

# Acute ingestion of copper sulphate: A review on its clinical manifestations and management

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## Abstract

Ingestion of copper sulphate is an uncommon mode of poisoning in the Indian subcontinent. Cases are mainly suicidal in nature. The clinical course of the copper sulphate intoxicated patient is often complex involving intravascular hemolysis, jaundice and renal failure. The treatment is mainly supportive. In severe cases methemoglobinemia needs treatment. Mortality is quite high in severe cases. A comprehensive review of the clinical presentation and management of copper sulphate poisoning is done.

**Key words:** Acute ingestion, copper sulphate, poisoning

## Introduction

Copper sulphate forms bright blue crystals containing five molecules of water [CuSO<sub>4</sub>·5H<sub>2</sub>O]. It is commonly known as “Blue Vitriol” or “Blue Stone”. It is used chiefly for agricultural purposes as a pesticide and in leather industry. It was also being used as a precipitator in heavy metal poisoning and was used to treat gastric and topical exposure to phosphorous. It has a nauseous and metallic taste. Solutions are acid to litmus, freely soluble in water.<sup>[1,2]</sup> It is consumed mainly with suicidal intentions. Accidental poisonings have been reported from children as well.<sup>[3-7]</sup>

The incidence of copper sulphate poisoning varies at different geographical areas depending on the local use of copper sulphate and the availability of other suicidal poisons. Its incidence is reported to be 34% and 65% of the total poisoning cases in two studies from Agra and New Delhi in 1960's. The mortality rates vary from 14-18.8%.<sup>[8,9]</sup> In another study from Aligarh in 1970's, it

was the commonest mode of poisonings at that center accounting to 118 cases over four and a half years.<sup>[10]</sup> However, the incidence of copper sulphate poisoning is declining in certain parts of India. Chugh *et al.*, reported a decrease in the number of cases of acute renal failure attributed to intentional copper sulphate ingestion among patients admitted to a renal unit in northern India over a period of three decades from five per cent in the 1960s to one per cent in the 1980s.<sup>[11]</sup> In another autopsy series from north India, copper sulphate ingestion was responsible for 22% of deaths due to poisoning from 1972 to 1977.<sup>[12,13]</sup> However, it declined to 3.85 and 3.33% between 1977-1982 and 1982-1987 respectively. Pediatric cases of copper sulphate ingestion are rare, with only few case reports available in literature.<sup>[4-7]</sup>

As some of the clinicians are faced with unfamiliarity when challenged to manage the cases of copper sulphate poisoning, we have attempted a comprehensive review on the clinical manifestations and management of copper sulphate poisoning.

## Kinetics of Copper

The total body content of copper is 150 mg.<sup>[14]</sup> Approximately 30% is absorbed from the gastrointestinal tract.<sup>[15]</sup> In blood, copper is initially albumin-bound and transported via the hepatic portal circulation to the liver

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where it is incorporated into ceruloplasmin (an alpha globulin synthesized in hepatic microsomes). Copper is present in serum in two forms; 93% is tightly bound to ceruloplasmin and 7% is loosely bound to albumin.<sup>[14]</sup> The copper-albumin complex represents the toxicological active portion of the serum copper.<sup>[1]</sup> Systemic transport of copper from liver is primarily as ceruloplasmin, which appears to donate copper to tissues. Copper is distributed to all tissues with the highest concentrations in liver, heart, brain, kidneys and muscle. Intracellular copper is predominantly bound to metallothionein. Copper is found extensively in red blood cells as erythrocytine and other proteins. Fecal and biliary excretion accounts for 80 percent of excreted copper. Approximately four percent is excreted in the urine.<sup>[15]</sup> The average half-life of copper in a healthy individual is estimated to be 26 days.<sup>[16]</sup>

The kinetics of copper during over dose differs from that during the normal. The gastrointestinal absorption varies with the copper intake and it can be as low as 12% in patients with high copper intake. However, in the presence of damaged mucosa following acute overdose, the fractional absorption is likely to be higher.<sup>[17]</sup> In acute poisoning, albumin, rather than ceruloplasmin, binds the excess copper. The liver is the major site of deposition of copper following large ingestion, with most of the copper bound to metallothionein. The copper content in normal adult liver ranges from 18-45 mg/g dry weight. When the concentration of hepatic copper is greater than 50 mg/g dry weight, liver cell necrosis occurs with release of large amount of copper into the serum. This released copper is rapidly taken up by erythrocytes and results in oxidative damage and may result in hemolysis of RBCs.<sup>[1]</sup> This may account for the delayed secondary episode of hemolysis that occurs in some copper sulphate poisoning patients.<sup>[17]</sup>

### Mechanism of Toxicity

Copper sulphate is a powerful oxidizing agent, which is corrosive to mucous membranes. Concentrated solutions are acidic with pH 4. Cellular damage and cell death may result from excess copper accumulation. It is proposed that free reduced copper in the cell binds to sulfhydryl groups and inactivates enzymes such as glucose-6-phosphate dehydrogenase and glutathione reductase.<sup>[18]</sup> In addition copper may interact with oxygen species (e.g., superoxide anions and hydrogen peroxide) and catalyze the production of reactive toxic hydroxyl radicals. Lethal

dose is about 10-20 g.<sup>[14]</sup>

### Pathology of Copper Sulphate Poisoning

Main brunt of copper toxicity is borne in the order by the erythrocytes, the liver and then the kidneys.<sup>[19]</sup> Intravascular hemolysis appears 12-24h following ingestion of copper sulphate. Hemolytic anemia, is caused either by direct red cell membrane damage or indirectly as a result of the inactivation of enzymes (including glutathione reductase) which protect against oxidative stress.<sup>[2,20]</sup> Copper ions can oxidize hem iron to form methaemoglobin. This blood loses its oxygen carrying capacity. Clinically cyanosis and chocolate brown blood may be seen.<sup>[21]</sup> Patients with cyanosis show at least 1/3<sup>rd</sup> of the blood to be methemoglobin.

Jaundice in copper sulphate poisoning is partly hepatic in origin in addition to hemolysis.<sup>[19]</sup> Jaundice appears on the second or third day following ingestion. Liver damage has been attributed to liver mitochondrial dysfunction due to oxidized state.<sup>[22]</sup> Nature of liver damage is both cell necrosis as well as obstruction. Obstructive factor is seen predominantly as opposed to toxic hepatitis.<sup>[19]</sup> Level of bilirubin is directly proportional to the severity of the poisoning. Elevated levels of liver enzymes are seen in all except mild cases of poisoning.<sup>[10,19,23]</sup> Liver biopsy reveals centrilobular necrosis, mononuclear infiltration and biliary stasis.<sup>[9,24]</sup>

Intravascular hemolysis plays a major role in the pathogenesis of renal failure.<sup>[18,25]</sup> The hem pigment released due to hemolysis and direct toxic effect of copper released from lysed red cells contribute to tubular epithelial damage of the kidney. Severe vomiting, diarrhoea, lack of replacement of fluid and gastrointestinal bleed, leading to hypotension could also contribute to renal failure.<sup>[25]</sup> Renal complications are usually seen on the third or the fourth day and onwards after the poisoning.<sup>[26]</sup> In a report of acute renal failure manifestations following copper sulphate poisoning, histology of kidney revealed features of acute tubular necrosis in seven out of eight kidney biopsies and tubules contained hemoglobin casts. A single case of interstitial granuloma was also reported.<sup>[25]</sup>

Copper sulphate being a corrosive acid, results in caustic burns of the esophagus, superficial and deep ulcers in the stomach and the small intestine.<sup>[25]</sup> Changes

of acute gastritis, hemorrhages in the intestinal mucosa, necrosis of the intestinal mucosa and perforation have been reported.<sup>[5,27,28]</sup>

## Clinical Features

**Gastrointestinal:** The immediate symptoms following ingestion of copper sulphate universally is gastrointestinal in the form of nausea, vomiting and crampy abdominal pain.<sup>[25]</sup> Vomiting usually occurs within 15 minutes of ingestion. Vomitus is characteristically greenish-blue. Hemorrhagic gastroenteritis associated with mucosal erosions, a metallic taste, burning epigastric sensation and diarrhea may occur.<sup>[9]</sup> In severe cases hemetenesis and malena occur. In a case series including 19 patients requiring hemodialysis after copper sulphate ingestion, 7(37%) developed gastrointestinal bleeding and in 5(26%) this was severe enough to cause significant hypotension.<sup>[29]</sup>

**Cardiovascular:** In cases with severe poisoning cardiovascular collapse, hypotension and tachycardia can occur early within a few hours of poisoning and may be responsible for early fatalities or can occur late with other complications.<sup>[9]</sup> Vomiting, diarrhea and GI blood loss are the factors usually responsible for hypovolemia.<sup>[17]</sup> Severe methemoglobinemia can result in cardiac dysrhythmia and hypoxia which could contribute significantly to cardiovascular collapse.<sup>[30]</sup> Other factors implicated are direct effect of copper on vascular and cardiac cells and sepsis due to transmucosal invasion.<sup>[7,17]</sup> In a series of seven autopsies, five deaths occurred within an hour of admission due to shock.<sup>[27]</sup> Four percent of patients in a series of 50 cases by Wahal *et al* had early cardiovascular collapse and succumbed within 10 hours of consumption of the poison.<sup>[9]</sup>

**Hematological:** Intravascular hemolysis occurs 12-24h after ingestion. The discovery of significant methemoglobinemia occurs early in the patient's clinical course and is rapidly followed by hemolysis. Coagulopathy can occur due to liver injury or direct effect of free copper ions on the coagulation cascade.<sup>[17]</sup> The incidence of methemoglobinemia ranged from 3.4% to 42% and intravascular hemolysis ranged from 47-65% in two case series.<sup>[25,29]</sup>

**Hepatic:** Jaundice appears after 24-48h in more severe poisonings, which may be hemolytic or hepatocellular. It

may be associated with tender hepatomegaly. Jaundice was seen in 11(58%) patients and 1(5%) patient died of hepatic encephalopathy in one series.<sup>[29]</sup>

**Renal:** Renal complications are observed usually after 48h.<sup>[26]</sup> Acute renal failure developed in 20-40% of patients with acute copper sulphate poisoning.<sup>[18,25]</sup> Urinary abnormalities detected are oliguria, anuria, albuminuria, hemoglobinuria and hematuria.<sup>[18,25,26]</sup>

**Central nervous system:** Central nervous system depression ranging from lethargy to coma or seizure are likely epiphenomenon related to other organ involvement.<sup>[17]</sup>

**Muscular:** Rhabdomyolysis with high creatine phosphokinase (CPK) >3000IU have been reported.<sup>[31,32]</sup> In one case myoglobinuria was detected on the second day and peak CPK level was observed on the sixth day.<sup>[27]</sup>

### Clinical features in paediatric patients

From the limited case reports available in paediatric patients, the clinical features in paediatric group resembles that of adults with early gastrointestinal feature and hemolysis usually occurring after 24h. Hepatic and renal toxicities develop one to two days after ingestion as in adults.<sup>[4]</sup>

Cardiac abnormalities was reported with multiple ventricular extrasystoles, tachycardia and occasional unifocal bigeminy in a two-year-old boy who ingested 30 ml of a super-saturated copper sulphate solution (10 gm of copper sulphate).<sup>[7]</sup>

## Investigations

Baseline hemoglobin, liver function, renal function and electrolyte levels should be obtained and monitored as clinically indicated until symptoms abate. Hemoglobin should be monitored as clinically indicated to guide the need for blood transfusion. Monitoring renal functions and electrolytes is required to assess the fluid status and extent of renal failure and the renal toxicity of chelating agents like penicillamine. In patients with hepatitis and bleeding manifestations, coagulation parameters have to be monitored. Methemoglobin level is to be monitored in cyanotic patients to assess the need for methylene blue.<sup>[33]</sup> In one series where biochemical changes in blood were studied in copper sulphate poisoning, the authors

suggested a prognostic significance for estimation of levels of serum transaminases along with blood urea estimations with higher levels seen in more seriously ill patients.<sup>[19]</sup> However the significance of this observation was not statistically tested. Urine examination is required for evidence of hemoglobinuria and hematuria.

For diagnostic purpose, if the history is not clear, serum and whole blood copper estimation on a sample collected early in the course may be of help.<sup>[17,19]</sup> Serum copper concentrations normally range from 10.5 to 23 micromoles/liter.<sup>[16]</sup> However it is not mandatory if the diagnosis is obvious by history and clinical examination.

No correlation was found between plasma copper concentrations and prognosis in a study by Wahal *et al.*<sup>[23]</sup> In a study by Singh, an increase in serum copper was found within three hours of ingestion of copper sulphate and after reaching peak values within 48h it showed a gradual fall and attained normal levels within 17h to 7 days. The fall in blood copper levels was attributed to an increase in concentration of copper in tissues especially liver and the kidneys.<sup>[19]</sup> Although serum ceruloplasmin levels rise in patients with acute copper poisoning, because of increased hepatic synthesis, the ceruloplasmin cannot be used to define the patients' prognosis.<sup>[17,34]</sup>

## Treatment

### A) Decreasing absorption

After acute ingestion of copper sulphate, in the prehospital setup, immediate dilution with water or milk is advisable. The same action is extrapolated from recommendations for management of corrosive ingestions.<sup>[35-37]</sup> In corrosive ingestion one should avoid emesis and should begin early dilutional therapy. Water may be used initially to dislodge adherent solid particles, as well as to dilute the caustic ingestion. It is important not to be excessively aggressive with dilution, as this may cause nausea, vomiting and possible aspiration.

Emesis should be avoided to prevent reexposure of the esophagus to the corrosive agent.<sup>[37]</sup> In copper sulphate poisoning vomiting is likely to occur spontaneously and hence patient may require antiemetic therapy.<sup>[17]</sup> In corrosive acid ingestion, there is a risk of perforation if blind gastric lavage is attempted, however in patients with

large intentional ingestion of acid who presents within 30 min, consideration can be given to cautious placement of a narrow nasogastric tube suction to remove the remaining acid in the gut.<sup>[37]</sup>

Activated charcoal administration should be considered after a potentially dangerous ingestion.<sup>[38]</sup> A dose of oral activated charcoal, while of unproved benefit, is unlikely to be harmful and may have potential adsorptive capacity for copper.<sup>[17]</sup> Usual dose is 25 to 100 gm in adults and adolescents and 25 to 50 gm in children aged 1 to 12 years (or 0.5 to 1 gram/kilogram body weight). Administer charcoal as aqueous slurry; most effective when administered within one hour of ingestion. Use a minimum of 240 ml of water per 30 gm charcoal.<sup>[39]</sup>

### B) Supportive measures

#### 1) Management of corrosive burns:

If corrosive oesophageal or gastric damage is suspected upper GI endoscopy should be carried out, ideally within 12-24h, to gauge the severity of injury.<sup>[40-43]</sup> This recommendation is extrapolated from experience with ingestion of acids and /or alkaline corrosives.

Endoscopic procedures done during the early period after corrosive ingestion has shown to be relatively safe without any complications. In a series of 94 patients with corrosive ingestion, GI endoscopy was performed in 81 patients within 24h and in 12 patients within 48h. The procedure was not associated with any complications.<sup>[42]</sup> Similarly, in another series of 16 patients with corrosive acid ingestion, fiberoptic endoscopy was done in 13 patients within 24h. The authors concluded that endoscopy did not give rise to any complications and it helped in grading the injury caused by corrosive acids, planning the management of patients and also in predicting the prognosis.<sup>[43]</sup>

The period of wound softening starts on the second or third day post-injury and last for roughly two weeks during which time there is an increased risk of perforation if endoscopy is performed.<sup>[37]</sup> An early surgical opinion should be sought if there is any suspicion of pending gastrointestinal perforation or where endoscopy reveals evidence of grade III burns.

Sucralfate may help to relieve the symptoms of mucosal injury.<sup>[44]</sup> Adequate human data regarding role of steroid

in caustic burn is yet to be generated. The most suitable group to receive corticosteroid (with antibiotic) is probably the patients with grade IIb injuries (submucosal lesions, ulcerations and exudates with near circumferential injuries). In patients with grade III ulcers (deep ulcers and necrosis into periesophageal tissues) stricture formation occurs, irrespective of steroid administration. Moreover, steroids may mask or worsen the complications of corrosives in grade III patients and hence steroids are contraindicated.<sup>[41]</sup>

Considering the experience with the use of steroid in copper sulphate poisoning, in a study of copper sulphate poisoning by Gupta *et al.*, the mortality was lower in a group of 26 patients treated with steroids as compared to those without steroids.<sup>[2]</sup> However, this was not a randomized-controlled study. The role of steroid has not been tested in any other controlled studies to strongly recommend this therapeutic intervention.

## 2) Methemoglobinemia:

Patients with symptomatic methemoglobinemia should be treated with methylene blue. This usually occurs at methemoglobin levels above 20 to 30 percent, but may occur at lower methemoglobin levels in patients with anemia or underlying pulmonary or cardiovascular disorders. Administer oxygen while preparing for methylene blue therapy.

Methylene blue enhances the conversion of methemoglobin to hemoglobin by increasing the activity of the enzyme methemoglobin reductase. Initial dose is 1-2 mg/kg/dose (0.1 to 0.2 ml/kg of 1% solution) intravenously over 5 minutes. The dose may be repeated if cyanosis does not disappear within one hour.<sup>[45]</sup> At high levels of methemoglobin (>70%), methylene blue reduces the half life from an average of 15-20 hours to 40-90 min. Hence, improvement from methylene blue therapy should be observed within one hour of administration.

Failure of methylene blue therapy suggests inadequate dose of methylene blue, inadequate decontamination, G-6-PD deficiency, NADPH dependent methemoglobin reductase deficiency.<sup>[45]</sup> Further, methylene blue action requires intact erythrocytes and hence if hemolysis is severe, it may be ineffective in copper sulphate poisoning.<sup>[17]</sup> Large doses of methylene blue itself may

cause methemoglobinemia or hemolysis and the same needs to be considered while administering this agent.<sup>[33]</sup> It is contraindicated in G-6-PD deficient patients in whom it may cause hemolysis. Exchange transfusion and/or the transfusion of packed red blood cells may be useful for methylene blue failures or for patients with G6PD or NADPH methaemoglobin reductase deficiency. (Nitrates, Nitrites and methaemoglobinemia.<sup>[45]</sup> Hyperbaric oxygen may be beneficial if methylene blue is ineffective.<sup>[34]</sup> Hyperbaric oxygen increases the dissolved oxygen which can protect the patient while the body reduces methaemoglobin.<sup>[34]</sup> Another alternative to methylene blue is the reducing agent ascorbic acid which can be administered 100-500 mg twice daily either orally or intravenously. But, this agent probably has a minor effect on increasing methemoglobin reduction and the clinical experience with the use of this agent is limited.<sup>[45]</sup>

## 3) Hypotensive episode:

Hypotensive episode should be treated with fluids, dopamine and noradrenaline

## 4) Rhabdomyolysis:

Early judicious fluid replacement of 4-6L/day with careful monitoring for fluid overload, mannitol (100 mg/day) and urine alkalinization are suggested early in the course, but definite evidence for the efficacy of these measures is lacking.<sup>[46]</sup>

## C) Chelation therapy

There is little clinical experience with the use of chelators for acute copper sulphate intoxication. Data on efficacy is derived from patients with chronic copper intoxication (Wilson's disease, Indian childhood cirrhosis) and experimental animal studies. British anti Lewisite (BAL), D-penicillamine, 2, 3-dimercapto-1-propane sulfonate, Na<sup>+</sup> (DMPS) and ethylene diamine tetra acetate (EDTA) have been used. In severely poisoned patients the presence of acute renal failure often limits the potential for antidotes.

## 1) Penicillamine:

D-penicillamine has been used to treat acute copper intoxication, but data regarding efficacy are lacking.<sup>[32,33,47,48]</sup>

Adult dose: 1000 to 1500 mg/day divided every six to

12h, before meals.

Pediatric dose: Initially 10 mg/kg/day, gradually increase to 30 mg/kg/day divided in two or three doses as tolerated. Doses up to 100 mg/kg/day in four divided doses; maximum one gram/day may be used depending on the severity of poisoning and adverse effects.<sup>[49]</sup>

Avoid in patients with penicillin allergy. Proteinuria, hematuria, renal failure, bone marrow suppression and hepatotoxicity are the common adverse effects.

## 2) Dimercaprol / BAL:

Intramuscular BAL is probably appropriate in patients in whom vomiting and gastrointestinal injury prevents oral D-penicillamine administration. BAL- copper complex primarily undergoes biliary elimination and hence it is useful in patients with renal failure. However, BAL may be less effective than D-penicillamine and hence, when tolerated, D-penicillamine therapy should be started simultaneously or shortly after the initiation of therapy with BAL.<sup>[17]</sup>

Dose: 3 to 5 mg/kg/dose deep intramuscularly every four hours for two days, every four to six hours for an additional two days, then every four to 12h for up to seven additional days.<sup>[6,31,47,50]</sup> Adverse reactions are urticaria and persistent hyperpyrexia.

## 3) Edetate calcium disodium

The dose of this agent is 75 mg/kg/day deep intramuscularly or slow intravenous infusion given in three to six divided doses for up to five days; may be repeated for a second course after a minimum of two days; each course should not exceed a total of 500 mg/kg. Complications include renal tubular necrosis.<sup>[6]</sup>

## D) Enhanced elimination

Hemodialysis to remove copper is ineffective, but may be indicated in patients with renal failure secondary to copper poisoning.<sup>[33,51]</sup>

Peritoneal dialysis with salt-poor albumin resulted in extraction of more copper than dialysate without albumin. However, the amount of copper removed by peritoneal dialysis was very small.<sup>[7]</sup> There is insufficient evidence regarding any role of hemoperfusion and hemodiafiltration for copper elimination.<sup>[31]</sup>

## Conclusion

Copper sulphate poisoning, which is mostly suicidal, is associated with high mortality in severe cases due to methemoglobinemia, hepatotoxicity and renal failure. Mainstay of treatment is supportive, including careful fluid therapy and methylene in symptomatic methemoglobinemia. Chelation therapy though tried in many cases, their benefits are not established in controlled trials. The role of dialysis is limited to the management of associated renal failure.

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