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HIGH-DOSE INSULIN IS A GOOD OPTIONAL TREATMENT FOR ALUMINUM PHOSPHIDE POISONING: A LONGITUDINAL STUDY

Nasrin Khakpoornia[1], Babak Mostafazadeh[1*], Shahin Shadnia[1], Mitra Rahimi[1], Peyman Erfan Talab Evini[1], Maral Ramezani[2, 3]

[1*]Toxicological Research Center, Clinical Toxicology Department, Excellence Center of Clinical Toxicology, Loghman Hakim University Hospital Poison Center, Shahid Beheshti University of Medical Sciences, Tehran-Iran
[2]Department of Pharmacology, School of Medicine, Arak University of Medical Sciences, Arak, Iran
[3]Traditional and Complementary Medicine Research Center, Arak University of Medical Sciences, Arak, Iran

***Corresponding Author:** Babak Mostafazadeh
*Toxicological Research Center, Clinical Toxicology Department, Excellence Center of Clinical Toxicology, Loghman Hakim University Hospital Poison Center, Shahid Beheshti University of Medical Sciences, Tehran-Iran, Email: mstzbmd@sbmu.ac.ir

Abstract
Background: The poisoning caused by aluminum phosphide is a critical medical emergency that necessitates immediate and suitable treatment. Recently, the use of high doses of insulin has been suggested in the treatment of this poisoning. We conducted a study to examine how effective various insulin doses are in treating aluminum phosphide poisoning.
Material and Method: This was a descriptive and analytical study on patients poisoned with Aluminum phosphide hospitalized in the ICU department of Loghman Hakim Hospital in 2022. High dose insulin (HDI) protocol was used. Systolic and diastolic blood pressure, urine output, pH, bicarbonate, blood carbon dioxide pressure (PCO_2), and ejection fraction (EF) were measured during treatment. Data were analyzed by SPSS software.
Results: The study included 66 men (65.3%) and 35 women (34.7%). The average age of the participants was 32.99±11.45 years. Insulin administration has an inverse correlation with blood PH level, with a 1mIU increase resulting in a 0.31 decrease in PH level. Additionally, there is a significant association between insulin and systolic blood pressure, with a 1IU increase causing a 0.02 mmHg rise in blood pressure. HCO_3 level, PCO_2, systolic and diastolic blood pressure were significantly higher during the final measurement compared to the time of arrival in patients. The mortality rate was 61.4%. Out of the total cases, 93 (92.1%) were intubated.
Conclusion: High-dose insulin protocol may improve blood pressure, cardiac function, and blood bicarbonate levels in rice tablet poisoning patients.

Keywords: Aluminum phosphide, glucose/insulin/potassium, hyperinsulinemia-euglycemia therapy, pesticide, poisoning.

Introduction:

Metal phosphides are commonly utilized for safeguarding stored grains due to their desirable characteristics such as their ability to combat different pests, high potency, and production of non-toxic residues in crops. In countries with like Iran, India, and Egypt, metal phosphides are extensively employed in agriculture. Some examples of metal phosphides are aluminum phosphide (AlP), zinc phosphide (Zn_3P_2), magnesium phosphide (Mg_3P_2), and calcium phosphide (Ca_3P_2) (1).
Aluminum phosphide which is a potent poison with an oral LD_{50} of 11.5 mg/kg, is utilized as an insecticide, rodenticide, and fumigant. It is available in the form of tablets, commonly referred to as rice tablets or wheat bills. The rice tablet weighs three grams and contains 56% AlP and 44% aluminum carbonate. When it comes into contact with moisture, it releases one gram of Phosphine (PH_3) (2). Phosphine gas is rapidly absorbed from the respiratory or gastrointestinal tract (GIT) to reach the systemic circulation (3). PH_3, which is absorbed, is a toxic substance that can cause various harmful effects such as collapse of the cardiovascular system, damage to the lungs, and liver dysfunction. Additionally, it can lead to significant imbalances in the body's acid-base and electrolyte levels, resulting in conditions such as metabolic acidosis, hypokalemia, hypermagnesemia, or hypomagnesemia. As a result, fatalities resulting from metal phosphide exposure are usually caused by a combination of cardiogenic shock, metabolic acidosis, acute pulmonary edema, and liver failure that are difficult to treat (1, 4, 5).
There is no known antidote for ALP poisoning, so treatment is only supportive. The success of treatment depends on the severity of the poisoning and how quickly the patient receives medical attention (5). Although the public sale of rice tablets has been banned in Iran since 2012, the country still experiences a significant number of cases of ALP poisoning, whether intentional or accidental. Iran reported a total of 3,150 poisoning cases and 606 fatalities between 2000 and 2019, according to articles (6). Treatment with high doses of insulin (HDI) while maintaining euglycemia is an effective method to treat the toxicity of cardiovascular drugs (7-9). The administration of insulin through infusion has the ability to enhance the heart's inotropy and increase peripheral vascular resistance, while also reversing acidosis by promoting the uptake and utilization of carbohydrates by myocytes (10).
The dose of insulin given to a patient is determined by their body weight and overall health, as per existing studies. Our study aimed to determine the effectiveness of different doses of high-dose insulin protocol (HDI) in aluminum phosphide poisoning.

Material and Methods:

This was a descriptive and analytical study that was conducted on patients poisoned with Aluminum phosphide hospitalized in the ICU department of Loghman Hakim Hospital in Tehran from February 2022 to February 2023. The formula for determining the sample size was the estimated ratio with a confidence level of 95% and the power of the test was 80%. Based on the information from Khodabandeh et al.'s study (11), the sample size was determined to be 100 people.
All patients who were 13 years old and above and were admitted to the Intensive care unit of Loghman hakim university hospital poison center with signs, symptoms and statements of their companions based on aluminum phosphide poisoning were considered for inclusion in the study. The exclusion criteria for this study are the absence of clinical symptoms such as systolic blood pressure below 90 mmHg and laboratory findings related to metabolic acidosis caused by aluminum phosphide poisoning. Additionally, participants who have not undergone echocardiography and those who are concurrently using other drugs with aluminum phosphide will also be excluded.
High dose insulin (HDI) protocol was used. During the study, the patient's vital signs were checked every hour, and if the systolic blood pressure dropped to less than 90 mmHg, insulin was started at a dose of 1 IU/kg of body weight, and if the systolic blood pressure did not increase, the dose of insulin was increased to 2, 3 and more up to ten IU/Kg of body weight until the systolic blood pressure reached more than 90. All patients underwent echocardiography at least once during hospitalization. Metabolic acidosis is considered as $PH<7.45$ and $HCO_3<24$. The patient's VBG

blood gases were measured every 6 hours. The urinary output of the patients was measured by the nurse every hour.
The variables of age, sex, number of tablets taken, time of taking tablets, PH, blood bicarbonate (HCO_3), ejection fraction (EF), dose of injected insulin, systolic and diastolic blood pressure (DBP and SBP), urine output (UOP), need for intubation and death or recovery of the patient were investigated.
The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.RETECH.REC.1400.1213.

Statistical analysis
The data was analyzed using IBM SPSS 23 software. The dispersion and descriptive indices of the variables were investigated. The Chi-square test was used to compare qualitative variables. To obtain the effectiveness, Generalized Estimating Equations (GEE) and logistic regression were used. The t-test (paired or independent) was also used to compare the mean. A significance level of $P \leq 0.05$ was considered.

Results:
This study included a total of 101 participants, with 66 (65.3%) being men and 35 (34.7%) being women. The difference between the numbers of men and women was statistically significant with a p-value of 0.002. The age range varied from 13 to 66 years old. The average age of individuals was 32.99±11.45 years. Out of the total cases, 93 (92.1%) were intubated (Table 1).
The number of tablets consumed ranged from half a tablet to a maximum of 6. The shortest interval between taking tablets and going to the hospital was 30 minutes and the longest was 1200 minutes. The dose range of insulin used for treatment was 30 to 600 IU. The mortality rate was 61.4% (62 cases) (Table 1). Those who recovered and those who died did not show any significant difference in terms of age and gender. There was no significant difference in the average age between men and women.

Table 1. Demographic information and examinations upon arrival of patients

Variables	Frequency (%) or mean±SD (min-max)
Male	66 (65.3%)
Female	35 (34.7%)
Age (year)	32.99±11.45 (13-66)
Number of tablet taken	1.77±1.3 (0.5-6)
Interval between ingestion and referral to the hospital (minute)	240.5±220.5 (30-1200)
Intubation	93 (92.1%)
Non-survive patients	62 (61.4%)
INS Dosage range (IU)	30-600
PH upon arrival	7.26±0.16 (6.8-7.53)
HCO3 upon arrival (mEq/L)	15.86±4.47 (2.2-23)
PCO2 upon arrival (mmHg)	38.7±16.13 (8-107)
EF% upon arrival	34.36±13.1 (10-55)
SBP upon arrival (mmHg)	84.7±13.2 (52-122)
DBP upon arrival (mmHg)	51.9±10.6 (30-79)
UOP upon arrival (mL)	57.7±43.5 (3-200)

The average PH, HCO_3, EF, SBP, DBP and urine output on arrival were 7.26, 15.86 mEq/L, 34.36%, 84.7 mmHg, 51.9 mmHg and 57.7 mL respectively (Table 1). The average of the above parameters in the last measurement was 7.22, 19.7 mEq/L, 42.5%, 96.6 mmHg, 59.7 mmHg and 68.8 mL respectively. According to the GEE analysis, there is an inverse correlation between the amount of insulin administered and the PH level of the blood. This means that for every 1mIU increase in insulin, there is a corresponding decrease of 0.31 in the PH level. A noteworthy association was found between the amount of insulin administered and the systolic blood pressure, indicating that for every IU increase in insulin, there was a rise of 0.02 mmHg in blood pressure (Table 2).

Table 2. Generalized Estimating Equations analysis (Based on mIU of insulin)

	B	Standard Error	P-value
PH	-0.308	0.1	0.002*
HCO3	4.409	3.7545	0.24
EF	12.578	13.096	0.337
SBP	20.106	9.567	0.039*
DBP	4.879	7.123	0.493
UOP	4.512	39.441	0.909

*P<0.05

Logistic regression was used to investigate the relationship between patients' outcomes and the last dose of insulin received by the patient. The regression model that was developed showed a sensitivity of 78.7%, specificity of 82.1%, and accuracy of 80%. The model demonstrated that with every 1IU increase in insulin, the chance of a patient's survival increased by 1.028, based on the odds ratio obtained (Table 3-1 & 3-2).

Table 3-1. Classification Table [a]

Observed		Predicted		
		Outcome		Percentage Correct
		Survival	Non-Survival	
Outcome	Survival	32	7	82.1
	Non-Survival	13	48	78.7
Overall Percentage				80.0

a. The cut value is 0.500

Table 3-2. Logistic regression between patients' outcome and the last dose of insulin received, age and gender

	B	Standard Error	P-value	Odd Ratio	95% CI for odd ratio	
					Lower	Upper
Last dose INS	.028	0.006	0.00001	1.028	1.016	1.041
Age	-.001	0.028	0.964	0.999	0.946	1.054
Sex(male)	0.976	0.613	0.112	2.653	0.797	8.827

The comparison of average values between the time of arrival and the final measurement of various variables in patients revealed that blood bicarbonate, systolic blood pressure, and diastolic blood pressure values were considerably elevated during the final measurement. This indicates that the patients' conditions improved over time (Table 4). The comparison between survivors and non-survivors showed that PH and HCO_3 levels on arrival were significantly lower in non-survivors. Also, PH, HCO_3, systolic and diastolic blood pressure and urine output in the last measurement were significantly lower in non-survivors. Blood carbon dioxide pressure (PCO2) values were significantly lower in survivors both at the time of entry and the last measurement (Table 4).

Table 4. Comparison of the investigated parameters at the beginning and end of the study and comparison of the last examination based on the outcome of the patients

	Paired- t test			Independent- t test		
	Upon arrival	Last measurement	P-value	Survival	Non-survival	P-value
PH	7.26±0.16	7.22±0.2	0.053	7.38±0.05	7.12±0.18	0.0001
HCO_3	15.86±4.47	19.2±6.9	0.0001	25.19±4.1	16.19±6.2	0.0001
EF	37.5±15.05	42.5±11.7	0.203	46.7±5.8	38.3±16.1	0.446
SBP	84.7±13.2	96.5±18.9	0.0001	111.4±14.14	87±15.03	0.0001
DBP	51.9±10.6	59.6±14.7	0.0001	71±11.8	52.6±11.5	0.0001
UOP	56.5±43.2	67.7±49.6	0.103	101.81±47.1	46.3±40.9	0.0001
PCO_2	38.7±16.13	48.7±16.1	0.0001	42.7±9.99	52.4±17.99	0.001

Discussion:

This study showed that insulin treatment significantly increases bicarbonate concentration and systolic and diastolic blood pressure. Also, for each unit increase in insulin dose, the probability of patient survival increases 1.028 times. Conversely, it was noted that there is a correlation between insulin dosage and blood PH, whereby an elevation of one mIU of insulin dosage causes a reduction in pH by 0.308. Sixty-one and four-tenths percent (61.4%) of the participants in this study died.

The main purpose of hyperinsulinemia-euglycemia therapy (HIET) is to manage the effects of excessive calcium channel blocker consumption, but it can also provide inotropic support for individuals who have been poisoned by beta-blockers (7, 12). For the first time in 2008, a few patients were treated with hyperinsulinemia-euglycemia therapy as a potential remedy for rice tablet poisoning (13). This study was carried out to investigate the efficacy of different insulin doses in the treatment of aluminum phosphide poisoning.

Severe low blood pressure can result from ALP poisoning, which is believed to be caused by various factors such as the toxic impact of phosphine gas on cardiac myocytes, fluid loss, and other factors (4, 14). Insulin causes sodium and water retention, which can contribute to increased blood pressure (15). The study by Bhalla et al showed that the administration of glucose-insulin-potassium (GIK) resulted in an improvement in blood pressure, including systolic, diastolic, and mean arterial pressure. The measurements taken at 12, 24, and 48 hours after treatment were notably higher than the initial readings (16). According to the Hassanian-Moghaddam study, in patients with alp poisoning, the GIK protocol resulted in a significantly higher mean SBP (81.1±19.9mmHg) compared to the standard conventional protocol (73.8±13.5mmHg) after treatment (17). Our study also showed that insulin treatment significantly improves systolic and diastolic blood pressure and every 1 IU increase in insulin causes an increase of 0.02 mmHg in systolic pressure.

A decrease in PH and HCO_3 levels is one of the clinical symptoms of rice tablet poisoning (18-21), which was also observed in our study. Insulin secretion and activity can be influenced by the pH value. The promotion of glycolysis by insulin affects acidosis. It is not clear how, but the decrease in pH inhibits insulin sensitivity or activity (22). In vitro studies have shown that insulin is responsible for the movement of H^+ from the intracellular fluid to the extracellular fluid. The administration of insulin for the treatment of diabetic ketoacidosis may result in a higher level of acidity in the extracellular fluid immediately after its use (23). The effect of a GIK mixture on acid-base equilibrium indicators in patients with acute myocardial infarction who received fibrinolytic treatment was evaluated in a study. The study revealed that after 24 hours of infusion, there was an increase in PH and a decrease in PCO_2 compared to the initial examination. However, no significant alterations in bicarbonates were noted (24).

Hassanian-Moghaddam and Pannu's studies on the effect of GIK on rice tablet poisoning did not show any significant difference in blood pH and bicarbonate levels between the control group and those treated with high doses of insulin (16, 17). The results of our study showed that there is a significant increase in HCO_3 levels in patients after treatment. There was no significant difference in pH levels between before the start of treatment and at the end of treatment. However, a negative relationship between insulin doses and blood pH was found. With the increase of every 1 mIU of insulin, the value of pH decreases by 0.308. This finding can be explained according to the effect of insulin on the H^+ transport mentioned above. The increase of bicarbonate has happened to compensate for this drop.

Hassanian-Moghaddam has also mentioned in his article that the blood PH on arrival and the minimum pH in the survivors of the treatment group were significantly higher than those who did not survive, but there was no difference in the level of bicarbonate and PCO_2 (17). Our results showed that PH and bicarbonate values were significantly higher in survivors both at the time of arrival and at the last measurement. Blood PCO_2 values were significantly lower in survivors both at the time of entry and the last measurement.

Compensatory hyperventilation caused by acidosis can result in a reduction in PCO_2 levels. Nonetheless, the correlation between acidosis and PCO_2 levels is intricate and contingent on several factors, including the root cause of acidosis and the body's compensatory mechanisms (18, 25). Our results also showed that the level of PCO_2 at the arrival of patients was significantly low, which indicates a compensatory mechanism against acidosis caused by poisoning. Respiratory acidosis is a concern in intubated patients, especially those with severe metabolic acidosis (26). In our study, patients had metabolic acidosis caused by rice tablets upon arrival, and 92.1% of them were intubated. Considering the working mechanism of the ventilator and the complex pathways of the body to correct acid-base disorders, the significant increase in PCO_2 in the last measurement of the patients can be for all the reasons mentioned.

Limitation:

The study had some limitations, such as the absence of a separate control group. However, the patient's information at the time of admission was considered as a control for the individual. Additionally, in most cases, echocardiography and calculation of EF were not performed during the last examination, and paired T-test was only possible for a limited number of patients. This caused the improvement at the end of treatment was not statistically significant.

Conclusion:

The use of a high-dose insulin protocol may be effective in improving blood pressure, cardiac function, and blood bicarbonate levels in patients with aluminum phosphide poisoning. However, it is important to exercise extreme caution due to the severe metabolic acidosis of the poisoned individual, the effects of insulin on hydrogen ions, and the need for intubation to prevent respiratory acidosis.

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Authors' contribution:

All authors contributed significantly to the reported work, including the conception, study design, execution, data acquisition, analysis and interpretation. They were involved in drafting, revising or critically reviewing the article and gave final approval for publication. The authors have also agreed on the journal to which the article has been submitted and accept accountability for all aspects of the work.

Conflict of interest:

We declare that we have no conflicts of interest.

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