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CASE REPORT

Hepatotoxicity due to zinc phosphide poisoning in two patients: role of *N*-acetylcysteine

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Key Clinical Message

Zinc phosphide (Zn_3P_2/ZnP) is used as a rodenticide. The most common signs of toxicity are nausea, vomiting, hypotension, and metabolic acidosis; patients presenting such signs are referred to the emergency department (ED) of the hospitals. Therefore, this study aimed to report two cases of hepatotoxicity following accidental and intentional ZnP poisoning and successful management with *N*-acetylcysteine (NAC).

Keywords

Common signs, hepatotoxicity, *N*-acetylcysteine, rodenticide, successful management.

Introduction

Zinc phosphide (Zn_3P_2/ZnP) is used as a highly effective rodenticide to protect grain from rodents and is usually produced as a dark gray powder [1]. When ingested by accident, through suicidal or homicidal attempts, in the presence of water and acid in the stomach, it transforms into phosphine gas (PH_3) and affects different parts of the body especially the heart, liver, and lungs. Till date, there is no known specific antidote [1]. The estimated mortality rate of ZnP poisoning is around 37–100% [2].

The mechanism of action is similar to aluminum phosphide as both produce PH_3 gas, which inhibits cytochrome C oxidase. However, this inhibition occurs to a lesser extent, in vivo versus in vitro, indicating that impairment at the cellular level could be due to a mechanism other than the inhibition of cytochrome C oxidase, such as catalase (CAT) and peroxidase prevention activity that finally caused lipid peroxidation (LPO), disruption of the mitochondrial system, oxidative respiration, and DNA damage [3].

The most common clinical signs and symptoms of toxicity are nausea, vomiting, abdominal and chest discomfort, profound hypotension, severe metabolic acidosis or mixed metabolic acidosis, respiratory alkalosis, and acute renal failure may occur [3]. Also, some rare complications have been reported such as pulmonary edema [2], acute pancreatitis, transient leukopenia, and transient hyperglycemia [4–6].

Moreover, treatment of ZnP is supportive and symptomatic. The use of activated charcoal is challenging; however, it is recommended that a dose of activated charcoal should be given to poisoned patients as soon as they are received by the emergency department (ED) or clinical toxicology hospital center [7]. In addition, poisoned patients should be placed on a ventilator for cardiorespiratory monitoring in the intensive care unit (ICU) or cardio care unit (CCU). Also, electrolytes and calcium or renal and hepatic functions including the determination of liver enzymes, such as aspartate aminotransferase (AST or SGOT), alanine transaminase (ALT or SGPT), and alkaline phosphatase (ALP), should be monitored daily [7] (Fig. 1). However, a few studies have emphasized on its antidote therapy. Therefore, this study was carried to report the successful treatment of two cases of acute hepatotoxicity due to ZnP ingestion. The cases involved 31- and 20-year-old men who were admitted to the ED with hepatotoxicity, following accidental and intentional ZnP poisoning. Data were obtained from the ZnP-poisoned patients using a questionnaire.

Case Story

In the first case, a 31-year-old young man ingested four tablespoons of ZnP (80%) accidentally. As soon as he realized that it was toxic, he was rushed to a local hospital and received supportive care. After 2 days, the patient was referred to our hospital for further treatment. On admission, the vital signs observed were as follows: BP, 110/80; T, 37.6°C; PR, 80; RR, 23; O_2sat, 96% on ambient air. The patient complained of drowsiness, abdominal pain, vertigo, headache, fever, nausea, vomiting, and diarrhea. On physical examination, icteric sclera and generalized tenderness of the body were detected. Other examinations and electrocardiogram were normal. Laboratory data revealed hepatotoxicity (Table 1). The patient underwent antioxidant therapy with *N*-acetylcysteine (NAC) at a dose of 150 mg/kg in 200 cc DW 5% in 15 min intravenously (IV) as loading, followed by 50 mg/kg in 500 cc DW 5% in 4 h IV, and then 100 mg/kg in 1000 cc DW 5% in 24 h as maintenance. After 24 h, the patient was awake and the results of liver function tests were obviously near normal and as such

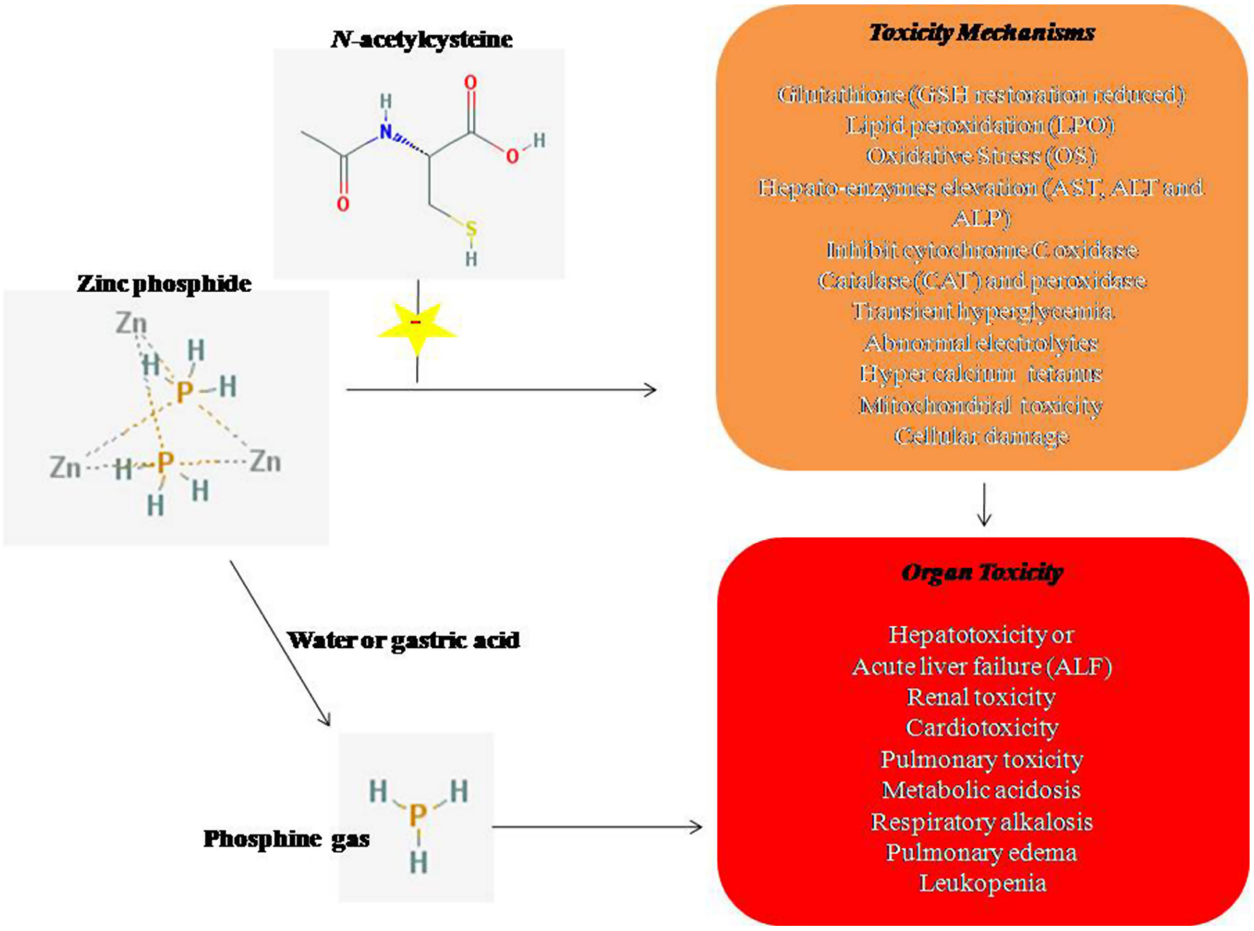

Figure 1. Summarize positive role of N-acetylcysteine (NAC) against Zinc phosphide (ZnP) or phosphine gas (PH_3) poisoning.

the patient was discharged on day 3 with good condition. Thereafter, he was followed-up for 6 days.

Second, during a suicidal attempt, a 20-year-old young man ingested four pockets of ZnP, a few alprazolam and tramadol tablets ($n = 70$). After 12 h, he was found unconscious by family members and therefore admitted in a local hospital where he underwent gastric lavage and conservative therapy. After 4 days, the patient was referred to our hospital due to hepatotoxicity (Table 2). On admission, the following vital signs were observed: BP, 155/90 mmHg; core T, 37.8°C; PR, 111/min; RR, 25/min; O_2sat, 90% on room air. During physical examination, it was observed that the patient woke up with yellow skin and the patient's electrocardiogram revealed sinus tachycardia. Other examinations were normal (Table 3). The patient was subjected to antioxidant therapy with NAC at a dose of 150 mg/kg in 200 cc DW 5% in 15 min/IV as loading and thereafter 50 mg/kg in 500 cc DW 5% in 4 h/IV and 100 mg/kg in 1000 cc DW 5% in 24 h as maintenance. Treatment continued with a dose of 150 mg/kg/daily IV infusion for 3 days. The patient was discharged from hospital on day 4 with good condition and near normal liver function. Thereafter, he was followed-up for 6 days.

Table 2. Laboratory tests in local hospital.

Laboratory parameters	On admission	Day 4
FBS (mg/dL)	116	106
Urea (mg/dL)	20	59
Cr (mg/dL)	1.1	0.6
AST (IU/L)	85	79
ALT (IU/L)	55	149
ALP (U/L)	215	343
Bil-T (mg/dL)	1.8	9.8
Bil-D (mg/dL)	0.4	3.7
PTT (sec)	42	35
PT (sec)	17	15
INR	1.5	1.1
Plt ($\times 10^3$/mL)	171	125
pH	7.32	ND
pCO_2 (mmHg)	38	ND
HCO_3^- (mEq/L)	19.6	ND

ND, not determined.

Discussion

Zinc phosphide (ZnP) or generally metal phosphides has been used as rodenticides. A mixture of food and ZnP is placed where rodents can eat it. However, it may be consumed by humans accidentally or for suicidal purpose [8]. It has been reported that the average age of patients who tried to commit suicide with ZnP was 27 years [1, 9].

Unlike aluminum phosphide and calcium phosphide, ZnP has no specific antidote. In agreement with this study, it has been shown that it could cause acute liver failure (ALF), and when standard conservative treatment fails, the only option to save the life of ZnP-poisoned

Table 1. Serial laboratory findings.

Laboratory parameters	On admission	12 h	Day 1	Day 2	Day 3	Normal range
FBS (mg/dL)	124	129	133	137	129	60–110
Urea (mg/dL)	32	25	21	23	19	15–45
Cr (mg/dL)	0.2	0.4	0.4	0.7	0.7	0.7–1.4
AST (IU/L)	544	ND	232	141	124	Up to 37
ALT (IU/L)	1058	ND	451	385	248	Up to 50
ALP (U/L)	193	ND	172	192	167	80–306
Bil-T (mg/dL)	16.5	ND	8	3.8	3.5	0.1–1.2
Bil-D (mg/dL)	4.6	ND	1.3	1.3	1.2	<0.3
WBC ($\times 10^3/\mu$L)	4.3	5.4	5.8	10.9	9.6	4.8–10.8
Na^+ (mEq/L)	137	141	145	143	ND	135–150
K^+ (mEq/L)	3.5	3.6	3.9	3.9	ND	3.2–5.5
PT (sec)	20	16.7	14.5	12	13	12–14
PTT (sec)	55	34	44	26	31	24–36
INR	2.4	1.6	1.3	1	1	Up to 1
Hb (g/dL)	11.7	11.8	11.6	11	11	14–18
Plt ($\times 10^3$/mL)	200	210	184	153	152	140–450
LDH (U/L)	ND	ND	957	ND	ND	88–230
pH	7.48	ND	ND	ND	ND	7.31–7.41
pCO_2 (mmHg)	42.3	ND	ND	ND	ND	41–54
HCO_3^- (mEq/L)	20.8	ND	ND	ND	ND	19–27

FBS, fasting blood sugar; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; Bil-T, bilirubin-total; Bil-D, bilirubin-direct; WBC, white blood cell; Na^+, sodium; K^+, potassium; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; Hb, hemoglobin; Plt, platelet count; LDH, lactate dehydrogenase; ND, not determined.

Table 3. Laboratory tests in referral center.

Laboratory parameters	On admission	Day 1	Day 3
FBS (mg/dL)	90	ND	ND
Urea (mg/dL)	52	69	39
Cr (mg/dL)	0.4	0.7	0.6
AST (IU/L)	95	177	81
ALT (IU/L)	158	204	187
ALP (U/L)	528	769	839
Bil-T (mg/dL)	10.1	9.4	3.7
Bil-D (mg/dL)	4.2	4.4	1.4
CPK (U/L)	ND	463	ND
PT (sec)	14	13	13
PTT (sec)	35	31	33
INR	1.2	1	1
Hb (g/dL)	11	ND	10.6
Plt ($\times 10^3$/mL)	176	ND	208
pH	7.50	7.48	ND
pCO_2 (mmHg)	37	33.6	ND
HCO_3^- (mEq/L)	29.2	24.8	ND

CPK, creatine phosphokinase (normal range: 24–195 U/L); ND, not determined.

patients with irreversible ALF is liver transplantation [10]. Consistent with this study, other studies have shown that the most common clinical signs of ZnP-poisoned patients include vomiting (100%), abdominal pain (100%), palpitation and sweating (80%), dyspnea and tachypnea (75%), metabolic acidosis (60%), shock (40%), and hypotension (40%) [11]. Furthermore, studies have demonstrated that the levels of ALT and AST as two important hepatic enzymes might be elevated during ZnP poisoning [1, 12]. It is worthy of note that NAC can be used for the treatment of toxicity, especially hepatotoxicity through nonspecific mechanisms that preserve multiorgan functions and diminish liver enzymes elevation, and also for the treatment of hyperbilirubin which resulted from encephalopathy due to hepatotoxicity.

Furthermore, NAC has been shown to prevent organ toxicity including hepatotoxicity by serving as a glutathione (GSH) precursor or GSH restorer, and could be converted to cysteine or mercaptate conjugates in acetaminophen (NAPQI or *N*-acetyl-*p*-benzoquinone imine) or mercury-induced poisoning. Therefore, most poisoned patients who are treated with NAC do not develop hepatotoxicity and have a short duration of hospital stay.

Acute phosphide poisoning (zinc or aluminum) produced PH_3 within 30 min of ingestion in the body, which is extremely toxic and highly irritating to the respiratory tract and also caused severe systemic toxicity. Death may result in less than 6 h due to pulmonary edema, cardiotoxicity, refractory hypotension, cardiogenic shock, and multiorgan failure [13, 14]. Occasionally, there may be a delay in the onset of symptoms by 3 days and therefore, it is suggested that the patient should be placed under observation for at least 72 h after the ingestion of phosphine containing products. Keeping a healthy patient with better prognosis or with no toxicity progression could prevent spending on high-cost medical care or the healthcare system [15]. Until now, the two most current regimes have been defined: a 21-h intravenous (IV) infusion and a second 72-h oral dosing protocol [16–20]. These ZnP toxicities were associated with the release of toxic PH_3, which can be detected in most cases using qualitative silver nitrate paper test [10].

Based on the results of this study, it can be suggested that NAC is a good antidote therapy for saving ZnP-poisoned patients from death or electrolytes abnormality. Till date, only few studies have reported this fact. However, NAC has been demonstrated as a potential antidote for the treatment of thinner and acetaminophen-intoxicated patients or as nephroprotective agent to attenuate chemical or biochemical and electrolytes imbalance [21–23].

Its potential is not just as an antioxidant to increase the GSH levels or as a GSH precursor to prevent cellular or tissue damage, but also to exert its protective effect in part by directly scavenging reactive oxygen species (ROS) or oxygen-free radicals and in part through extracellular regulated kinase1/2 (ERK1/2) signaling pathway [24]. NAC is a source of sulfhydryl groups and a by-product of GSH. It is commonly known due to its cysteine residues and the role it plays in GSH maintenance and metabolism, and also in the provision of remarkable reduction in the LPO of cellular membranes and some other damage that could occur with oxidative stress [25].

In conclusion, ZnP is an effective rodenticide that causes the disruption of cellular and mitochondrial systems through dissuasion of cytochrome C oxidase, as well as LPO due to generation of free radicals, electrolytes abnormality, and changes in essential enzymes of the liver or other organs like the kidney and lung, resulting in organs toxicity such as hepatotoxicity. Unfortunately, there is neither an antidote nor a specific treatment for it. However, NAC has been demonstrated as a supportive substance for the management of ZnP toxicity. Nevertheless, more studies need to be conducted in order to further determine the protective mechanisms of NAC against ZnP or generally the metal phosphides-induced poisoning in patients.

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None.

Conflict of Interest

The authors declare that they have no competing interests.

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