorates vital signs, a big challenge in managing AlP toxicity is the speed of delivering the protective agents to the body. Therefore, it is preferred not to administer these agents orally in AlP poisoning because it may cause more complications. In cases of AlP poisoning, the administration of water, or even lavage, is not recommended because the contact of AlP with water results in more release of PH_3, the ultimate toxin, in the GI tract, which can worsen the patient's condition. Therefore, oils such as coconut oil are recommended to prevent the contact of the solid AlP residues with water and acid [11,26]. Hence, the parenteral delivery of protective agents is ideal. The current formulation of I.V. DHA is the first kind in this field, which could rapidly reverse the adverse effects of PH_3 on organelles such as mitochondria. As this formulation is not administered by the oral route, there is no risk of enhancing AlP poisoning.

In the current study, patients with confirmed AlP poisoning received I.V. DHA (at least one dose of 500 ml of 5 % w: v of DHA solution) in addition to systematic AlP poisoning treatment protocols. Several biomarkers and patients' survival were evaluated and

compared with AlP-poisoned patients without DHA therapy. This data could pave the way to effectively treating AlP poisoning and decreasing the high mortality rate of this lethal toxin by administering the rapid-acting parenteral formulation of DHA, which is associated with minimum adverse effects.

2. Materials and methods

2.1. Dihydroxyacetone intravenous formulation

Dihydroxyacetone pharmaceutical-grade powder was purchased from Merck, Germany. It was formulated and prepared under sterile conditions as a 5 % solution in 500 ml bottles by Shiraz Serum Pharmaceutical Company, Shiraz, Iran (https://www.shirazserum.com). The prepared DHA solution had all the necessities of an intravenous formulation. Our laboratory studies showed that 2.6 % solution of DHA is isotonic to the blood. The administration of 5 % solution had no significant adverse effects in the current study as precisely monitored by physicians/clinical toxicologists involved in this project by continuously monitoring patients' vital signs. The expiration date of the solution at room temperature (protected from light) was more than three years.

2.2. Study design and patients

This study enrolled patients aged 17–60 (male and female) diagnosed with confirmed AlP poisoning with significant blood acidosis, decreased PaO_2, and increased $PaCO_2$ in arterial blood gas analysis from October 2016 to December 2021. The study was conducted on patients referred to the Emergency wards of Shahid Faghihi, Aliasghar, and Namazi Hospitals, Shiraz University of Medical Sciences, Shiraz, Iran, and Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Patients were excluded if there was an incomplete follow-up during hospitalization or suspicious poisoning with other agents rather than AlP. The flow chart for selecting patients for receiving DHA and standard routine treatments for AlP-poisoned patients is shown in Fig. 1. In the primary assessment, n = 111 patients were evaluated for eligibility criteria. Among these patients, n = 35 cases were excluded due to incomplete data (n = 11) and suspicion of poisoning with compounds other than AlP (n = 24). Meanwhile, n = 76 cases with confirmed AlP poisoning were included in the study. AlP-poisoned patients who did not receive DHA (n = 18) were used as the control group. Other patients (n = 58) received at least one dose of DHA (500 ml of 5 % DHA solution w/v, i.v.) in addition to the routine treatments (Fig. 1). Arterial blood gas (ABG), blood pH, bicarbonate levels, and other vital signs and biochemical measurements were monitored. Moreover, the mortality rate and time of hospitalization were evaluated in both DHA-treated (n = 58) and AlP-poisoned patients without DHA administration (n = 18) (Fig. 1). Several biomarkers were assessed before (upon hospitalization) and after DHA treatment. The routine tests for AlP-poisoned patients in this study were the measurement of electrolytes (K^+ and Na^+), WBC, RBC, hemoglobin, INR, carbonate (HCO_3), blood pH, $PaCO_2$, and PaO_2 and SGPT, SGOT, BUN, Cr. As AlP poisoning is an emergency medical condition, a pre-randomization (that is, assigning the therapy to be used before the toxic events occur) of AlP-poisoned patients was

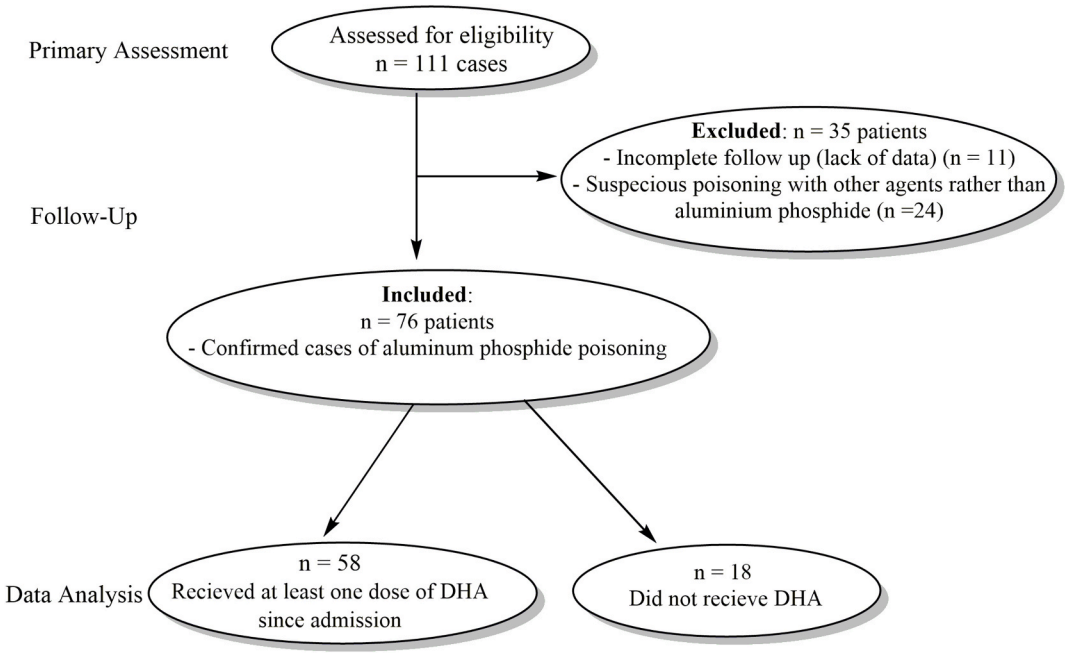

Fig. 1. A flowchart of patient selection for evaluating the antidotal role of an intravenous formulation of dihydroxyacetone (DHA) in aluminum phosphide poisoned cases.

used in this study [42,43]. Hence, DHA was administered to confirmed AlP-poisoned cases, which signed an informed consent form (n = 58). It also should be noted that because AlP is a fatal severe poison, and because DHA administration showed very positive and life-saving effects in the first several patients, the physicians at the poison treatment centers decided that most of the admitted patients receive DHA. Hence, the sample size of the control (DHA-untreated) group was smaller than the DHA-receiving patients. Moreover, we studied four large poison control centers in Iran with the highest cases of AlP poisoning for five years (from October 2016 to December 2021) to collect the highest possible data.

2.3. Dihydroxyacetone treatment protocol

In addition to routine treatments for AlP poisoning (Fig. 2), the first 500 ml of 5 % DHA was infused over 1 h. Afterward, each 500 ml bottle was infused over 3–4 h, if needed, till the patients' condition became normal. Usually, 2000–2500 ml of 5 % DHA was required for each patient.

2.4. Statistical analysis

Data are represented as mean ± SD. The data comparison for biomarkers assessed before and after DHA administration was done using a paired T-test. The data distribution for hospitalization time was not parametric, and the Wilcoxon test was used for data comparison. The chi-square test was used to compare the differences in basic characteristics among the intervention and control groups. Data comparison for Fig. 4 was carried out by a One-Way-ANOVA with a Tukey *post hoc*.

3. Results

Based on the comparison of the characteristics of patients involved in the current study, it was found that most of the cases of phosphine poisoning were occurred between the ages of 17–27 years (Table 1). No significant changes between the gender of phosphine-poisoned patients were detected in the current study (Table 1).

Several parameters, including biomarkers of organ injury (SGPT, SGOT, BUN, Cr), electrolytes (K^+ and Na^+), WBC, RBC, hemoglobin, INR, carbonate (HCO_3), blood pH, $PaCO_2$, and PaO_2 were assessed in confirmed cases of AlP-poisoned patients (n = 58) (Fig. 2). No significant changes in biomarkers such as organ injury markers (SGPT, SGOT, BUN, Cr), CBC, hemoglobin, hematocrit, blood

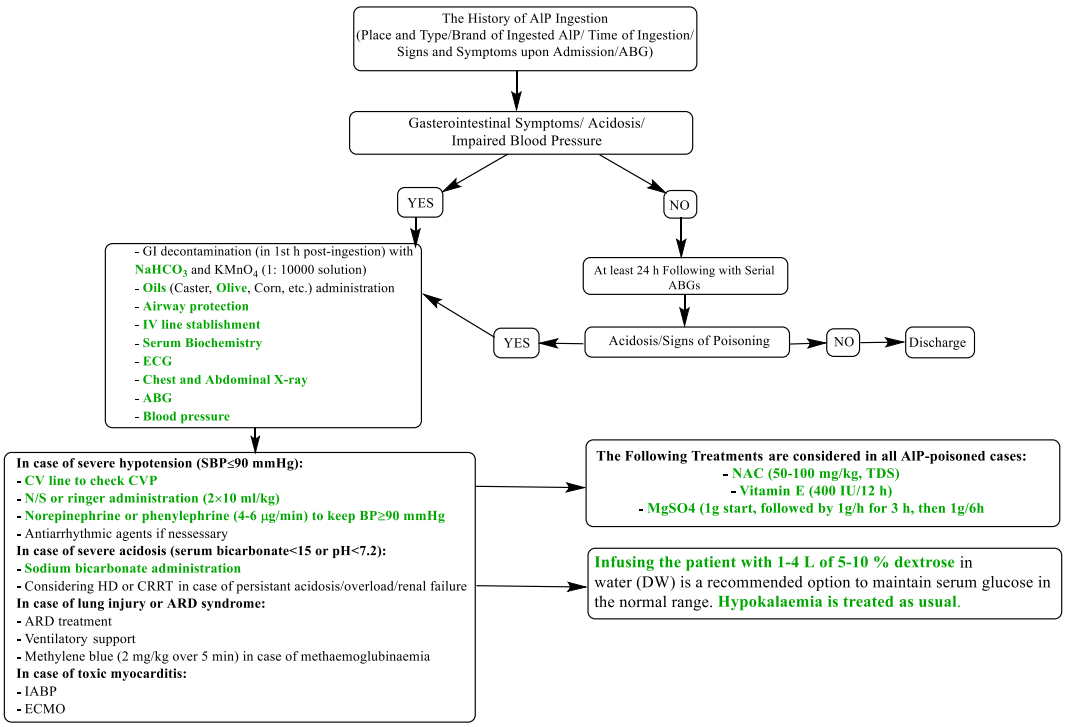

Fig. 2. The flowchart of a standard aluminum phosphide (AlP) poisoning treatment procedure in hospitals included in the current investigation. The standard treatments used for AlP poisoning in centers investigated in the present study are marked with green color. Intravenous dihydroxyacetone (DHA) was administered in addition to routine treatments in AlP-poisoned cases. SBP: Systolic blood pressure; N/S: Normal saline; CVP: Central venous pressure; ABG: Arterial blood gas; ECG: Electrocardiogram; CV: Central Vein; HD: hemodialysis; CRRT: Continuous renal replacement therapy; ARD: Acute respiratory distress; IABP: intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation; DW: Dextrose water.

Table 1
Comparison of some basic characteristics of the intervention and control groups.

Characteristics	Category	DHA-Untreated	DHA-Treated	χ^2	*P*-Value
		n Proportion (%)	n Proportion (%)		
Gender	Male	12 66.67	35 60.34	2	0.1573
	Female	6 33.33	23 39.66		
Age	17–27	29 50.00	13 72.22	25.11	0.0001
	28–38	16 27.59	5 27.78		
	39–49	9 15.52	0 0		
	50–60	4 6.897	0 0		

coagulation, and electrolytes were detected in AlP-intoxicated cases included in the current study (Fig. 3). On the other hand, it was found that blood pH, PaO_2, and HCO_3 were significantly decreased, whereas $PaCO_2$ was increased in AlP-poisoned patients (Fig. 3). Therefore, these markers (pH, PaO_2, $PaCO_2$, and HCO_3) were selected as hallmarks of AlP poisoning and monitored in patients treated with DHA (Fig. 4).

The effects of DHA on these parameters before and after treatment with DHA are shown in Fig. 4. It was found that acidosis was blunted, PaO_2 was increased, HCO_3 was normalized, and $PaCO_2$ was significantly decreased in AlP-poisoned patients treated with DHA (Fig. 4).

A critical finding of the current study was associated with factors related to poor prognosis in AlP-intoxicated patients (Fig. 5). It was found that patients with blood pH $\leq$ 7.2 and/or $PaO_2 \leq$ 40 mmHg died despite receiving DHA (Fig. 5), however, some times patients with blood pH as low as 7.0 survived by infusion of DHA. DHA infusion usually increases blood pH (Fig. 4), and stopping the infusion would decrease the blood pH again.

The mortality rate was another critical factor evaluated in DHA-treated patients and patients with routine AlP treatment protocols (Fig. 6). It was found that DHA administration significantly decreased the mortality rate (about 67 % in non-treated vs. about 35 % in DHA-treated cases) (Fig. 6). Although it was not statistically significant, the hospitalization time also tended to decrease in DHA-treated patients (Fig. 6).

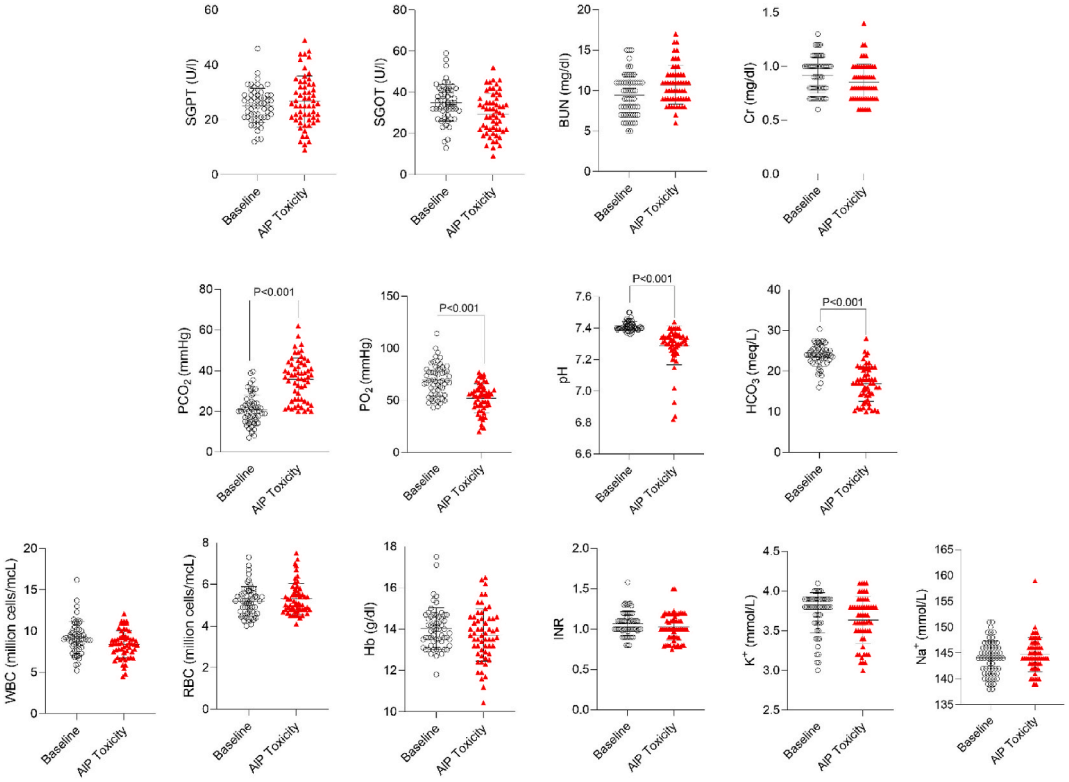

Fig. 3. Analysis of blood parameters (arterial blood gas; ABG) of patients in aluminum phosphide (AlP)-intoxicated cases. Significant elevation in blood $PaCO_2$ and decreased PaO_2 and acidosis (low blood pH) were hallmarks of AlP poisoning. Baselines belong to the control (Non-poisoned/not DHA-treated patients).
Data are represented as mean ± SD.

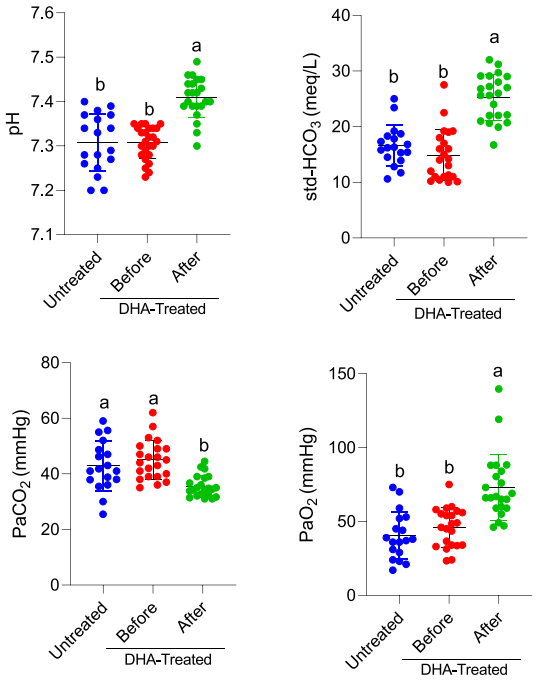

Fig. 4. Arterial blood gases (ABG), bicarbonate (std-HCO_3), and blood pH as hallmarks of aluminum phosphide poisoning in patients before (upon admission) and after dihydroxyacetone (DHA) therapy and routine therapeutic protocols for AlP poisoning. Untreated: includes patients receiving standard AlP poisoning treatments without DHA. The data is represented as mean ± SD. Data sets with different alphabetical superscripts are significantly different ($P < 0.05$).

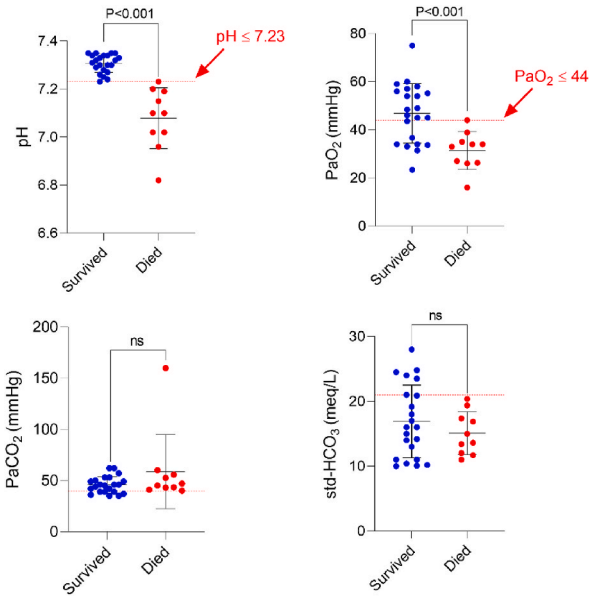

Fig. 5. Factors related to poor prognosis in patients intoxicated with aluminum phosphide. Based on the data obtained in the current study, $PaO_2 \leq 44$ and $pH \leq 7.23$ could be considered risk factors for patient mortality. Patients with the mentioned criteria died despite dihydroxyacetone (DHA) administration and following other routine therapeutic protocols.

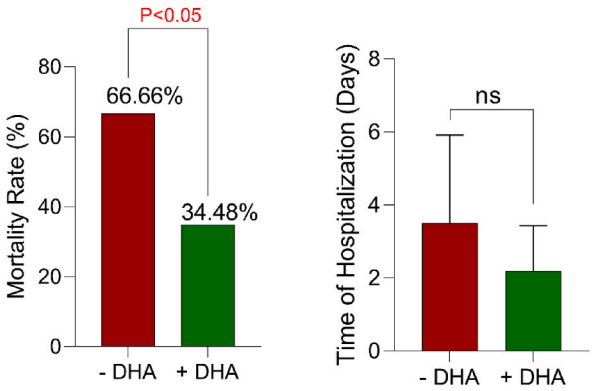

Fig. 6. Mortality rate and time of hospitalization of dihydroxyacetone (DHA)-treated patients (+DHA; n = 58) in comparison to aluminum phosphide-poisoned patients that did not receive DHA (-DHA; n = 18) and were treated based on the routine hospital protocols.

4. Discussion

AlP is widely used in Iran and several other countries as a pesticide for preserving stored grain, especially rice, from weevil damage [1]. A significant number of accidental or intentional (suicidal attempts) cases of AlP poisoning are recorded annually, and its toxicity is associated with a high mortality rate [7,44,45]. Unfortunately, no specific therapeutic intervention for AlP poisoning exists, and treatments are primarily supportive care. In the current study, we assessed the antidotal effect of a novel formulation of DHA for intravenous administration in AlP-intoxicated patients. The results indicate prominent antidotal effects of DHA against AlP poisoning as it decreased the mortality rate and normalized biochemical alterations in AlP-poisoned patients.

We have previously shown that DHA could antagonize the toxicity of phosphine in cell culture [40] and *in vivo* in mice [38,39], probably by reversible binding to PH_3. Our earlier studies also revealed that DHA could effectively prevent toxicity induced by lethal doses of the prompt-acting mitochondrial toxin cyanide *in vitro* in rat hepatocytes and *in vivo* in mice and rabbits, primarily by reversibly binding to CN^- ion [35–37].

DHA is produced in the form of dihydroxyacetone phosphate in the glycolysis pathway in the cell and plays an essential role in the synthesis of ATP. Since the primary mechanism of PH_3 toxicity is mediated through the inhibition of ATP production in the cell, entering DHA into the glycolysis pathway can also prevent the energy (ATP) crisis in cells and inhibit cell death. This is critical for avoiding PH_3-induced organ damage, especially in high energy-demanding organs such as the heart and brain. In a recent preclinical animal study, we found that DHA could significantly decrease the mortality rate in PH_3-treated mice [39]. It also considerably restored the cytochrome *c* oxidase enzyme activity as the primary target for PH_3 toxicity in various tissues of PH_3-exposed animals [39], possibly by reversibly binding to PH_3 and partially restoring cytochrome *c* oxidase activity [39]. Therefore, the direct effect of DHA on mitochondrial function and energy metabolism plays a central role in its protective properties against AlP toxicity. DHA could also ease ATP production through the glycolysis process in a mitochondria-independent manner [36], which may help reduce cell ATP depletion. This unique characteristic of DHA could save the functionality of vital organs such as the brain and heart until appropriate ATP production is restored upon increased cytochrome *c* oxidase activity.

An interesting finding in the current study was related to some biomarkers, such as acidosis and PaO_2 in AlP-poisoned cases (Figs. 4 and 5). Our data indicated that significant acidosis and decreased PaO_2 are severe clinical manifestations of AlP toxicity associated with a poor prognosis (Figs. 4 and 5). We found that most of the poisoned patients who died had a pH $\leq$ 7.2 and a $PaO_2 \leq 40$ (Fig. 5); however, sometimes, patients with a blood pH of about 7.0 survived by infusion of DHA. DHA infusion usually increases blood pH (Fig. 4), and stopping the infusion would decrease the blood pH again. This further confirms that DHA binds to PH_3 and is rapidly metabolized. Based on this data, starting DHA therapy as soon as possible would be better before pH or PaO_2 levels fall below the above-mentioned values. This simple point might significantly increase the survival rate of AlP-intoxicated patients.

On the other hand, it was found that DHA significantly improved severe acidosis and PaO_2 in AlP-poisoned patients (Fig. 4). Based on these data, the effects of DHA on these critical factors could play a vital role in its antidotal mechanisms in AlP toxicity. Although the routine treatment protocols, including gastric decontamination (*e.g.*, caster oil), correcting blood acidosis by bicarbonate, administration of drugs for the management of patient agitation, and antihypertensive drugs are carefully followed (Fig. 2), still the mortality rate of AlP is very high (up to 80 %), depending on factors such as the quality of supportive care, the dose of ingested AlP, and the time of hospitalization [46,47]. Therefore, there is a need for an effective and rapidly acting agent. Fortunately, in addition to its significant antidotal effect, this novel I.V. DHA formulation has a rapid action time, which is its great strength. However, DHA must be administered in a continuous infusion manner to be effective, probably because most DHA molecules are rapidly converted to dihydroxyacetone-phosphate, which cannot bind PH_3 in the cell [36,39]. This can cause depletion of DHA free molecules, and continuous administration is necessary to maintain a stable concentration of DHA molecules in the blood and tissues.

The oral administration of oils, charcoal, and other current treatments in the cases of AlP poisoning can only partially inhibit the absorption of PH_3 created in the GI tract upon contact of AlP with the stomach acid and water but cannot affect the already absorbed PH_3. Recently, a case report of DHA administration in AlP poisoning has been described, in which DHA dissolved in sodium

bicarbonate was orally administered to two cases of AlP-poisoned patients. The study involved just two instances of AlP poisoning, and only the cardiovascular events have been monitored [48]. On the other hand, oral administration of DHA solution may not be reasonable, as water could increase the risk of PH_3 release from ingested AlP and may worsen the patient's condition.

Therefore, administration of I.V. DHA can bind the PH_3 already absorbed and circulating in the blood and present in the cell, as DHA can readily enter the cell. In fact, one of the most important strengths of the current study is the use of the parenteral route of DHA administration to preserve the function of the organs, such as the heart and brain. Also, DHA is endogenously produced in the body as dihydroxyacetone phosphate. Moreover, the safety of DHA has been studied extensively, and it was reported as very safe, with an LD_{50} of about 8 g/kg in rats [34]. It was also recommended for the treatment of hemorrhagic shock as an injectable form [34]. Therefore, it could be a safe and effective agent for treating PH_3 poisoning. However, further optimization of the DHA formulations and evaluating its possible adverse effects in a larger scale study is a prerequisite for its administration as an officially approved treatment for PH_3 poisoning.

5. Conclusions

Decreasing the mortality rate of AlP-poisoned patients is the tremendous clinical achievement of the current study. We found that parenteral DHA administration tremendously decreased DHA-poisoned patients' mortality rate by about 65 %. Interpreting the results of the present study and reaching conclusions are matters of assessing the integrity of the trial's design and the validity of the findings in a more controlled environment as well as on more patients. Finally, this novelty-designed formulation could ultimately find its application as an effective treatment for PH_3 poisoning.

Ethics statements

The study was approved by the ethics committee of Shiraz University of Medical Sciences on October 4, 2015 (Ethical code: IR.SUMS.REC.1394.102). Written informed consent was obtained after a complete description of the study to the patients or their families.

Data availability statement

Deidentified raw data are available upon reasonable request.

Fundings

This study was financially supported by the Vice-Chancellor of Research Affairs of Shiraz University of Medical Sciences (Grant#7363).

CRediT authorship contribution statement

Hossein Niknahad: comprehended and designed this study. Reza Heidari performed data visualization, manuscript draft preparation, and statistical analysis. Vahidreza Asghari prepared the injectable formulation in Shiraz Serum company. Ali jangjou, Fatemeh M. Niknahad, Fazel Goudarzi, Nasim Tavakoli, Mitra Rahimi, and Amir Mohammad Niknahad were involved in patients treatment, data collection, and interpretation. All authors were involved in the initial drafting and editing of the manuscript and approved the final version before submission. The corresponding author guarantor and attests that all listed authors meet authorship criteria and no others meeting the standards have been ommitted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to gratefully thank the physicians and medical personnel of Shahid Faghihi, Aliasghar, Namazi, and Loghman Hakim Hospitals for their cooperation in the administration of DHA formulation and patient monitoring as well as for supplying the data of the AlP-poisoned patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22165.

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