Effects of melatonin and N-acetylcysteine on aluminum phosphide poisoning in rats

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Abstract

Introduction: Aluminum phosphide (ALP) poisoning is one of the deadliest types of poisoning in the world. The antioxidant properties of melatonin and N-acetylcysteine and their effects on reducing cell death have been identified. The aim of this study was to evaluate the effects of N-acetylcysteine and melatonin in the treatment of aluminum phosphide poisoning in rats.

Materials and Methods: Fifty male Wistar rats weighing 200–250 g were tested in five groups of ten. The first group was the control group; the second group received (10 mg/kg) of ALP, the third group received (10 mg/kg) of ALP and (10 mg/kg) of melatonin, the fourth group received (10 mg/kg) of ALP and (10 mg/kg) of N-acetylcysteine, and the last group received (10 mg/kg) of ALP and (10 mg/kg) of melatonin and N-acetylcysteine. The plasma of samples was isolated, and the activity of antioxidant enzymes (glutathione S-transferase (GST), Superoxide dismutase (SOD), and catalase (CAT)) was analyzed.

Results: The concentrations of CAT, GST, Glutathione, GSH were decreased in plasma, liver, and kidneys of mice treated with aluminum phosphide; also, the concentrations of aspartate aminotransferase (AST), ALT, and ALK were increased ($P < 0.05$), while the activity of SOD did not change significantly ($P > 0.05$). Treatment with N-acetylcysteine and melatonin led to an increase in the activity of CAT, GST, and GSH in plasma, liver, and kidney. After the administration of N-acetylcysteine and melatonin to mice, the levels of all enzymes were close to normal, and the mice survived for 12–15 hours after administration.

Discussion: The administration of N-acetylcysteine (NAC) and melatonin at a dose of 10 mg/kg improves hepatic manifestations and prevents liver necrosis; also, they are considered potential therapeutic agents in the treatment of this poisoning.

Keywords: Aluminum phosphide, liver enzymes, melatonin, N-acetylcysteine, phosphine gas

Introduction

Correct, scientific, and rational use of pesticides for agricultural purposes has increased the quantity and quality of crops through pest control and has a very important role in providing the food needed by humans. However, improper use of these toxins can lead to a variety of acute and chronic poisonings in humans.¹

References

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high in both the gastrointestinal and respiratory tract, and the phosphine produced is easily absorbed from the gastrointestinal tract and lung epithelium.\[9\]

This gas inhibits cytochrome c oxidase, the electron transport chain, and eventually stops cellular respiration. These changes result in the production of free radicals that can damage organs. The main fatal consequence of aluminum phosphide is usually a disorder of the cardiovascular system through the direct effect of phosphine gas on the myocardium and arrhythmia.\[4\] Also, phosphine can inhibit the function of catalase, reduce the concentration of glutathione, and cause dysfunction of cell walls and channels.\[6\]

Acute lethal poisonings due to metal phosphides have been extensively reported in less-developed countries such as India, Sri Lanka, Iran, Iraq, Morocco, Saudi Arabia, Pakistan, and Jordan, and the incidence of fatal poisonings with this toxin is lower in other countries, especially European countries and the United States. Low cost, availability, lack of strict rules in the distribution and sale of this toxin, and lack of awareness of the community about the high toxicity of this pesticide are among the factors that cause the high prevalence of this type of poisoning in these countries.\[7\]

N-acetylcysteine (NAC) is a dietary and pharmacological supplement which is used as a mucolytic agent in the treatment of acute acetaminophen poisoning. This compound is known as a dietary supplement with antioxidant properties and protective effects on the liver.\[8\] Acetylcysteine breaks disulfide bonds in mucosa and fluids and facilitates the passage of sputum out of the respiratory tract. This action is useful in diluting thick mucus in patients with pulmonary fibrosis and cystic fibrosis.\[9\]

Melatonin is a hormone that is secreted by the pineal gland and tissues such as the retina, intestines, bone marrow, kidneys, platelets, and glial cells, and due to its anti-apoptotic and antioxidant properties, it is used to treat various diseases.\[10\] Melatonin is specifically used to correct electrophysiological disorders of the heart. In addition, its amphiphilic structure allows it to penetrate into intracellular parts, including the mitochondria. In addition, melatonin acts as an antioxidant for increasing adenosine triphosphate (atp) production; it also prevents cell death by inhibiting mitochondrial permeability and inhibiting caspase activation after cytochrome C inhibition. Therefore, melatonin can be a useful agent for the treatment of aluminum phosphide poisoning.\[11\] Since there are no specific antidotes for treatment and aluminum phosphide poisoning is associated with a high mortality rate in the first 24–48 hours, finding a medication for the treatment of this poisoning is highly important. Therefore, the aim of this study was to investigate the effect of N-acetylcysteine and melatonin on the toxicity of aluminum phosphide in rats.

**Materials and Methods**

**Study design**

In this experimental study conducted in 2019, aluminum phosphide, N-acetylcysteine, and melatonin, which were produced by Sigma Company, were used. The research followed the tenets of the Declaration of Helsinki. The project was approved by the research department of the Faculty of Medicine (IR.ARAKMU.REC.1397.40).

**Description of experiment**

In this study, 50 male Wistar rats weighing 200–250 g were used in five study groups. Group 1 was the control group and consisted of ten mice. Group 2 consisted of ten mice that received aluminum phosphide (ALP) (10 mg/kg) orally by gavage. Group 3 consisted of ten mice that initially received ALP (10 mg/kg), and 15 minutes after the administration of ALP, melatonin (10 mg/kg) was administered by intraperitoneal injection for every ten mice. Group 4 consisted of ten mice that were first given ALP (10 mg/kg), and after 15 minutes, N-acetylcysteine (10 mg/kg) was administered. Group 5 consisted of ten mice that received melatonin and n-acetylcysteine (10 mg/kg) simultaneously, 15 minutes after the administration of ALP (10 mg/kg).

Five mice from each group were anesthetized for biochemical tests, and the rest of the mice were kept for assessment of survival time.

Blood samples were collected from mice and poured into tubes containing heparin as an anticoagulant and immediately placed on ice. The plasma of blood samples was obtained through a standard method, using a centrifuge at 2500 rpm for 20 minutes.\[12\] Plasma was used for evaluation of the activity of antioxidant enzymes (glutathione s transferase (GST); superoxide dismutase (SOD); catalase (CAT)). The liver and kidneys of rats were washed using a cold saline solution.

Tissues were carefully weighed and homogenized at a ratio of 1:10 in saline phosphate buffer. The samples were then centrifuged at 14,000 g at 4°C for 15 minutes. The supernatant was used to measure the desired biochemical indicators.

The enzymatic activity of aspartate aminotransferase (AST)-Alanine transaminase ALT-ALP in tissues and plasma, as well as GST-SOD-glutathione (GSH) and catalase, were determined according to the standard protocol and compared with the control group.

**Statistical analysis**

Data were analyzed using descriptive statistics (mean), independent t-test, and Chi-square. The Statistical Package for the Social Sciences (SPSS) V.25 was used applied for statistical analysis. Statistical significance was assessed at the 5% level.

**Results**

Evaluation and comparison of liver enzymes (ALT, AST, ALP) and concentrations of SOD, CAT, GST, GSH in blood, liver, and kidney samples of the studied mice showed that treatment with aluminum phosphide increased the activity of AST, ALT,
and alkaline phosphatase (ALK) in plasma and liver of rats, in comparison with the control group (P < 0.05) [Table 1].

The results also showed that the concentrations of CAT, GST, and GSH in plasma, liver, and kidneys of mice treated with aluminum phosphide decreased, while the activity of SOD did not change significantly (P > 0.05). Simultaneous treatment with N-acetylcysteine and melatonin caused a greater increase in the activity of CAT, GST, and GSH in plasma, liver, and kidney compared to the effect of N-acetylcysteine and melatonin alone [Table 2].

**Survival time**

In group 2 (aluminum phosphide), behavioral changes were observed in mice after ALP gavage. After 15–20 minutes, the animals showed the first symptoms, increased activity and anxiety, followed by a gradual decrease in activity; eventually, very reduced activity, occasional standing, and finally death was reported. The average survival time of the animals was 50–65 minutes.

In group 3 (aluminum phosphide + melatonin), on average, mice survived for 14–18 hours.

In group 4 (aluminum phosphide + N-acetylcysteine), mice survived longer than the previous two groups (24–28 hours).

In group 5 (aluminum phosphide + melatonin + n-acetylcysteine), mice survived for an average of 30–35 hours.

Although administration of melatonin and N-acetylcysteine delayed death in the treatment group compared with the control group, death was reported in all groups at different time intervals after treatment.

**Discussion**

Rice tablet is a chemical compound that is widely used as an effective rodenticide and insecticide to protect grains during storage and transportation in developing countries. The exact mechanism of the effects of aluminum phosphide in humans is not clear, and it seems that severe cell damage is the main target of the function of aluminum phosphide (ALP). In vitro, phosphine gas has been shown to inhibit cytochrome oxidase C in mitochondria; this enzyme plays an important role in the respiratory system and cellular metabolism, and inhibition of this enzyme causes cellular hypoxia and extensive tissue damage.

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**Table 1: Results of the effect of each of the studied variables on ALT, AST, and ALK enzymes in the study groups**

| Enzyme | Control | Aluminum phosphide | Aluminum phosphide + melatonin | aluminum phosphide + NAC | aluminum phosphide + NAC + melatonin |
|--------|---------|--------------------|---------------------------------|--------------------------|-------------------------------------|
| Plasma |         |                    |                                 |                          |                                     |
| ALT    | 64.52   | 78.5               | 66.2                            | 68.3                     | 60.2                                | 0.021 |
| AST    | 123.06  | 141.7              | 128.1                           | 129.4                    | 120.1                               | 0.045 |
| ALK    | 557.5   | 623.2              | 559.2                           | 561.3                    | 555                                 | 0.046 |
| Liver  |         |                    |                                 |                          |                                     |
| ALT    | 94.8    | 110.6              | 95.6                            | 96.3                     | 94.0                                | 0.035 |
| AST    | 151.4   | 170.2              | 155.0                           | 156                      | 151                                 | 0.044 |
| ALK    | 169     | 191                | 172                             | 174                      | 170                                 | 0.027 |

**Table 2: Evaluation of the concentrations of CAT, GST, and GSH in plasma and liver of mice exposed to research variables**

| Parameter | Control | Aluminum phosphide | Aluminum phosphide + melatonin | aluminum phosphide + NAC | aluminum phosphide + NAC + melatonin |
|-----------|---------|--------------------|---------------------------------|--------------------------|-------------------------------------|
| Plasma    |         |                    |                                 |                          |                                     |
| GST (µmol/hr/ml) | 168.85 | 148.2              | 168.8                           | 165.4                    | 170                                 | 0.042 |
| GSH (µmol/mg tissue) | 181.03 | 168.6              | 175.1                           | 174.2                    | 178.8                               | 0.015 |
| Catalase (µmolH₂O₂/min/mg protein) | 24.36 | 19.2 | 22 | 21.8 | 25.10 | 0.043 |
| SOD (U/ml) | 0.83   | 0.78               | 0.80                           | 0.85                     | 0.82                                | 0.176 |
| Liver     |         |                    |                                 |                          |                                     |
| GST (µmol/hr/mg) | 146.27 | 133.63             | 144.47                          | 148.08                   | 149.88                              | 0.011 |
| GSH (µmol/mg tissue) | 427.7 | 394.4              | 424.6                           | 426.6                    | 428                                 | 0.049 |
| Catalase (µmolH₂O₂/min/mg protein) | 7.15  | 6.13               | 6.9                            | 6.78                     | 7.06                                | 0.012 |
| SOD (U/mg protein) | 7.54  | 7.25               | 8.20                           | 7.8                      | 8.3                                 | 0.194 |
| Kidney    |         |                    |                                 |                          |                                     |
| GST (µmol/hr/mg protein) | 391.1  | 355.5              | 374.8                           | 381.8                    | 387.4                               | 0.043 |
| GSH (µmol/mg tissue) | 144.47 | 135.5             | 141.6                           | 142.2                    | 145.1                               | 0.022 |
| SOD (U/mg protein) | 8.04   | 7.9                | 8                              | 7.95                     | 8.2                                 | 0.125 |
| Catalase (µmolH₂O₂/min/mg protein) | 48.05  | 35.18              | 45.56                           | 46.68                    | 48.5                                | 0.036 |
Electron current disturbance also causes the emergence of free radicals and the destruction of multiple organs. Evidence of toxicity with oxygen free-radicals generated as a result of ALP poisoning has been observed in mice. A similar mechanism could be involved in the pathogenesis of rice tablet poisoning in humans. Phosphine gas also inhibits protein synthesis and enzymatic activity, especially in the mitochondria of heart and lung cells.\[^{18}\]

The present study showed that the use of N-acetylcysteine and melatonin after exposure to aluminum phosphide, possibly through their antioxidant mechanism, reduces the activity of AST, ALT, ALP enzymes in the liver and kidneys, increases the activity of CAT, GST, GSH in plasma, liver, and kidneys, and neutralizes the toxic effects of pH 3 in the cells. A study conducted by Asghari et al.\[^{19}\] showed that aluminum phosphide decreased the activity of glutathione S-transferase (GST), catalase (CAT), and glutathione (GSH) in plasma, liver, and kidney, and increased superoxide dismutase (SOD) and liver enzymes in mice. It has also been shown that the administration of melatonin and N-acetylcysteine, simultaneously or separately, reduces the toxic effects of aluminum phosphide.\[^{19}\] Some studies have reported that phosphine causes cytotoxicity by inhibiting SOD activity and affecting cellular antioxidants.

Mathai et al.\[^{24}\] conducted a study on the changes of liver enzymes in aluminum phosphide poisoning patients that were admitted to Rasht hospital in 2008–2009, and an increase in liver enzymes of one-third of the subjects was reported. Other studies have reported changes in liver enzymes of up to two-thirds or more of the subjects.

NAC is considered one of the most important antioxidants and cellular protective agents against free radicals. NAC acts as an antioxidant by increasing glutathione, and since oxygen free radicals are involved in a wide range of diseases, it can be expected that NAC would be used in a wide range of diseases.\[^{21}\]

In a study by Moghadamnia et al.,\[^{25}\] albino male rats were used to study the effects of various treatments on ALP-infected mice. Sodium selenite had no effect on mortality and survival time; however, it improves pathological findings such as lung and liver complications. Also, N-acetylcysteine (NAC) caused a definite improvement in liver complications. Vitamin C, on the other hand, delayed death, while magnesium sulfate did not alter survival time in ALP-infected mice.\[^{21}\]

In another study by Hsu et al.,\[^{21}\] the effects of melatonin, vitamin C, and beta-carotene on the effects of pH 3 were assessed. PH 3-induced changes were significantly or completely blocked by melatonin, while vitamin C and beta-carotene were less effective or ineffective. This study showed that melatonin is the most effective antioxidant.\[^{28}\] In our study, after the use of melatonin on mice treated with aluminum phosphide, an average of 12 enzyme units of ALT, AST, ALP in plasma and 15 units of ALT, AST, and ALP in the liver were reduced, indicating the effect of melatonin on aluminum phosphide poisoning. These results were consistent with HSU findings.

Also, in a study conducted in 2016 on the effectiveness of lipoic acid on the toxicity of aluminum phosphide, it was found that treatment with aluminum phosphide led to a significant reduction in total plasma protein and glucose and an increase in liver enzymes, phosphatases, urea, creatinine, and bilirubin. Treatment with aluminum phosphide reduced glutathione S-transferase (GST), catalase (CAT), and glutathione (GSH) in plasma, liver, and kidneys. Whereas thiobarbituric acid reactants (TBARS), as an indicator of lipid peroxidation and superoxide dismutase (SOD), increased in plasma and liver of all rats treated with aluminum phosphide. These results are consistent with the results of this study.\[^{24}\]

In a study by Agarwal et al.,\[^{25}\] it was found that NAC, combined with supportive care, may help in improving patients with aluminum phosphide poisoning. In a clinical study conducted by Tehrani et al.,\[^{26}\] it was shown that intravenous NAC administration in patients with acute aluminum phosphide poisoning significantly reduced oxidative stress indices in patients’ serum and also reduced the duration of hospitalization.

In a study conducted by Moghadamnia et al.,\[^{25}\] male rats were used to evaluate the effect of different therapies on ALP-poisoned mice. Sodium selenite had no effect on mortality rate or survival time. However, it improves pathological findings such as lung and liver complications. N-acetylcysteine (NAC) delayed death and resulted in definitive improvement of liver complications. These results were consistent with the findings of this study, which demonstrated the reduction of the activity of AST, ALT, and ALP enzymes in the presence of N-acetylcysteine in mice treated with aluminum phosphide.\[^{22}\]

The present study showed that aluminum phosphide causes liver damage and increases the activity of AST, ALT, and ALP in plasma and the liver. Since the liver is one of the most important target organs for phosphine poisoning in the human body after consumption, phosphine gas is rapidly absorbed in the gastrointestinal tract and is partially transported to the liver by the portal vein. The use of melatonin and N-acetylcysteine after aluminum phosphide poisoning prevents the increase in the activity of liver enzymes, which indicates the protective effect of the studied materials against the toxic effects of aluminum phosphide.

In this study, N-acetylcysteine (NAC) at a dose of 10 mg/kg was shown to improve hepatic manifestations and prevent liver necrosis. This finding has also been demonstrated in some other studies.\[^{21,27,28}\] The NAC also delayed death time for 138 ± 13 minutes on average.\[^{21}\] In our study, the time of death was delayed by 12 hours.

**Conclusion**

The use of N-acetylcysteine and melatonin after exposure to aluminum phosphide, possibly through their antioxidant
mechanism, reduces the activity of AST, ALT, ALP enzymes in the liver and kidneys, increases the activity of CAT, GST, GSH in plasma, liver, and kidneys, and neutralizes the toxic effects of pH 3 in the cells. In this study, although death was the end result in all rats at different times after administration, it was shown that the use of N-acetylcysteine and melatonin (alone or in combination) not only reduce the toxic effects of ALP on the liver and kidneys but also significantly increase the survival time of mice exposed to aluminum phosphide. Therefore, N-acetylcysteine and melatonin can be used as potential agents in the treatment of aluminum phosphide poisoning. However, it is suggested that further studies be performed to determine the optimal dosage and frequency of administration.

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Conflicts of interest
There are no conflicts of interest.

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