

# Phosphide-induced Liver Injury - The “Drug-induced Liver Injury” Dilemma

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## Abstract

**Introduction:** Phosphide containing rodenticide poisoning is a recognized cause of acute liver failure (ALF). Its treatment has a myriad of obstacles and treatment modalities range from medical (N-acetyl cysteine) to surgical (liver transplantation). We report five cases of drug-induced liver injury (DILI) following ingestion of phosphide containing rodenticide for suicidal purpose and their outcomes.

**Methods:** Retrospective analysis of five cases of the phosphide containing rodenticide poisoning admitted to St. John’s Medical College Hospital during the period of 2015–2017.

**Results:** All five patients were females with median age of 25 years (range 24–31). None had history of alcohol consumption, chronic liver disease, or other comorbidities. All five patients were nursed in intensive care unit (ICU). During the course of stay, all patients had deranged liver function test and coagulation profile. Complications noted during the period were acute kidney injury (80%,  $n = 4$ ), of which three required hemodialysis, worsening metabolic acidosis (60%,  $n = 3$ ) and adult respiratory distress syndrome (40%,  $n = 2$ ) requiring mechanical ventilation. Two patients (40%) recovered with conservative management (N-acetyl cysteine) and three patients (60%) succumbed to their illness in ICU. Average length of stay was 11.2 days (5–21) with recovery noted in patients who presented early.

**Conclusion:** ALF due to DILI affects young individuals and has high risk of morbidity and mortality. As there is no effective antidote, liver transplantation often remains the only lifesaving therapy. Regularly used criteria for transplantation do not address phosphide poisoning, and hence, a scoring model for the same is warranted.

**Key words:** Drug-induced liver injury, Phosphide poisoning, Rodenticide

## INTRODUCTION

Phosphide was first introduced as a pesticide in India. The rate of reported cases of the phosphide poisoning has increased significantly in India over the past few decades due to its ingestion to commit suicide. Deliberate self-ingestion of Zn/AlP is a particular problem in rural parts of India. Easy availability of rat poison has increased incidence of its misuse and most cases of rat poisoning are reported from India.

Phosphide affects different parts of the body, especially heart, liver, and lungs. Patients generally succumb

due to multiorgan failure. Cardiopulmonary collapse and metabolic acidosis are probably the severe most conditions that do not respond to regular treatment. Phosphide containing rodenticide poisoning is a recognized cause of acute liver failure (ALF). Drug-induced liver injury (DILI) can be caused by a multitude of drugs. Suicidal or accidental poisoning is a more frequent cause of drug-induced ALF than paracetamol. Successful treatment of phosphide-induced DILI has multiple roadblocks and treatment modalities ranging from medical therapy (N-acetyl cysteine) to surgical, namely liver transplantation, especially in patients with irreversible ALF.

There is no specific antidote for phosphide poisoning till date and mortality rate is documented to be >70%.<sup>[1]</sup> There are a variety of clinical features associated with phosphide poisoning mostly non-specific, but most patients develop severe metabolic acidosis along with gastrointestinal symptoms.

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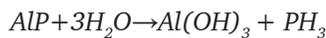
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This study is aimed at reporting five cases of DILI following accidental ingestion of rat poison for suicidal purpose and their management.

**Properties of Phosphide**

Being an ideal seed fumigant, there are no residual toxic hazards and deliver a predetermined amount of phosphine (PH<sub>3</sub>) gas per tablet. It also has an added advantage of not affecting the viability of seeds. The tablets are composed of aluminum phosphide (ALP) as active ingredient and ammonium carbamate/carbonate as the inert ingredient in ratio 56:44, respectively. NH<sub>4</sub> carbamate/carbonate prevents ignition of PH<sub>3</sub> gas.



PH<sub>3</sub> is ideally colorless and odorless, but due to impurities in formulations, the gas develops a specific garlic odor. Toxicokinetics of ALP or PH<sub>3</sub> is not clearly understood and there are no formal experimental animal or human studies on its absorption, distribution, metabolism, and excretion. Ingestion results in contact of phosphides

with moist surface of gastric acid which releases PH<sub>3</sub> gas which gets absorbed through mucosa. Blood PH<sub>3</sub> levels are correlated with clinical grades of toxicity and dose of pesticide and consumed and also with mortality. PH<sub>3</sub> gas is mainly excreted in exhaled air.

ALF due to DILI often affects young persons and carries high morbidity and mortality. As there is no effective antidote for phosphide poisoning, liver transplantation often remains the only lifesaving therapy when patient develops ALF following phosphide poisoning. Traditional scoring models for predicting need for liver transplantation in ALF such as King’s College criteria or Indian criteria do not address phosphide poisoning.

**METHODS**

Retrospective analysis of five cases of the phosphide containing rodenticide poisoning admitted to St. John’s Medical College Hospital during the period of 2015–2017.

**RESULTS**

All five patients were female with a median age of 25 years (range 24–31). No one had history of alcohol consumption, chronic liver disease, or other comorbidities [Table 1]. All five patients were nursed in intensive care unit (ICU).

During the course of stay, all patients had deranged liver function test and coagulation profile [Figures 1 and 2].

Complications noted during the period were acute kidney injury (80%, n = 4), of which three required hemodialysis, worsening metabolic acidosis (60%, n = 3) and adult respiratory distress syndrome (40%, n = 2) requiring mechanical ventilation. Two patients (40%) recovered with conservative management (N-acetyl cysteine) and three patients (60%) succumbed to their illness in ICU [Table 2]. Average length of stay was 11.2 days (5–21) with recovery noted in patients who presented early.

**DISCUSSION**

Acute poisoning with metal phosphides, particularly aluminum phosphide, is a worldwide problem most

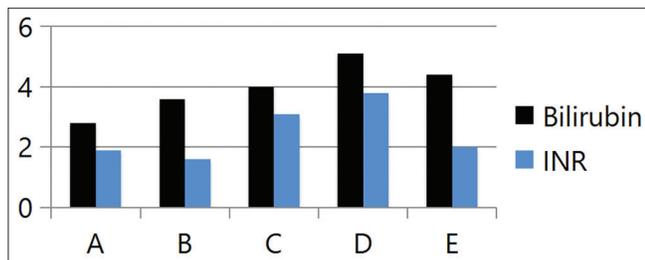


Figure 1: Liver function and coagulation derangements

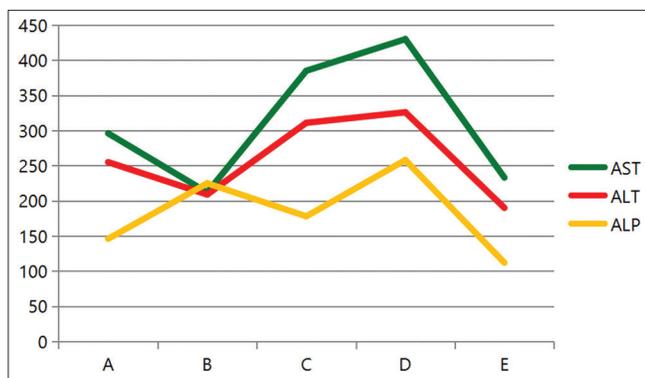


Figure 2: Liver enzymes during admission to intensive care unit

Table 1: Baseline characteristics

| Patient       | 1         | 2      | 3         | 4         | 5         |
|---------------|-----------|--------|-----------|-----------|-----------|
| Age           | 28        | 24     | 24        | 31        | 25        |
| Gender        | Female    | Female | Female    | Female    | Female    |
| Occupation    | Homemaker | Farmer | Homemaker | Homemaker | Homemaker |
| Alcohol       | -         | -      | -         | -         | -         |
| Liver disease | -         | -      | -         | -         | -         |
| Comorbidities | -         | -      | -         | -         | -         |

**Table 2: Morbidity associated and length of stay**

| Patient               | A   | B  | C   | D         | E         |
|-----------------------|-----|----|-----|-----------|-----------|
| Metabolic acidosis    | +   | -  | +   | +         | +         |
| Inotropic support     | -   | -  | +   | +         | +         |
| Complications         | AKI | -  | AKI | AKI, ARDS | AKI, ARDS |
| Length of stay (days) | 13  | 10 | 21  | 7         | 5         |
| Mortality             | -   | -  | +   | +         | +         |

commonly encountered in the Indian subcontinent. The clinical features have been well described though it is only recently that the mechanisms of toxicity have been more clearly understood. Poisoning from phosphides is mediated by  $\text{PH}_3$  which has been shown to rapidly perturb mitochondrial morphology, inhibit oxidative respiration, and cause a severe drop in mitochondrial membrane potential.<sup>[2]</sup> This failure of cellular respiration is likely to be due to a mechanism other than inhibition of cytochrome C oxidase as  $\text{PH}_3$  inhibits cytochrome C oxidase activity less dramatically *in vivo* than *in vitro* and only partially inhibits cytochrome C oxidase activity in humans.<sup>[3]</sup> Phosphine can also form the highly reactive hydroxyl radical and inhibit both catalase and peroxidase, leading to lipid peroxidation. The gas or gases given in addition to  $\text{PH}_3$  when phosphide formulations come into contact with water or acid need to be identified and their toxicity determined.

Phosphide induces ALF by increasing the activities of aspartate aminotransferase (AST), alanine aminotransferase, and ALP in both plasma and liver.<sup>[4]</sup> Liver is one of the important target organs of  $\text{PH}_3$  poisoning in the human body. After ingestion,  $\text{PH}_3$  gas is rapidly absorbed through the gastrointestinal tract and it is partly carried to the liver by the portal vein.<sup>[5]</sup> Phosphine can cause liver dysfunction, especially after the 1<sup>st</sup> day of poisoning.

Transient elevations of alanine aminotransferase and AST activities are common after ingestion of metal phosphides, but jaundice secondary to liver damage is much less common.<sup>[6]</sup> Jaundice was alleged to be present in 100% of cases who ingested  $\text{PH}_3$  with suicidal intent associated with elevated serum bilirubin concentrations and transaminase activities. Acute hepatic failure and multiple organ dysfunction syndrome were considered to be the cause of death in two patients.

The observation that  $\text{PH}_3$  may inhibit acetylcholinesterase activity needs to be investigated further as does the report that the administration of atropine and pralidoxime reduces morbidity and mortality in phosphide poisoning. There is conflicting evidence also on the occurrence and clinical importance of magnesium disturbances which some have described. The benefit of magnesium supplementation has still to be determined.

## CONCLUSION

ALF due to DILI often affects young individuals and has a high risk of morbidity and mortality. There is an increasing need for improved knowledge of these risks with an emphasis on recognition, management, and prevention. The fast progression to life-threatening symptoms, ineffective therapeutic ways to solve its intoxication and limited data on the efficacy of therapeutic interventions pose challenges to the clinicians and emergency staffs.

As there is no effective antidote for phosphide poisoning, liver transplantation at the earliest often remains the only lifesaving therapy for severe ALF. Regularly used criteria for transplantation do not address phosphide poisoning, and hence, a scoring model for the same is warranted. People handling this fumigant must be aware of its lethal aspects. They should be prohibited from keeping and using this poison at the home. They should be advised to cover the tablets in open fields after use. They should keep their tablets away from the reach of children and other family members. Official health-care system should restrict the open sales of this pesticide. Vendors and shopkeepers should not sell the tablets to young people and children without proper verification and confirmation and strict regulations should be instituted for confirming the compliance toward the same.

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