Intravascular Hemolysis, Methemogolbinemia and Acute Renal Failure in a Young Female

Abstract

Copper sulfate occurs as large blue crystals in nature, commonly known as "blue vitriol" or "blue stone." It is a potentially lethal poison with significant mortality. Copper sulfate is a powerful oxidizing agent and causes corrosive injury to the mucous membrane. The clinical course involves intravascular hemolysis resulting in anemia, jaundice, and renal failure. Laboratory diagnosis of the condition is not an issue; the difficulty is suspecting it, promptly initiating chelation therapy, and other supportive symptomatic treatment. We present a case of copper sulfate poisoning in a young female with suicidal intent resulting in severe acute toxicity, which was successfully managed by copper chelator (d-Penicillamine) and other supportive measures.

Keywords: *Acute renal failure, copper sulfate, intravascular hemolysis, methemoglobinemia*

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Introduction

Copper sulfate is a rare mode of poisoning except in the Indian subcontinent where it is commonly used as a pesticide, in the leather industry and in making glue. Further, burning of copper sulfate is a common practice here for religious activities. Mostly suicidal, but occasional accidental poisoning has been reported in children due to the attractive marine blue colour of its hydrated form. The clinical course of this rare form of poisoning is often complex, ranging from only gastrointestinal symptoms in mild intoxication to gastrointestinal bleeding, intravascular hemolysis, hemoglobinuria, acute kidney injury, and even death in severe cases. Among those who develop renal failure, the mortality rate is high.[1] As a result of the decline in the incidence of this poisoning, clinicians have become unfamiliar with manifestations, complications, and management of this once common entity.

Case Presentation

A 26-year-old female was admitted with complaints of nausea, vomiting, and restlessness with a history of suicidal consumption of a blue-colored liquid approximately 6 hours back after an altercation with her husband. On further questioning, she told that she drank some liquid called "Neela Thotha," which is a commonly available commercial preparation of copper sulfate solution. On examination, she had a bluish hue of tongue with bluish-colored vomitus and bluish staining of her clothes. She had a pulse rate of 116/min and blood pressure (BP) 80/60 mm Hg. She was conscious, alert, not pale, jaundiced or cyanosed, and not in respiratory distress. However, her oxygen saturation (SpO_2) was 88% on room air, while arterial blood gas analysis showed SpO_2 was 99% on room air. This is indicative of methemoglobinemia (methHb), which was found to be raised—4.3% in the arterial blood gas (ABG) done in emergency on presentation. Chest examination was normal, and abdomen examination revealed mild tenderness in the epigastrium. She was admitted to ICU and was managed with IV fluids, proton pump inhibitor, and other supportive measures. Initial laboratory results were hemoglobin- 11.6 gm/dl, white cell count- 12.5 x 10^3, serum creatinine- 0.6 mg/dl, aspartate transaminase (AST)- 28 U/L, alanine transaminase (ALT)- 5 U/L, and lactate dehydrogenase (LDH)- 249. Quantitative methHb levels were sent. Oral penicillamine 500 mg thrice a day was started as a copper chelator. Pantoprazole infusion and oral

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sucralfate were administered to reduce gastrointestinal symptoms and prevent bleeding complications. High flow of warm humidified oxygen through a nasal cannula at a flow rate of 55 l/min and a fraction of inspired oxygen (FiO_2) of 70% was given. IV methylene blue was administered at a dose of 100 mg over 15 min together with oral vitamin C 500 mg twice daily.

On day 3, her hemoglobin dropped to 8.6 together with a rising white cell count (TLC- 26000), LDH (910), creatine phosphokinase (CPK, 535), AST (229), and worsening kidney functions (urea- 37, creatinine- 1.7). The next day, her hemoglobin dropped to 6.8, creatinine rose to 2.4, and she developed icterus as evidenced by rising bilirubin (total bilirubin: 2.1, indirect bilirubin: 1.9). Urine output was good. The same day, she started passing cola-colored urine and urinalysis revealed protein +++, 8 red blood cells. Urinary free hemoglobin was positive, and peripheral smear showed contracted, crenated, and fragmented red cells, features typical of intravascular hemolysis. Interval endoscopy was done due to persistent vomiting and to look for blood loss which revealed denuded mucosa in the proximal stomach with erosions, large ulcer in the mid-body along the greater curvature extending up to pylorus with whitish black slough covering it. Stool occult blood could not be done due to constipation. Oral sips of water were continued along with a cold bland diet. Her hemoglobin dropped to 5.7 in spite of blood transfusion. Nephrologist opinion was also taken due to worsening kidney functions.

Her methHb was monitored on daily basis through daily arterial blood gas analysis which showed a progressive rise for the next 3 days to a maximum of 8.6 on day 6; thus, methylene blue was administered daily for the next 3 days following which her methHb started to come down to 4.9 and 2.9 respectively on day 7 and day 8, coinciding with improvement in her saturation gap. She made a good clinical recovery and was discharged on day 10 after admission. She had no further complications, and her blood parameters were with normal limits in a follow-up 2 weeks later.

Discussion

Copper is a trace element essential for human life. The total body content of copper is 150 mg, maximum concentrations of which are in the heart, muscles, brain, kidney, and liver.[1] In blood, 90% of it is bound to ceruloplasmin. The free form of copper, weakly bound to albumin, is the toxic form and is responsible for cell damage through the formation of free radicals and inhibition of enzymes, most importantly glucose-6phosphate dehydrogenase (G6PD). The most common route of intoxication is oral; however, intravenous, cutaneous, and even intrauterine routes have been reported.[2,3] Ingestion of more than 1 gm of copper sulfate results in toxic manifestations,[4] whereas the lethal dose of ingested copper sulfate is 10–20 gm.[5]

The clinical manifestations of copper sulfate poisoning include erosive gastropathy, intravascular hemolysis, methemoglobinemia, hepatitis, acute kidney injury, and rhabdomyolysis. The earliest and most frequent symptom of copper sulfate is vomiting, hematemesis, melena, and diarrhea. A characteristic sign is bluish vomiting.[6] Copper is directly toxic to gastric and intestinal mucosal cells, causing ulcerations. These symptoms seem to be unrelated to the mode of poisoning, whether oral or parenteral.[4,7,8] This is closely followed by liver injury in the form of hepatomegaly, icterus, transaminitis, and elevation of prothrombin time. Acute liver failure may occur due to direct toxicity of copper sulfate and usually occurs in severe poisoning.

Two major hematological complications of copper sulfate poisoning are intravascular hemolysis and methemoglobinemia.[1] Copper is known to produce hemolysis by damaging the red cell membrane, denaturation of hemoglobin, Heinz body formation, or by inhibiting cellular metabolism. Inhibition of enzymes responsible for protecting the red blood cells against oxidative stress, mainly G6PD and glutathione reductase, has been postulated as the major pathophysiology behind copper-induced hemolysis.[9,10] Intravascular hemolysis has been usually described to occur as early as within the first 24 h after ingestion, but this patient developed hemolysis around day 3–4 as evidenced by fall in hemoglobin and rise in bilirubin, reticulocytosis, and presence of crenated, fragmented red cells in the peripheral blood smear.[1] We did not investigate the plasma copper levels as the diagnosis was obvious by history and clinical examination. Also, as described by Chuttani *et al*., 1963, and Ivanovich, Manzler, and Drake, 1969, there appears to be no correlation between serum copper levels and production of intravascular hemolysis.[11,12]

Methemoglobinemia is hemoglobin in which oxidized iron has been transformed from the ferrous state (Fe++) to the ferric state (Fe+++) as a result decreasing the oxygen-binding capacity and hampering the release of oxygen to cells.[13] This shifts the oxygen curve to the left. Methemoglobinemia is asymptomatic below 10%. At high levels, the patient may have tissue hypoxia despite adequate oxygenation and hemoglobin levels an entity commonly called functional anemia. The presence of normal arterial pressure of oxygen but a low SpO_2 is called saturation gap and is an indication of methemoglobinemia.[13,14] Cyanosis is usually noted at levels above 15%, and chocolate brown color of blood is usually indicative of levels between 15% and 30%.[15] Levels above 50% may result in central nervous system depression, cardiac arrhythmias, and death.[16] Other more common causes of methemoglobinemia include poisoning with dapsone or amyl nitrites through the use of poppers.[17]

About 40% of cases of acute copper sulfate poisoning are complicated by acute kidney injury (AKI).[16] Several

pathophysiological mechanisms could be involved in the development of AKI which may include myoglobinuria, hemoglobinuria, direct toxicity of copper, and hypovolemia related to gastrointestinal symptoms. In a study by Chugh *et al*. on 29 patients with acute copper sulfate poisoning, intravascular hemolysis played a major role in the copper intoxicated patients. From the observations made by them, renal failure developed in 11 of 17 patients (64.7%) who showed hemolysis; none of the 12 without hemolysis developed renal failure. The second factor that seems to be relevant in the above study is the direct toxic action of the metal on the kidney as copper released from the hemolyzed RBC is deposited in the tubular epithelium of the kidney. Pre-renal causes such as severe vomiting, diarrhea, lack of replacement fluid, and gastrointestinal bleeding were significant only in two patients. Free hemoglobin levels in the plasma of above 200 mg/dl have been reported to be particularly toxic to the renal tubular cells as postulated by Yeh *et al*., 1964.[18] In the presence of factors such as dehydration, hypotension, and anoxia, which in themselves may not be significant, even smaller amounts of free hemoglobin may produce AKI. All these factors are invariably present in cases of copper sulfate poisoning. Acute liver injury occurs early in copper poisoning as the majority of absorbed copper is deposited in the liver after being delivered from the portal circulation, usually occurring in severe poisoning as a result of direct toxicity. The above patient had a mild elevation of transaminases with relative sparing of alanine transaminase.

Following the initial resuscitation and stabilization, further management of copper sulfate poisoning involves absorption reduction, chelation, and supportive symptomatic treatment. The absorption of toxin can be reduced by vigorous dilution with milk and water or by administration of activated charcoal (50 gm in 200 ml water, which may be repeated at 6-h intervals).[19] Emesis must be avoided as repeated exposure of the esophagus to the corrosive agent may inflict further damage on the mucosa. All complications mentioned above must be monitored for the first 24 h onwards.

Anemia from hemolysis or bleeding must be corrected with transfusion of red cell concentrates. Methemoglobinemia is treated with methylene blue at a dose of 1–2 mg/kg/dose and repeated if cyanosis persists beyond 1 h. High doses of methylene blue can cause hemolysis and hence is contraindicated in G6PD deficiency. Causes of failure of methylene blue treatment include an inadequate dose of methylene blue, G6PD deficiency, and NADPH-dependent methemoglobin reductase deficiency.[20] Another important point to be considered is that methylene blue action requires intact erythrocytes, and if there is hemolysis as in our patient, it may be ineffective. Alternatives to methylene blue in such situations include hyperbaric oxygen and ascorbic acid. Our patient received a combination of ascorbic acid (500 mg 12 hourly), methylene blue, and high-flow warm humidified oxygen through a nasal cannula at a flow rate of 55 l/min and FiO_2 of 70%.

Renal failure must be recognized promptly through the measurement of kidney functions and urine output. Good hydration oral or intravenous fluid therapy is needed to prevent or treat renal failure. Hemodialysis is not very helpful for the removal of copper. The evidence so far available suggests that removal of copper by dialysis is certainly indicated in the early stages of poisoning when the metal is still present in the circulation as free copper. Hemodialysis is still an essential requirement for the management of AKI and its complications often associated with this poisoning.[1] Peritoneal dialysis may be an option when hemodialysis facilities are not available as copper was recovered from the dialysate during peritoneal dialysis in one patient who was admitted within 2 h of ingesting copper sulfate. Our patient recovered without the need for dialysis.

Chelation therapy in copper sulfate poisoning aims at removing ingested copper from the body. The efficacy and data of these chelating agents are unproven and lacking.[7] These agents chelate copper and promote its elimination through the urinary tract and hence its use in anuric patients is controversial as they have been successfully used in some cases reported to be anuric.[21] The rationale behind using chelators is that hemodialysis can filter copper-bound chelators. Penicillamine is a commonly used chelating agent at a dose of 1–1.5 mg/d in 2–4 divided doses.[1] Our patient received oral penicillamine and it was well tolerated. It must be used carefully in places without renal replacement therapy as penicillamine is nephrotoxic. If oral penicillamine is not tolerated or contraindicated due to corrosive injury, intramuscular dimercaprol or British anti-Lewisite (BAL) can be administered. The duration of chelation therapy is not established by evidence. It is recommended to treat with chelators as long as the serum copper level remains above normal. The literature also reports cases successfully treated with plasmapheresis,[22] and more recently, the use of venovenous extracorporeal membrane oxygenation (ECMO) for treatment of acute respiratory distress syndrome secondary to copper sulfate poisoning.[23]

To summarize, copper sulfate poisoning remains rare, but it causes significant mortality and morbidity. It must be promptly recognized to quickly start appropriate treatment and manage complications. Treatment involves administering chelators and symptomatic treatment, along with a multidisciplinary approach involving a gastroenterologist and a nephrologist.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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