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Review Article

Plasma Exchange as an Effective Treatment for Severe Copper Sulphate Poisoning: A Review of Copper Sulphate and Zinc Phosphide Poisoning

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ABSTRACT

Copper sulphate and zinc phosphide poisoning can have profound fatal effects on multiple organ systems and present significant challenges in clinical management.

We report a case of a 24-year-old female who developed methaemoglobinemia following acute poisoning from copper sulphate and zinc phosphide. In spite of initial treatment with methylene blue, vitamin C and D-penicillamine, the patient continued to experience haemolysis. Based on the available evidence, plasma exchange therapy was administered to address the persistent haemolysis. Significant improvement in haemolytic parameters were seen post treatment, showing a positive response to plasma exchange.

The case presented here underscores the importance of a multidisciplinary approach in managing complex poisonings and highlights the potential effectiveness of plasma exchange as an adjuvant therapy for treating haemolysis caused by severe copper sulphate poisoning.

To the best of our knowledge, this is the first documented case of combine copper sulfate and zinc phosphide poisoning worldwide.

Keywords: Copper poisoning; Zinc poisoning; Plasma exchange; Methaemoglobinemia; Intravascular haemolysis

INTRODUCTION

Copper sulphate and zinc phosphide are two chemical substances despite serving a variety of industrial and agricultural purposes, can pose significant health risks if handled or consumed improperly.

Salts containing copper are commonly used in the leather industry and as pesticides in agriculture. Copper sulphate is one of the most widely available copper salts in Sri Lanka, also known as “Palmanikkam” in native language. However, copper sulphate is a less commonly reported cause of suicide than other chemicals like organophosphates. A dose of copper sulphate greater than 1 g causes toxicity. The main clinical manifestations are due to methaemoglobinemia, gastrointestinal tract erosions, intravascular haemolysis and acute kidney injury. Ultimately, multi-organ failure occurs as a result of circulatory collapse [1].

Zinc phosphide is a potent toxin used in commercial rodenticides and pesticides, which is commonly used to protect crops during storage and transportation. Due to its low cost, the compound is easily accessible to subsistence farmers in the tropics. Through the production of phosphine gas, zinc phosphide manifests its immediate toxicity through nausea, vomiting, dyspnea and immediate death due to pulmonary edema. In addition to the immediate effects, delayed effects accompany the absorption of phosphide, primarily affecting the liver, heart and kidneys.

Treatment of zinc phosphide poisoning is mainly supportive. There are three main approaches to treating copper sulphate poisoning: Absorption reduction, chelation and supportive symptomatic treatment.

We share our experience in treating a patient with concomitant self-ingestion of copper sulphate and zinc phosphide in suicidal intention and discuss clinical features and management issues [2].

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LITERATURE REVIEW

A 24-year-old previously healthy female patient admitted following self-ingestion of copper sulphate 20 g with zinc phosphide 35 g (rat poisoning) with suicidal intention following a dispute with her boyfriend. She was admitted to national hospital Kandy about 30 minutes later, after her mother found out about the incidence due to vomiting.

On admission to Kandy hospital, the patient had loose stools and vomiting indicative of Gastrointestinal (GI) distress. She was hypotensive on admission with a blood pressure of 80/60 mmHg and tachycardia of 104 bpm.

Haemodynamic parameters were improved following a normal saline bolus. Her saturation was 76% on room air and improved only up to 86%-88% with 15 L of oxygen. Other systemic examination findings were unremarkable.

Activated charcoal was administered to reduce the absorption of ingested toxins. There was a partially compensated metabolic acidosis in Arterial Blood Gas (ABG) with pH 7.32, PO_2 of 212.4 mmHg, PCO_2 23 mmHg, lactate 3.8 mmol/L, bicarbonate of 12.5 mmol/L and oxygen saturation 99.6%. Haemoglobin (Hb) was 15.2 g/dl. Saturation discrepancy in pulse oximeter and ABG was suggestive of methaemoglobinemia in the context of copper sulphate poisoning and Intra Venous (IV) methylene blue 2 mg/kg (80 mg) were administered. Later the patient was transferred to the toxicology Intensive Care Unit (ICU) of Teaching Hospital Peradeniya (THP) for specialized toxicology management [3].

Repeat ABG at THP revealed pH 7.30, PO_2 250 mmHg, PCO_2 26 mmHg, lactate 2.8 mmol/L, bicarbonate 14.3 mmol/L and oxygen saturation of 99%. Oxygen saturation with 15 L of oxygen was 87%. Methylene blue 80 mg was repeated due to persistent methaemoglobinemia. Supportive treatment with hydration, anti-emetics and Proton Pump Inhibiter (PPI) were started to alleviate her GI symptoms. As we did not have co-oximetry, Meth Hb level was checked with bed side colorimetric chart and was 12%. Additionally, she was started on oral D-penicillamine 500 mg 6 hourly as a copper chelating agent.

The following day, the patient developed haematuria and melaena, indicating potential damage to the gastrointestinal and genitourinary systems. The haemoglobin level significantly dropped from 15 g/dL to 10 g/dL needing urgent blood transfusion.

Despite supportive measures, the patient's renal and hepatic functions began to deteriorate rapidly, indicating multi-organ involvement and systemic toxicity. By the 2nd day of admission, her GCS started to deteriorate gradually from 15 to 12. Clinical and biochemical parameters were suggestive of hepatic encephalopathy and she was placed on a hepatic encephalopathy regimen, which included rifaximin 550 mg twice daily and IV ceftriaxone 1 g daily, by day two. Due to deterioration of her GCS, she was intubated on day three [4].

In spite of adequate fluid management, she gradually became oliguric and her serum creatinine, which was normal on admission, rose to 235U/L (normal 0-40) by day 3. She also had hyperkalemia and metabolic acidosis, poorly responding to medical management. A nephrology team was consulted to manage renal failure and haemodialysis was started by day four.

Throughout this period, she had ongoing haemolysis, indicative of a drop in Hb despite regular, frequent blood transfusions.

Despite adequate treatment, we were unable to resolve the cause of the ongoing haemolysis. A patient with methaemoglobinemia may experience persistent haemolysis as a result of underlying Glucose-6-Phosphate-Dehydogenese (G6PD) deficiency when high doses of methylene blue are administered. But our patient received only 2 doses of methylene blue which is below the toxic levels (7 mg/kg). So, methylene blue toxicity was unlikely here. We were unable to check her G6PD levels due to unavailability of the resources.

In view of persistent haemolysis, the haematology team was consulted. G6PD levels could not be measured due to the unavailability of the resources and blood picture findings were also inconclusive in the context of acute haemolysis. Folic acid 5 mg daily dose and IV vitamin C 100 mg twice daily were started on her following haematology opinion, for possible G6PD deficiency. However, the ongoing haemolysis could not be stopped and the Hb level continued to decline.

In an effort to assess the possibility of conducting an exchange transfusion, we sought the advice of a transfusion specialist. Her methaemoglobin levels were consistently below 12%. This did not warrant the use of exchange transfusion. In an effort to identify a successful therapeutic option for ongoing haemolysis, similar clinical cases that had been successfully treated with Total Plasma Exchange (TPE) were identified.

Based on available evidence, TPE arranged on day three with liaison to transfusion team. A significant improvement was noted in haemolytic parameters following three cycles of TPE, including stabilization of haemoglobin without the need for blood transfusions. A total of five cycles of TPE were performed, leading to a remarkable recovery [5].

Following the completion of four cycles of HD along with supportive therapy, renal function improved. She received a total of 8 pack red cell transfusion. The patient made a good recovery and was discharged from the hospital after 16 days of hospitalization.

DISCUSSION

Copper is an important cofactor for oxidative enzymes such as peroxidase, catalase, G6PD, glutathione reductase and cytochrome oxidase in the human body. It has a vital role in protecting cells from oxidative stress. There are two forms of copper found in serum: Copper bound to ceruloplasmin (93%) and copper bound to albumin (7%). Fecal excretion through enterohepatic circulation is the primary mechanism of excretion, while urine excretion accounts for approximately 4% of total excretion.

Due to its powerful oxidizing properties, copper sulphate exerts its toxic effects predominantly through oxidative damage. Poisoning primarily affects red blood cells, Gastrointestinal

system (GI), kidneys and cardiovascular system. Ingestion of 10 g to 20 g of copper have been associated with high mortality rate.

As can be seen in the case of our patient, oral ingestion has immediate effects on the GI system manifesting as erosive gastroenteritis with nausea, vomiting, loose stools and melaena. Two major haematological manifestations of copper sulphate include intravascular haemolysis and methaemoglobinemia. Intravascular haemolysis occurs as early as 12 to 24 hours following ingestion as we observed in our patient. The condition can occur as a result of direct toxicity to the cell membrane and oxidative damage caused by the inhibition of glutathione reductase. The copper ion oxidizes the ferrous ions to ferric ions in Hb resulting in formation of methaemoglobin. This manifests as cyanosis and tissue hypoxia [6].

Acute renal failure is a much commoner manifestation of copper poisoning occurs in about 20% to 40% of patients usually observed after 48 hours of ingestion. Mechanisms include acute tubular injury due to direct toxicity, haemoglobinuria, rhabdomyolysis and prerenal hypotension. In severe poisoning as in our patient, hepatic failure can occur due to oxidative damage as liver is the major storage for copper. Cardiovascular collapse and rhabdomyolysis were also reported with severe copper poisoning.

Our patient ingested zinc phosphide with copper sulphate, which has milder symptoms than copper. The reaction between zinc phosphide and water, moisture in the air or hydrochloric acid in the stomach results in the release of phosphine gas, which is rapidly absorbed by the gastrointestinal tract and lungs. Phosphine inhibits cytochrome C oxidase, causing mitochondrial oxidative phosphorylation to be inhibited, leading to histotoxic hypoxia. Common symptoms of toxicity include GI symptoms manifesting as vomiting and loose stools. Less commonly liver failure and respiratory symptoms also reported with zinc phosphide poisoning. Intravascular haemolysis is reported as a rare presentation of zinc phosphide poisoning.

Although zinc phosphide can result in life-threatening complications, neither a specific treatment nor an antidote have been discovered yet. Management is mostly supportive till phosphene gas is excreted from the body. However, a study done in Egypt, to evaluate the role of vitamin C in oxidative stress due to zinc phosphide poisoning, concluded that vitamin C has potential benefits from its antioxidant properties on zinc phosphide induced oxidative stress [7].

The management of copper sulphate poisoning requires a more comprehensive approach than that of zinc phosphide poisoning which includes absorption reduction, chelation and symptomatic treatment.

If the patient is conscious and cooperative and is present within 4-6 hours, dilution of the gastric content can be accomplished by using water and milk. As copper is a corrosive agent emesis and gastric lavage should be avoided. Activated charcoal can be administered within 1 to 2 hours after ingestion, though it has not been proven to be beneficial but is unlikely to cause harm.

Copper chelators includes D-penicillamine, British Anti Lewisite (BAL), Ethylene Diamine Tetra Acetate (EDTA) and 2-3-Dimercapto-1-Propane Sulphate (DMPS). Although their use has been primarily studied in chronic poisoning, there is limited data regarding their efficacy in acute poisoning.

In the event of methaemoglobinemia, methylene blue (1 mg/kg-2 mg/kg) is the antidote and can be repeated if cyanosis persists after one hour. A high dose of methylene blue (more than 7 mg/kg) itself can cause haemolysis and is contraindicated in G6PD deficiency. Vitamin C and hyperbaric oxygen can be used as alternatives if methylene blue is ineffective. However, the clinical experience with vitamin C is limited and it may only have a small effect on increasing methaemoglobin reduction. Additionally, methylene blue action requires intact erythrocytes, so severe haemolysis may render it ineffective as seen in our patient. The use of exchange transfusions and/or packed red blood cells may be useful in cases of methylene blue failure [8].

Insufficient dose of methylene blue, inadequate decontamination and NADPH dependent methaemoglobin reductase deficiency are other possible reasons for failure of methylene blue therapy.

Copper sulphate and zinc phosphide were ingested simultaneously in this case. It was found that both substances induce haemolysis through oxidative stress. Hence, the synergistic effect of these toxins might be responsible for the persistence of haemolysis despite treatment in our patient [9].

Phosphine gas is rapidly expelled from the body. Therefore, expediting the removal of copper could arrest haemolysis. Because copper is largely eliminated through bile flow, the kidneys play a relatively small role in removing copper. Due to this, haemodialysis alone does not effectively remove copper sulphate, which binds to plasma proteins and is then rapidly stored in liver, erythrocytes and muscles.

Therapeutic Plasma Exchange (TPE) has been identified as an effective means of removing copper bound to plasma proteins. The goal of this intervention is to mitigate the risk of tissue deposition of copper and associated complications, thereby reducing morbidity and mortality.

According to available evidence, our patient underwent TPE, which resulted in a notable improvement in haemolysis [10].

CONCLUSION

Despite being less commonly reported, copper sulphate poisoning carries a significant mortality risk if not treated appropriately. This case illustrates the utility of therapeutic plasma exchange in managing copper sulphate poisoning complicated by zinc phosphide poisoning, particularly when persistent haemolysis is present. Here we highlight the importance of awareness, prompt intervention and collaboration among healthcare professionals in managing rare but potentially lethal toxicological emergencies.

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