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A promising method for the treatment of aluminum phosphide poisoning: An experimental study in rats

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ABSTRACT

Aluminum phosphide (ALP) poisoning has a high mortality rate. The purpose of this study was to evaluate the efficacy of lipid emulsion (ILE) and N-acetyl cysteine (NAC) in the treatment of aluminum poisoning in the rat model. This experimental study was conducted on thirty-three rats. Six rats in the control group were given oral corn oil and twenty-seven rats in the other groups were orally poisoned using ALP dissolved in corn oil (Control group, ALP group, ALP-NAC group, ALP-ILE group). All the rats were monitored for hemodynamics and ECG parameters. Mixed ANOVA analysis was applied to compare means across groups. Actuarial life table analysis was applied to compare the survival rate of rats. In terms of hemodynamics, ALP group had a significant difference in means of heart rate (HR) and shock index (SI) compared to the control group (P = 0.04; P = 0.00, respectively). The ALP-ILE group had no significant difference in means SBP, HR and SI compared to control group (p=1.00, p= 0.58, p=1.00, respectively). In ALP-NAC group, there was a significant difference in means HR and SI compared to the control group (p=0.01, p= 0.00, respectively). The ALP-NAC group had no significant differences in means of SBP, HR ,and SI compared to ALP group but the ALP-ILE group had significant differences in means of SBP and SI. Considering ECG in ALP, ALP-NAC and ALP-ILE groups, changes in the PR interval and duration of QT were not significant compared to the control group. In the ALP-NAC and ALP-ILE groups had no significant differences in means of QT and PR interval compared to the ALP group.There was a 45% survival rate in the ALP-ILE group at the end of 3rd day. Lipid peroxidation in the ALP and ALP-ILE groups significantly increased in comparison to the control group. The total antioxidant capacity (TAC) in the ALP-ILE group increased significantly compared to the control group but was significantly lower than those treated with NAC. In this study, two therapeutic strategies were compared in the treatment of ALP-poisoning. NAC with antioxidant properties and ILE with lipophilicity property. ILE due to its different osmolarity with intravascular osmolarity improves hemodynamic changes and compensates for the systemic effects of aluminum phosphide.

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INTRODUCTION

Aluminum phosphide (ALP) is a very effective rodenticide in protecting agricultural products in Iran.

Although its use is very restricted due to its high risks, it is still found in the market under the name "rice tablets." Each 3 gr tablet releases about 1 gr of lethal phosphine gas (PH3) [1]. Its lethal dose is 0.5 gr [2]. People who have stayed alive after taking the tablet are the ones taking a low dose, expired pills, or the pills that have gradually released PH3 gas in contact with air [1-3]. Immediately after contact with water or stomach content, PH3 releases and readily absorbs throughout the intestine and causes tissue hypoxia, cell damage and, eventually, multiple organ failures [1,2]. Although the precise mechanism of action of this poison is not known, some mechanism of actions has been proposed such as inhibiting mitochondrial cytochrome oxidase, induction of lipid peroxidation and release of superoxide free radicals [2]. The main causes of death in the first 24 hours are the cardiovascular collapse and the shock caused by the toxic effect of this poison, and after this time, the failure of several organs [3,4]. The most important factor in the treatment of AlP poisoning is starting supportive treatment as soon as possible immediately after the patient's entry. However, despite the use of multiple invasive and non-invasive methods to treat the patients, due to the absence of specific antidote there is a high degree of mortality [2-7].

Several decontamination methods, supportive care, and drugs (cardiovascular, antioxidants) have been utilized to reduce mortality and morbidity [5-7]. N-acetylcysteine (NAC) is an antioxidant and cytoprotective compound that brings about cardioprotective effects against oxidative stress due to free radicals and inhibits the effect of PH3 on cytochrome oxidase c of mitochondria by increasing intracellular glutathione. This compound may reduce mortality in this poisoning and have a therapeutic and protective effect against the toxic effects of poisons [8-11]. One therapeutic strategy, on which few studies have been conducted to evaluate its effectiveness of therapeutic effect, is intravenous lipid emulsion (ILE). Lipid helps dissolve the PH3 absorbed into the bloodstream, which is one of the advantages of this therapeutic method. Its possible mechanism is Lipid Sink or lipid compartment that reduces the concentration and toxicity of poisons through diluting and fragmenting the intravascular poison by lipid droplets, increasing the release of toxin into stagnant adipose tissue and releasing toxin from susceptible target tissues into adipose tissues. Thus, considering these benefits and also its complications, fat emulsion might be helpful as an antidote in life-threatening poisoning [12,13].

In this study, by examining the efficacy of ILE and NAC in the treatment of poisoning with ALP in rat model through hemodynamics and ECG, we tried to compare the response of these two drugs to treatment as well as mortality reduction. We also described tissue damage by measuring oxidative stress biomarkers.

MATERIAL AND METHODS

Animals

This experimental study was conducted on thirty-three male rats randomly divided into four groups. We got Wistar male rats weighing from 200 to 250 gr from the Neuroscience Research Center of Kerman University of Medical Sciences and kept the animals at the laboratory for at least 7 days to make them adapt to the environment. The rats were kept in stainless steel cages (6 rats per cage) in the room with air conditioning and controlled temperature (25°C) along with a 12-hour cycle of light and darkness. The rat's diet was standard pellets and water was freely available to them.

Animal treatment

Six rats in the control group received oral corn oil. Twenty-seven rats in the other groups (8 in ALP group, 8 in ALP-NAC group, 11 in ALP-ILE group) were orally poisoned by ALP (12.5 mg/kg) dissolved in corn oil [4,14]. After thirty minutes, the first group received no treatment (ALP group), and the second group received intravenous NAC at the dose of 150 mg/kg IV stat, followed by 50 mg/kg over 4 h followed by 100 mg/kg over 16 h [15-17]. The third group received intravenous ILE 20% at the dose of 1.5 cc/kg IV stat and then 0.25 cc/kg/min (max 15 cc/kg) [18,19].

This study was approved by the Ethics Committee of the Vice-Chancellor for Research and Technology of Kerman University of Medical Sciences, based on international ethical considerations on laboratory animals, and according to the provisions "Guides For the Care and use of laboratory animals." All steps and recording data were performed by a general practitioner and a master of laboratory science under the direct supervision of an emergency medicine specialist and a Ph.D. pharmacist. Given the lack of adequate studies on the treatment of AlP poisoning using ILE and given the review of the previous studies on the use of ILE in the treatment of other poisonings, we considered the sample size 33 in four groups.

Evaluation of hemodynamic parameters and ECG

All the rats in the control and other groups were examined for hemodynamics (SBP, HR, SI) and ECG changes 30, 60, 90 and 120 minutes after receiving corn oil using the PowerLab ADinstruments, (Australia).

Evaluation of oxidative stress biomarkers

At the end of the study and after anesthetizing the rats with ketamine and xylazine, all the rats were killed and blood samples were taken via cardiac puncture [20]. The level of lipid peroxidation was measured by thiobarbituric acid reactive substances method. Total antioxidant capacity (TAC) of plasma was measured by the ferric reducing ability of plasma (FRAP) method [21].

Statistical analysis

All experiments were repeated at least six times and to take into account the dependency of repeated measures, mixed ANOVA model was used to compare means across four treatment groups. Results were expressed as the mean ± standard error and the values with the p-value less than 0.05

Table 1. Characteristics of hemodynamic parameters among the four groups

Variables	*Control (mean±SE)*	*ALP (mean±SE)*	*ALP-NAC (mean±SE)*	*ALP-ILE (mean±SE)*
SBP	75.87±5.195	59.66±4.56	60.73±4.56	81.1±3.87
P value		0.15	0.22	1.00
HR	238.18±14.27	292.49±12.51	299.99±12.51	268.68±10.63
P value		0.04	0.01	0.58
SI	3.19±0.42	5.72±0.38	5.26±0.38	3.41±0.32
P value		0.00	0.00	1.00

ALP; Aluminium phosphide, NAC; N-acetyl cysteine, ILE; Intravenous lipid emulsion, SBP; Systolic blood pressure, HR; Heart rate, SI; Shock index

were considered significant. We applied actuarial life table analysis and plotted Kaplan-Meier curve to compare the survival rate in four treatment groups.

RESULTS

Hemodynamic and ECG results

In terms of hemodynamics, the ALP group had a significant difference in means of heart rate (HR) and shock index (SI) compared to the control group (292.49±12.51 vs. 238.18±14.27; p= 0.04 and 5.72±0.38 vs. 3.19±0.42; p= 0.00, respectively), although, mean of systolic blood pressure (SBP) was no significant (p=0.15).

The ALP-ILE group had no significant difference in means SBP, HR and SI compared to control group (p=1.00, p= 0.58, p=1.00, respectively). In ALP-NAC group, there was a significant difference in means HR and SI compared to the control group (p=0.01, p= 0.00, respectively)., although, mean of SBP was no significant (Table 1).

The ALP-NAC group had no significant differences in means of SBP, HR and SI compared to ALP group. In the ALP-ILE group had significant differences in means of SBP and SI, although there was no significant difference in mean of HR compared to the ALP group (Table 2).

The hemodynamic parameters, including SBP, HR, and SI among the treatment groups are shown in Fig. 1. The changes in hemodynamic parameters are seen in the four-

Figure 1. Hemodynamic parameters among the four groups. The mean±standard error of the mean.
SBP; Systolic blood pressure, HR; Heart rate, SI; Shock index.Time 1: 30th min; Time 2: 60th min; Time 3: 90th min; Time 4: 120th min. Control is shown in blue, ALP is shown in red, ALP+NAG is shown in gray, and ALP+ILE is shown in yellow.

Table 2. Characteristics of hemodynamic parameters among ALP-NAC and ALP-ILE with ALP groups

Variables	*ALP-NAC (P-value)*	*ALP-ILE (P-value)*
SBP	1.00	0.00
HR	1.00	0.29
SI	1.00	0.00

Table 3. Characteristics of electrocardiogram (EKG) among four groups

Variables	*Control (mean±SE)*	*ALP (mean±SE)*	*ALP-NAC (mean±SE)*	*ALP-ILE (mean±SE)*
PR	48.37±1.50	47.73±1.31	45.70±1.11	45.94±1.31
P value		1.00	1.00	0.98
QT	95.87±7.25	99.55±6.77	112.63±7.03	89.92±6.09
P value		1.00	0.65	1.00

ALP; Aluminium phosphide, NAC; N-acetyl cystein, ILE; Intravenous lipid emulsion

times interval. In the ALP-ILE group, the mean of SBP is higher than other groups, while in the ALP and ALP-NAC groups, after 30 minutes, the downward trend is observed. The mean heart rate in the control group and then in the ALP-ILE group is lower than the other groups. In the ALP-NAC group, the increase in heart rate is shown and in the ALP group, it is the significant upward trend from the 90th minute. The SI changes in both ALP and ALP-NAC groups has increased from the 60th minute, while the changes in the ALP-ILE and control group were not significant.

Considering ECG in ALP and ALP-NAC groups, changes in the PR interval and duration of QT were not significant compared to the control group.

Considering ECG, there was no significant difference between the ALP-ILE compared to the control group in mean PR interval (45.94±1.31 vs. 48.37±1.50; p= 0.98). In ALP-ILE group, there was no significant difference in mean QT compared to control group (89.92±6.09 vs. 95.87±7.25; p= 1.00) (Table 3). In the ALP-NAC and ALP-ILE groups had no significant differences in means of QT and PR interval compared to the ALP group (p= 1.00, p=1.00).

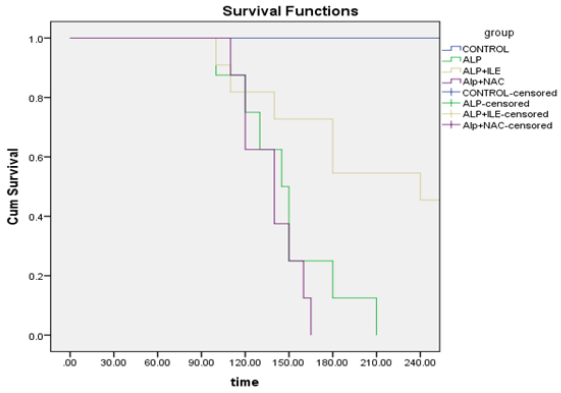

Figure 2. Kaplan–Meier survival analysis

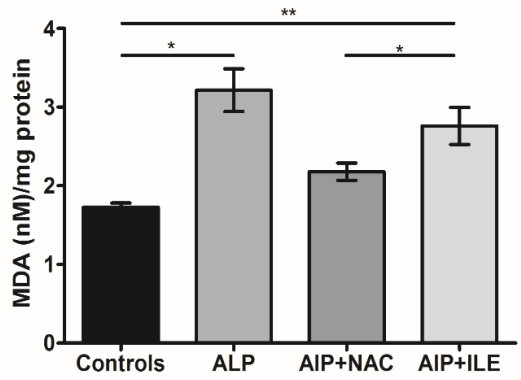

Figure 3. Lipid peroxidation measurement by thiobarbituric acid reactive substances method

Survival rate

In the control group, the survival rate always was 100%. In the ALP group, the survival rate in 90th, 150th, 210th min was 88%, 25%, 0%, respectively. In ALP-NAC group, the survival rate in 150th min was 0%. In ALP-ILE group, the survival rate in 90th, 150th min and at the end of 3th day was 82%, 73%, and 45.45%, respectively. The Kaplan–Meier survival analysis was shown that in ALP and ALP-NAC groups, there was no survival after 240 min, though; there was 45.45% survival in the ALP-ILE group (Fig. 2).

Oxidative stress results

Lipid peroxidation in the poisoned rats and in the poisoned rats that were treated with ILE (ALP-ILE group) significantly increased in comparison to the control group. However, there was no significant difference in lipid peroxidation in the rats treated with NAC (ALP-NAC group) compared to the control group (Fig. 3).

The total antioxidant capacity (TAC) in rats poisoned with ALP decreased in comparison to the control group but the differences were not significant. Poisoned rats treated with NAC significantly showed an increase in TAC compared to control group. The TAC in the poisoned rats treated with ILE (ALP-ILE group) also increased significantly compared to the control group but was significantly lower than those treated with NAC (Fig. 4).

DISCUSSION

Due to the lack of specific antidotes for ALP poisoning and its high fatality, several therapeutic methods have been used in the management of these patients. Life-threatening

cardiotoxicity is the main cause of death in the poisoned cases and other treatments were not effective [22, 23]. This experimental study conducted on the rats poisoned with ALP indicated that treatment with ILE has beneficial effects in the correction of SBP, HR, and SI. The survival rate in the rat was reported to be 45%, which was a significant reduction compared to other groups.

The ILE could reduce the mortality of ALP poisoning by various mechanisms. Dissolution of PH3 in the lipid in the bloodstream and its transfer into adipose tissues decrease its toxic effect on vital organs. Accumulation of PH3 in adipose tissues also activates the phenomenon of the release of toxin from other organs into adipose tissues. In addition, according to lipid sink theory, increased in fatty acids catabolism for the synthesis of ATP in metabolic toxicity brings a positive effect on the function of sodium and calcium channels, an increase of calcium concentration in myocytes, inhibition of oxidative myocardial phosphorylation, and elevation of cardiac function (positive inotropic and chronotropic) are other well-known therapeutic mechanisms of ILE. In a case report study conducted by Baruah et al. on two patients with ALP poisoning, both poisoned cases survived due to the use of intravenous ILE [24-26].

The use of NAC has been recommended given its therapeutic effects due to antioxidant effects and through increased cellular glutathione in the treatment of ALP poisoning [27]. However, few studies have been conducted in this regard, and controversial results have been attained [28, 29]. In a study on rats, Azad et al. showed that NAC can extend the survival time in rats by reducing myocardial oxidative damage [29]. Tehrani et al. showed that this drug can produce protective effects against this poison through its anti-oxidant effects and reduce mortality. In a study on rats, Gheshlaghi et al. suggested that NAC cannot be effective in increasing survival and questioned its use to reduce mortality [17]. Given the few studies conducted and the contradictory results, it appears that the decision to use NAC is too early and further studies are required [9]. In our study, NAC-treated rats, unlike ALP-ILE group, had no significant correction in hemodynamics and their mortality was reported 100% at the end of the third day, questioning the efficacy of it in the treatment of the ALP poisoning.

In the toxicity of ALP, PH3 is an effective factor in inhibiting cytochrome c oxidase and disrupting the electron transport chain and producing free oxygen radicals. Free oxygen radicals are responsible for the hypoxia of organs, and this hypoxia is a hallmark of PH3 poisoning [30,31]. Another mechanism of PH3-induced damage is the disruption of the synthesis of enzymes and proteins in lipid peroxidation as a major effect of free radicals. Lipid peroxidation products disrupt the physicochemical properties, fluidity, and integrity of the cell membrane, and increase the susceptibility to cell necrosis [32]. In our study, the level of lipid peroxidation was increased in the group of rats with poisonous ALP. Also, in the ALP-ILE group, there was a significant difference with the control group. One of the reasons for this increase in the peroxidation of lipid after administration of ILE could be increased in plasma lipid content. In this lipid shift situation, the toxicity on target organs such as the brain, liver, and kidney can be reduced by increasing lipid peroxidation in the peripheral adipose. TAC findings indicate although ILE is not as effective as NAC in increasing total antioxidant capacity, oxidative damage decreased compared to the poisoned group that did not receive any treatment.

Hemodynamics parameters are very crucial in determining the mortality of patients referring to the emergency department. The *shock index* (SI), defined as heart rate divided by systolic blood pressure, is an accurate diagnostic measure that is more useful than hypotension and tachycardia in isolation. Our previous studies, conducted on patients with the Emergency Severity Index (ESI) level 2 and 3, showed that systolic hypotension and shock index are helpful in predicting hospital mortality [33, 34]. Thus, while studying these parameters in rats, we also found that these two hemodynamics parameters are very helpful, reliable, and proper monitoring methods for determining the outcome and mortality of rats.

There were several limitations in this study. First, the physician and expert conducting the study were not blind. Second, it was not possible to monitor other hemodynamics, such as diastolic blood pressure and invasive hemodynamic measurements. Third, it was not possible to conduct blood tests during the study and daily monitoring of laboratory tests due to lack of access to enough blood samples from the animal. Finally, it was not possible to keep the rats for longer periods to study long-term mortality.

CONCLUSION

In this study, two therapeutic strategies were compared in the treatment of ALP-poisoning. NAC with antioxidant properties preventing the release of free radicals and oxidative damage and intravenous injection of ILE trapping and removing PH3 from the circulatory system by using lipophilicity property of PH3. It also seems that ILE due to its different osmolarity with intravascular osmolarity causes the fluid shift, which improves hemodynamic changes and compensates for the systemic effects of aluminum phosphide. Thus, given the low quality of evidence due to the lack of antidotes and the ineffectiveness of other therapeutic methods, the use of ILE may reduce the mortality of these patients.

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