

## A Vitriolic End: A Case of Intentional Copper Sulphate Poisoning

Blydenstein SAV<sup>1\*</sup>, Wong M<sup>2</sup> and Vaughan J<sup>3</sup>

<sup>1</sup>Department of Medicine, Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa

<sup>2</sup>Department of Pulmonology, Internal Medicine, Chris Hani Baragwanath Academic Hospital, South Africa

<sup>3</sup>Department of Molecular Medicine and Hematology, University of Witwatersrand, South Africa

### Abstract

Copper sulphate poisoning is uncommon. We describe a patient with intentional copper sulphate poisoning and review the literature on the subject. This case report describes the rare entity of copper sulphate poisoning, its clinical features and reviews the current literature. A 28-year-old male, presented in November 2015 to the Department of Medicine, Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg, with a history of intentional self-harm by poisoning. On examination he was centrally cyanosed, SpO<sub>2</sub> 81% on ambient air, with a metabolic acidosis and methaemoglobinaemia.

**Keywords:** Copper sulphate; Peritonitis; Toxicity

### Introduction

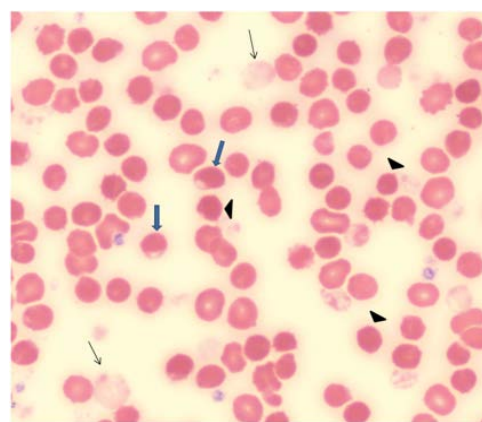
Copper sulphate poisoning is uncommon. Most reports are case reports, and the infrequency of this entity makes it difficult to prognosticate, and to recommend best therapy. We describe a patient with intentional copper sulphate poisoning and review the literature on the subject.

### Case Presentation

A 28-year-old male, with no background medical conditions, presented in November 2015 to the Department of Medicine, Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg, with a history of intentional self-harm by poisoning. Although initially awake and alert, he would not disclose the nature of the substance ingested, but presented more than 9 hours after ingestion, with diarrhoea and abdominal pain. On examination he was centrally cyanosed, SpO<sub>2</sub> 81% on ambient air, with a metabolic acidosis and methaemoglobinaemia. Although tender, there were no signs of peritonitis on abdominal examination. He had normal neurological function.

In the absence of an obvious recognised toxidrome, the patient was initially treated as a polypharmacy overdose, and supportive care was instituted in the form of supplemental oxygen, fluid resuscitation and pain control. Methylene blue was not administered, as the methaemoglobin level was 10.3%, well under the usual 20% trigger for treatment.

Haemolytic anaemia, severe abdominal pain and melaena developed within the first few hours of admission. The following morning, medical gastroenterology performed a gastroscopy which revealed oesophageal and duodenal ulceration with extensive sloughing. The patient was kept nil *per os*, and total parenteral nutrition was initiated. He required further support with blood transfusions, and a proton pump inhibitor was administered as an infusion. Oxygen, vitamins C and K, and thiamine were given. Haemodialysis was instituted based on worsening renal function, presumed due to rhabdomyolysis. The methaemoglobin level progressively worsened, reaching a peak of 20.3%. Unfortunately, there was no methylene blue available at the hospital, nor at any other surrounding hospitals or pharmacies. Urgent application was made to the Medicine Control Council (MCC) for the use of dimercaprol in this patient. However, there was no stock in the hospital, nor any Gauteng public hospital, and it could only be ordered and delivered once approval was obtained. Unfortunately, this approval was received on the fourth day of admission, and the patient passed away later that same day. Dimercaprol may not have been of benefit after the first day of admission in any event, as it is available only in an oral form



**Figure 1:** Peripheral blood red cell morphology showing irregularly contracted red cells (black arrow heads), blister cells (blue arrows) and ghost cells (black arrows). Peripheral blood stained with May-Grünwald Giemsa, 500x magnification.



**Figure 2:** Ingested substance.

\*Corresponding author: Blydenstein SAV, Department of Medicine, Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa, Tel: +27 71 893 7056; E-mail: [savanblydenstein@gmail.com](mailto:savanblydenstein@gmail.com)

Received December 08, 2018; Accepted December 13, 2018; Published December 17, 2018

Citation: Blydenstein SAV, Wong M, Vaughan J (2018) A Vitriolic End: A Case of Intentional Copper Sulphate Poisoning. J Clin Case Rep 8: 1197. doi: [10.4172/2165-7920.10001197](https://doi.org/10.4172/2165-7920.10001197)

Copyright: © 2018 Blydenstein SAV, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Variable	Admission	Later on admission	Day 1	Day 2	Day 3	Day 4	
<b>Arterial blood gas</b>							
pH	7.22	7.12	7.25	7.29	7.24	--	
SpO <sub>2</sub> (mm Hg)	85.5	--	--	97.5	71.2		
Saturation oxygen (5)	94.7	--	98.2	98.8	95		
Potassium (mmol/L)	5.4	5.0	6.7	4.1	14.5		
Bicarbonate (mmol/L)	11.1	16.1	11.8	20.3	--		
Methaemoglobin (%)	10.3	11.3	19	--	20.3		
Haemoglobin (g/dL)	19.5	17.5	11.9	11.1	6.6		
<b>Formal laboratory results</b>							
Haemoglobin (g/dL)	19	--	11	10.5	10.5	--	
Haptoglobin (g/dL)	--		0.1	0.26	--	--	
Caeruloplasmin (mg/dL)	--		--	0.23	--	--	
Creatine Kinase (U/L)	--		--	--	2198	--	--
Lactate dehydrogenase (U/L)	--		--	>2000	>2000	--	--
Aspartate transaminase (U/L)	192		--	180	237	237	67
Alanine transaminase (U/L)	19		--	27	67	56	12
Albumin (g/L)	33		--	22	18	12	--
International normalised ratio	1.08		--	--	1	--	--
Creatinine (umol/L)	392		--	453	520	573	--
Direct Coombs	--	Negative (poly-specific)					
Paracetamol (umol/L)	--	9 (well below therapeutic level)					

**Table 1:** Significant blood results over course of admission.

and the patient had such extensive gastrointestinal sloughing which would have precluded absorption. Also, there was concern about renal toxicity, given that the patient had already developed renal failure.

The patient deteriorated, with ongoing haemolysis, necessitating further blood transfusion, and progressive renal dysfunction with anuria. Liver failure, as evidenced by sub-massive hepatic necrosis on post mortem liver biopsy, with sepsis (*E. coli*), possibly resulting from intestinal barrier failure with bacterial translocation, led to the demise of the patient four days after admission.

Table 1 shows the pertinent blood results in this patient and Figure 1 is a picture of his peripheral blood smear taken on day three. Figure 2 shows the substance which the family found, and the patient later admitted to consuming.

## Discussion and Literature Review

Intentional acute poisoning by ingestion of copper sulphate is uncommon, with most cases being reported in India [1-14] and Pakistan [11].

Copper sulphate is an ingredient in fungicides, herbicides, is a soil additive and a local astringent [12,15], and can be found in many science classrooms [1].

Copper is a normal constituent of the human body [15], with normal total content of 50-150 mg [5,13]. The normal daily intake is around 2 mg per day, and the daily adult demand for copper is around 1.5-4 mg per day [10,15]. Copper forms part of essential enzymes, including cytochrome oxidase, superoxide dismutase and lysyl oxidase [10].

Copper is rapidly absorbed from the stomach and duodenum, and levels peak after 1-3 hours after ingestion [5,15], but may be delayed up to 48 hours post ingestion [13]. The binding proteins include amino acids, vitamins, albumin and the principal binding protein,  $\alpha_2$  globulin (caeruloplasmin) [9]. Caeruloplasmin is also a co-enzyme that is involved in iron oxidation. Copper is stored in the liver, bound to metallothionein [13], a cysteine rich low molecular weight protein [9].

Copper exhibits an enterohepatic cycle, where it is excreted in bile [15]. The bile and pancreatic secretions are reabsorbed in the duodenum (around 0.5-1.3 mg in bile), and only a small amount is excreted in the urine (0.01-0.06 mg in urine) [5,15].

During acute overdose, copper kinetics change [15], and the preferred method of transportation of copper switches from caeruloplasmin to albumin [13]. It is the copper-albumin complex which is toxic. Copper sulphate is a corrosive substance [16], and an oxidant [17], which binds to various sulfanyl groups and inactivates several enzymes, including glucose-6-phosphate dehydrogenase and glutathione reductase [16]. This increases cell wall permeability due to inhibition of the Na/K ATPase pump [17]. Toxicity affects mainly hepatocytes, myocytes and erythrocytes.

Initially, gastrointestinal symptoms predominate. Copper sulphate has a corrosive effect on the oesophagus, stomach and duodenum. Symptoms include a metallic taste after ingestion, heartburn, nausea and vomiting, of which vomiting is the most common [12]. There is necrosis of the intestinal mucosa, causing haemorrhage (reported to occur in 40% of patients), and in some cases, even intestinal perforation [13].

Haemolysis occurs in majority of patients (68%) [12]. The blood film typically shows anisocytosis, poikilocytosis, pyknocytosis (with precipitation of haemoglobin), basophilic stippling and microspherocytosis [17]. As in chronic copper overload, Heinz bodies can be found in acute copper poisoning [1,3]. Intravascular haemolysis takes place about 12-24 hours after ingestion. Copper sulphate causes direct oxidative damage to erythrocyte membranes [6], inactivates glutathione reductase and glucose-6-phosphate dehydrogenase [11], and inhibits cellular metabolism [3]. The level of serum copper bears no correlation with the severity of intravascular haemolysis [3].

Copper ions oxidise haemoglobin to form methaemoglobinaemia [13] by oxidizing  $Fe^{2+}$  to  $Fe^{3+}$ . This decreases the oxygen carrying capacity of the haemoglobin, and the blood takes on a chocolate brown colour. The mean methaemoglobin level has been reported in 2012 as 9.59% ( $\pm$  8.28) [12]. Arrhythmias resulting from methaemoglobinaemia can occur.

Jaundice and acute hepatitis usually occurs on day 2-3 post ingestion [13] and is the result of two separate pathologic processes: haemolysis and hepatitis. There is centrilobular liver cell necrosis, accompanied by a mononuclear infiltration causing biliary stasis [13]. This is reported to occur in 45% of patients [12].

On day 3-4 renal function often becomes compromised [13], reported in an Indian study to occur in 51% [12]. Multiple factors cause renal injury, including: haemolysis predisposing to acute tubular necrosis; vomiting, diarrhea and gastrointestinal bleeding resulting in hypovolaemia; rhabdomyolysis; and the direct toxic effect of copper bound to albumin, and possible sepsis from bacterial translocation from damaged gastrointestinal tract.

The diagnosis is made from history of copper sulphate ingestion [15], and from the clinical presentation. The measurement of serum copper does not correlate with clinical severity [8,13], with the use of whole blood copper measurement being preferential to serum copper levels [5,8]. The difficulty in correlation is due to the unpredictability of the kinetics of copper sulphate. There is a peak in serum copper after ingestion, and levels can fall to normal by as early as 17 hours or take as long as 7 days [13]. The fall in serum concentration is a result of increased tissue concentration of copper, particularly in the liver. A low serum copper level could even be the result of an increased liver uptake, which would indicate a worse prognosis [12]. Necrosis of hepatocytes can cause a release of serum copper late in the course of the disease [12]. There may also be a secondary peak in serum copper levels once the erythrocytes lyse, releasing the copper contained therein [13]. Diagnosis can be made after chemical analysis of gastric content [12].

The fatal dose of copper sulphate has not been precisely determined, with reports ranging from 1 g to 20 g [6,13]. A prospective study has shown the mortality for acute copper sulphate poisoning to be 22.9% [12]. A serum aspartate transaminase (AST) of greater than 234 U/L and alanine transaminase (ALT) of greater than 55 U/L have an 85.7% and 100% sensitivity in predicting mortality, respectively [12]. Death in the haemodialysis era is largely attributable to hepatic failure [12], where prior to renal support, nephrotoxicity was largely the cause of death.

Death most often occurs after at least the first 24 hours of ingestion, with only one case report describing an eleven-year-old who died within 6 hours of ingestion [7]. Most reports on copper sulphate are case reports, and only one study reports a 20% [15] fatality rate, making the average fatality rate difficult to determine. Treatment of acute copper sulphate poisoning is both supportive and specific.

Supportive measures are determined by the clinical presentation, and include decontamination, dilution of ingested copper sulphate (ingestion of milk) [13], and administering activated charcoal orally [6,13]. Neither lavage nor induction of emesis are indicated [6], and may be dangerous as copper sulphate is corrosive, with a risk of perforation. Early gastroscopy (within the first 24 hours) to assess extent of corrosive damage has been advocated [13]. Maintenance of intravascular volume by intravenous fluid therapy is advised.

Methylene blue is the recommended treatment for methaemoglobinaemia. Methylene blue increases the activity of NADPH-methaemoglobin reductase [11]. Treatment is required if methaemoglobin is 20-30%, but symptoms can occur at lower levels, if there is co-existent anaemia, respiratory or cardiovascular pathologies. Methylene blue increases the activity of methaemoglobin reductase, converting methaemoglobin to haemoglobin. The recommended dose is 1-2 mg/kg/dose of a 1% solution, given over 5 minutes intravenously

[11]. It can be repeated after one hour if the cyanosis does not resolve. Methylene blue will fail to correct methaemoglobinaemia if the dose is inadequate, if the exposure to the toxin (in this case, copper sulphate) is ongoing, or if haemolysis is severe. Methylene blue is contra-indicated in patients with glucose-6-phosphate dehydrogenase deficiency, as it causes haemolysis.

If methylene blue treatment is unsuccessful, or if haemolysis is severe, or in the case of glucose-6-phosphate dehydrogenase deficiency, exchange transfusion can be attempted [11,13]. Hyperbaric oxygen increases the amount of dissolved oxygen in blood and can be an added supportive treatment. Ascorbic acid is a reducing agent and can be attempted, although there is limited experience [13] to support this recommendation. Other drugs causing methaemoglobinaemia include aniline dyes, nitrites, dapsone and benzocaine. Rhabdomyolysis can be managed with appropriate fluid and alkalinisation therapy [13].

Copper sulphate is not a dialyzable toxin; however, haemodialysis may be instituted if the patient develops acute renal failure. There is a theoretical benefit to haemodialysis once a chelator has been given, as the chelator increases urinary copper excretion. Currently, the indication for haemodialysis is supportive in nature [5].

Specific treatment is based upon experience with chelating of copper in patients with chronic copper overload syndromes, for example, Wilson's disease, on animal experiments and on case reports and cohort studies [2]. Chelators used include D-penicillamine, 2, 3-dimercapto-1-propane sulfonate, and ethylene diamine tetra acetate (EDTA) [5].

D-penicillamine is given at 1000-1500 mg/day in 2 - 6 divided doses [6]. It is contra-indicated in patients with penicillin allergy. Side-effects include renal failure with proteinuria and haematuria, bone marrow suppression and hepatotoxicity [13]. It is an oral medication and use is limited in patients with severe gastrointestinal caustic damage. A prospective study, where 71.4% of patients were given D-penicillamine, reported no significant decrease in major complications, mortality or length of hospital stay [12]. Care should be exercised when using this drug if there is not access to renal replacement therapy [6].

Another treatment option is 2, 3-dimercapto-1-propane sulfonate. This is useful in patients with severe gastrointestinal complications, as it is administered intramuscularly. Furthermore, it forms complexes with copper which undergo hepatic elimination, so can be used in patients with renal injury. Some reports describe dimercaptopurol being less effective than D-penicillamine [13], and others suggest that dimercaptopurol may be better for short- and long-term copper overload. The dose is 3-5 mg/kg/dose intramuscularly 4 hourly for 2-4 days. It can cause hyperpyrexia and urticaria [13].

EDTA is an alternative chelating agent, given at a dose of 1 g 12 hourly in 250 ml of 5% dextrose water [15]. In patients who have developed renal failure, either the dose or the frequency of dosing can be decreased, as it can cause acute tubular necrosis [6].

Duration of treatment is unknown, and it is currently suggested that treatment with chelators be continued as long as whole blood copper values remain elevated, or as long as symptoms persist, usually 5-7 days. Acute kidney injury restricts the use of a potential chelator [16,17].

Given the rarity of this clinical scenario, no clinical trials have been conducted, nor conclusive treatment protocols established. Reports have described a variety of treatment modalities. For now, the prognosis of this rare poisoning depends on the dose ingested, but the

clinical entity is too rare to know which specific treatment is superior to any other.

## Conclusions

1. Copper sulphate is a corrosive substance, and it is an oxidant, and ingestion can cause methaemoglobinaemia, haemolytic anaemia, renal and hepatic dysfunction and local damage to the gastrointestinal tract.
2. Copper sulphate is not a dialyzable toxin, but haemodialysis may be required for supportive management of acute renal failure.
3. Methaemoglobinaemia can be treated with methylene blue, although care should be exercised in haemolysis.
4. Chelators used include D-penicillamine, 2, 3-dimercapto-1-propane sulfonate, and ethylene diamine tetra acetate (EDTA).

## Author Contributions

- SAVB: Manuscript preparation, management of patient.
- MW: Manuscript review, management of patient.
- JV: Pathology review and input regarding pathological findings.

## References

1. Blundell S, Curtin J, Fitzgerald D (2003) Blue lips, coma and haemolysis. *J Paediatr Child Health* 39: 67-68.
2. Cao Y, Skaug MA, Andersen O, Aaseth J (2015) Chelation therapy in intoxications with mercury, lead and copper. *J Trace Elem Med Biol* 31: 188-192.
3. Chugh KS, Sharma BK, Singhal PC, Das KC, Datta BN (1977) Acute renal failure following copper sulphate intoxication. *Postgrad Med J* 53: 18-23.
4. Chuttani HK, Gupta PS, Gulati S, Gupta DN (1965) Acute copper sulfate poisoning. *Am J Med* 39: 849-854.
5. Franchitto N, Gandia-Mailly P, Georges B, Galinier A, Telmon N, et al. (2008) Acute copper sulphate poisoning: A case report and literature review. *Resuscitation* 78: 92-96.
6. Gamakaranage CS, Rodrigo C, Weerasinghe S, Gnanathanan A, Puvanaraj V, et al. (2011) Complications and management of acute copper sulphate poisoning: A case discussion. *J Occup Med Toxicol* 6: 34.
7. Gulliver JM (1991) A fatal copper sulfate poisoning. *J Anal Toxicol* 15: 341-342.
8. Gunay N, Yildirim C, Karcioglu O, Gunay NE, Yilmaz M, et al. (2006) A series of patients in the emergency department diagnosed with copper poisoning: Recognition equals treatment. *Tohoku J Exp Med* 209: 243-248.
9. Kurisaki E, Kuroda Y, Sato M (1988) Copper-binding protein in acute copper poisoning. *Forensic Sci Int* 38: 3-11.
10. Makarski B, Gortat M, Lechowski J, Zukiewicz-Sobczak W, Sobczak P, et al. (2014) Impact of copper (Cu) at the dose of 50 Mg on haematological and biochemical blood parameters in Turkeys and level of Cu accumulation in the selected tissues as a source of information on product safety for consumers. *Ann Agric Environ Med* 21: 567-570.
11. Malik M, Mansur A (2011) Copper sulphate poisoning and exchange transfusion. *Saudi J Kidney Dis Transpl* 22: 1240-1242.
12. Naha K, Saravu K, Shastry BA (2012) Blue vitriol poisoning: A 10-year experience in a tertiary care hospital. *Clin Toxicol* 50: 197-201.
13. Kavitha S, Jimmy J, Bhat MN, Beena J, Shastry BA (2007) Acute ingestion of copper sulphate: A review on its clinical manifestations and management. *Indian J Crit Care Med* 11: 74-80.
14. Srivastava A, Peshin SS, Kaleekal T, Gupta SK (2005) An epidemiological study of poisoning cases reported to the National Poisons Information Centre, All India Institute of Medical Sciences, New Delhi. *Hum Exp Toxicol* 24: 279-285.
15. Vijayakumar S, Sasikala M, Dhanapal R (2012) Copper poisoning: A short review. *Int J Pharmacol Toxicol* 2: 39-43.
16. Sweni S, Meenakshisundaram R, Sakthirajan R, Rajendiran C, Thirumalaikolundusubramanian P (2012) Acute renal failure in acute poisoning: Prospective study from a tertiary care centre of South India. *J Ren Care* 38: 22-28.
17. Valsami S, Stamoulis K, Lydataki E, Fountoulaki-Paparizos L (2012) Acute copper sulphate poisoning: A forgotten cause of severe intravascular haemolysis. *Br J Haematol* 156: 294.