Cupric Sulfate Intoxication with Rhabdomyolysis, Treated with Chelating Agents and Blood Purification

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Abstract

We report a case of cupric sulfate intoxication complicated by hemolytic anemia, hepato-renal damage and acute rhabdomyolysis. The patient was successfully treated with dimercaprol, penicillamine, direct hemoperfusion and hemodiafiltration. We discuss the pathophysiology of cupric intoxication, and propose a treatment combined with chelating agents and blood purification.

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Key words: copper intoxication, direct hemoperfusion, hemodiafiltration

Introduction

Cupric sulfate is commercially available and found in products of fungicides for tropical fish in Japan. However, the pathophysiology of acute copper intoxication is not well understood and its management has not been established. We describe a case of cupric sulfate intoxication with acute rhabdomyolysis treated successfully with dimercaprol, penicillamine, hemoperfusion and hemodiafiltration.

Case Report

A healthy 18-year-old man without a significant past medical history was brought to the hospital one hour after drinking a solution as a suicidal attempt containing approximately 8 g of cupric sulfate, which he had been using for chemistry experiments. He was lethargic and vomiting spontaneously. Blue staining of the oral mucosa and vomitus on his clothes were noticed. The temperature was 36.2°C, the pulse rate was 92, the respirations were 30, and the blood pressure was 160/64 mmHg. No neurological focal sign was present on examinations. The laboratory data revealed hemoconcentration with 18.7 g/dl of hemoglobin and 55% of hematocrit. Although indirect bilirubin was 1.4 mg/dl, other renal and liver function

tests remained in the normal limit as shown in Table 1. Radiographs of the chest and abdomen were unremarkable. The patient was intubated, and gastric lavage was performed to remove the ingested blue solution. He was put on dimercaprol 1,800 mg/day and penicillamine 900 mg/day.

The next day, the urine color was noted to be a brown-red color. Urinalysis revealed hemoglobin, myoglobin (1,015 µg/day) and granular casts. Serum creatine phosphokinase (CPK) level was elevated to 519 IU/l (Fig. 1) and serum myoglobin level was over 300 ng/ml. Hemolysis and rhabdomyolysis were diagnosed, and acute tubular necrosis was suspected. In order to prevent the worsening of the acute renal failure, hydration was continued to maintain urine output (Fig. 2). Haptoglobin was administered for hemolysis. In addition, a double lumen catheter was placed in the right femoral vein for access for blood purification. Four sessions of direct hemoperfusion (DHP) for 4 hours using activated charcoal (Hemokalum®, Terumo, Tokyo) and 5 sessions of hemodiafiltration (HDF) for 4 hours without volume depletion using a polysulfone hollow fiber dialyzer with a membrane area of 1.25 m² (Fresenius Dialyzer PS-1.3UW®, Kawasumi Laboratories, Inc., Tokyo) were performed in 6 days to remove copper, hemoglobin, myoglobin and other debris from injured tissue. Nafamostat mesilate, a protease inhibitor, was applied as an anticoagulant at a dose of 0.2 mg/kg/hour during the blood purification.

CPK became elevated to 3,804 IU/l on the 6th day, and declined thereafter (Fig. 1). Serum urea nitrogen (UN), serum creatinine (CRE), creatinine clearance (Ccr) and excreted fraction of filtered sodium (FENa) was retained within the normal range during the treatment period. Urine color became clear yellow on the 8th hospital day. On the 10th day, the blood hemoglobin (Hb) level decreased to 7.2 g/dl and hematocrit (Ht) went down to 22.0% due to hemolysis, and thrombocytosis and hyperbilirubinemia followed afterward. Aspartate aminotransferase (AST) peaked at 119 IU/l on the 6th day and alanine aminotransferase (ALT) increased to 124 IU/l on the 18th day, and both liver function parameters subsided afterward.

Serum copper (Cu) concentration was 142 µg/dl (normal limit 78–131) on admission, and the urine copper excretion

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Table 1. The Laboratory Findings on Admission

Hematologic laboratory values:	
Hemoglobin	18.7 g/dl
Hematocrit	55.0%
White cell count	$10.4 \times 10^3/\mu\text{l}$
Platelet count	$23.1 \times 10^4/\mu\text{l}$
Prothrombin time	100%
Activated partial thromboplastin time	32.3 second
Blood chemical findings:	
Sodium	141 mmol/l
Potassium	3.1 mmol/l
Chloride	100 mmol/l
Calcium	10 mg/dl
Urea nitrogen	9.5 mg/dl
Creatinine	0.7 mg/dl
Total protein	8.9 g/dl
Albumin	5.9 g/dl
Total bilirubin	1.4 mg/dl
Direct bilirubin	0.3 mg/dl
Indirect bilirubin	1.1 mg/dl
Alkaline phosphatase	175 IU/l
Cholinesterase	5,466 IU/l
Aspartate aminotransferase	29 IU/l
Alanine aminotransferase	16 IU/l
Lactate dehydrogenase	394 IU/l
Creatine phosphokinase	163 IU/l
Amylase	151 IU/l
Glucose	131 mg/dl
C-reactive protein	0.0 mg/dl
Copper	142 $\mu\text{g/dl}$

was 3.95 mg/day during the first day. Since most of the absorbed copper binds to serum and tissue proteins, estimation of copper contents in the patient was considered impractical (1). Excess copper is excreted gradually, and chelates were thought to accelerate excretion through urine and artificial blood purification. The patient was discharged on the 15th hospital day, and treatment with penicillamine was continued for 4 weeks until hemolytic anemia was resolved. No complication was noticed during the 8-weeks follow-up period.

Discussion

The lethal dose of cupric sulfate has been described to be as low as 1 g (2). Ingested copper induces mucous irritation, nausea, vomiting and diarrhea. Ionized copper is rapidly absorbed from the stomach and intestine, and the serum copper level increases rapidly. The element is bound to albumin and ceruloplasmin, and is taken up by the liver, kidneys, lungs and red blood cells. Hemolytic anemia and renal tubular necrosis may follow 36–48 hours after exposure. The primary route of excretion is through bile and feces (3).

The toxicity of copper at a cellular level is probably related to the sulfhydryl groups. Copper inhibits the sulfhydryl moieties of glucose-6-phosphate dehydrogenase and glutathione,

Figure 1. Serum creatine phosphokinase (CPK) level. **Figure 2. Hydration and urine output in the beginning of treatment. Direct hemoperfusion and hemodiafiltration without volume depletion were performed in 6 days. DHP: direct hemoperfusion, HDF: hemodiafiltration.**

thereby reducing their free radical scavenging activities. Copper induces hemolysis through oxidation of hemoglobin sulfhydryl groups. Copper also inhibits Na⁺/K⁺-ATPase and increases the permeability of cell membrane. Since copper is known to damage human skeletal muscle cells (4), copper intoxication could cause rhabdomyolysis. Although a case of copper-induced acute rhabdomyolysis in Wilson's disease was reported (5), rhabdomyolysis in acute copper intoxication has been rarely reported (3). This might be because myoglobinuria might be overlooked by the coexistence of hemoglobinuria secondary to hemolytic anemia.

The treatment for ingested copper overdosage includes dermal decontamination, cautious gastric lavage and supportive therapy (6). Dimercaprol, penicillamine and edetate calcium disodium might be considered for massive copper ingestion, and persistent symptomatology or persistently elevated serum copper concentrations. For serious poisoning, it is considered best to administer dimercaprol intramuscularly 4 mg/kg/dose every 4 hours for 5–7 days. Penicillamine is usually administered orally in doses of 250–500 mg/dose every 8–12 hours. Edetate calcium disodium is also a drug of choice, but the agent has not been approved in Japan for copper intoxication and so was not used in this case. Dialysis or hemoperfusion has not been demonstrated to increase the elimination of copper, since copper binds to serum and tissue proteins. However, chelated copper would be removed from serum by diuresis and dialysis. Especially in this case direct hemoperfusion and

hemodiafiltration were performed to eliminate chelated copper and nephrotoxic substances, and the patient was successfully treated without developing acute renal failure. Then necessity of plasma exchange has not been established.

In summary, we described a case of cupric sulfate intoxication with rhabdomyolysis, treated with a combination of chelating agents and blood purification.

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