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A CASE OF COPPER SULFATE INTOXICATION THAT IS PRESENTED WITH PROLONGED HEMOLYSIS AND ACUTE RENAL FAILURE

UZAMIŞ HEMOLİZ VE AKUT BÖBREK YETERSİZLİĞİ İLE PREZENTE OLAN BİR BAKIR SULFAT ZEHİRLENMESİ OLGUSU

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ABSTRACT

Copper sulfate is a fungicide used for the control of bacterial and fungal diseases of vegetables, fruits, and grain products. Even a very small quantity is toxic. Its acute toxicity leads to hemolytic anemia, acute tubular necrosis, hepatotoxicity, and rhabdmyolysis.

A 55 year old man was hospitalized with nausea, vomiting and epigastric pain. We found hemolytic anemia, acute renal failure, hepatotoxicity (only an increase in AST) and rhabdomyolysis as a consequence of oral copper sulfate intake for suicidal purposes. The amount of urine was 3-4 L/day. D-penicillamine (900 mg/day) was started. Metabolic acidosis was recorded. Hemodialysis was performed 9 times in twenty days. Increased copper levels in serum and urine and methemoglobinemia levels decreased gradually (210 µg/dl→92 µg/dl, 98 µg/24 hour→62 µg/24 hours, 2.1%→1.6%, in the order given). Uric acid, phosphorus and bicarbonate levels were at normal levels in the urine. Anemia started to decrease on the 15th day of hemolysis and it recovered on day 30. Since nitrogen retention did not regress at the end of week three, renal biopsy was performed. Acute tubular necrosis was detected in the biopsy. The renal functions returned to normal levels on day 30. As result although renal function is normal, hemodialysis treatment together with chelating agent should be performed at an early stage in such patients.

Key words: Copper sulfate, intoxication, acute renal failure

ÖZET

Bakır sulfat, sebzelerin, meyvelerin ve tahıl ürünlerinin bakteriyel ve fungal hastalıklarının kontrolü için kullanılan bir fungusiddir. Çok küçük miktarları dahi toksiktir. Akut toksisitesinde hemolitik anemi, akut tubuler nekroz, hepatotoksisite ve rabdomyoliz gelişir.

Ellibeş yaşında bir erkek hasta midede yanma, bulantı, kusma ve epigastrik ağrı yakınmaları ile başvurdu.

İntihar amacıyla oral bakır sulfat alımına bağlı hemolitik anemi, akut böbrek yetersizliği, hepatotoksisite (sadece artmış AST) ve rabdomyoliz saptandı. İdrar miktarı 3-4 L/gün olarak seyretti. D-penisilamin (900 mg/gün) başlandı. Metabolik asidoz kaydedildi. Yirmi günde 9 kez hemodiyaliz uygulandı.

Serum ve idrarda artmış bakır düzeyleri ve yüksek methemoglobinemi düzeylerinde yavaş yavaş azalma gözlendi (210 µg/dl→92 µg/dl, 98 µg/24 saat →62 µg/24 saat, 2,1%→1,6%, sırasıyla). İdrardaki ürik asid, fosfor ve bikarbonat düzeyleri normaldi. Hemolizin 15. gününden itibaren gerilemeye başlayan anemi 30.günde tamamen düzeldi. Azot retansiyonunun üçüncü haftanın sonunda da gerilememesi üzerine böbrek biyopsisi yapıldı. Akut tubuler nekroz gösterildi. Böbrek fonksiyonu 30. günde normale döndü.

Anahtar kelimeler: Bakır sulfat, zehirlenme, akut böbrek yetersizliği

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INTRODUCTION

Copper sulfate is a fungicide used for the control of bacterial and fungal diseases of vegetables, fruits, and grain products. It is in powder form, dilatable powder, or liquid. It is a material that can be easily absorbed to the skin and the mucosa and lead to burning and acute toxicity. Although it is absorbed well in the acidic environment of the stomach, the intestines function as a natural barrier. After oral intake, more than 99% is excreted out by the feces. On the other hand, even a very small amount left inside leads to defects in the organ especially in the liver, kidneys, heart, brain and muscles (20). Even the intake in dosages of gram is toxic as well (16). It was indicated that the oral LD50 level in the rats is 472 mg/kg (15). It is noted that the lowest level of toxicity in humans is 11 mg/kg (8). Since it eliminated automatically by vomiting due to its irritant effect in the gastrointestinal mucosa, it is often not toxic. The symptoms come out generally after intake of 1-12 g. These are metallic taste in the mouth, retrosternal and epigastric burning, nausea, repeated vomiting, headache, sweating, shock, jaundice and oliguria. Clinical symptoms due to damage in the brain, liver, kidneys, stomach and intestines accompany the case (17). Especially its use in vineyards by means of spraying may lead to chronic toxicity within 3-15 years (15). Its long term effects as consequence of over absorption of copper are similar to those seen in the Wilson disease (4). The chronic effect of copper at low levels is anemia (15). Its long term effects in rats are growth retardation and even death. The research on animals reveals testicular atrophy, teratogenic, mutagenic, and cancerogenic effects at 10 mg/kg/day dosage (15).

We present a case with prolonged toxic hemolytic anemia, acute renal failure caused by acute tubular necrosis, disorder in liver functions, rhabdomyolysis and blurred consciousness which developed after oral intake of copper sulfate for suicidal purposes.

CASE

A 55 year-old man was hospitalized with complaints of nausea, vomiting and abdominal pain. His wife said that seven hours ago, he had taken half a spoon of powder copper sulfate which is agricultural chemical by adding water to it. His general condition was fine, his consciousness was clear; he was active and cooperative. His arterial blood pressure was 100/80 mm Hg. Physical examination was normal. Gastric lavage was performed with active coal. Parenteral hydration and 900 mg/day D-penicillamine was started. When he was hospitalized, the following values were recorded; Hct: 52%, Hb: 16.6 g/dl, MCV: 98.7 µ3, MCH: 31.5 pg, MCHC: 31.9 g/dl, leucocyte: 19600/ml, thrombocyte: 140000/ml, glucose: 117 mg/dl, BUN: 14 mg/dl, creatinine: 1.2 mg/dl, Na: 138 mmol/l, K: 5.1 mmol/l, Cl: 105 mmol/l, AST: 30 U/l (15-37), ALT: 21 U/l (30-65), ALP: 105 U/l (50-136), GGTP: 24 U/l (5-85), CK: 63 U/l (21-232), CK-MB: 32 U/l (0-24) (Table 1). At fifth hour, LDH: 261 U/l (100-190), total bilirubin: 2.29 mg/dl, direct bilirubin: 0.30 mg/dl, indirect bilirubin: 1.99 mg/dl. It was considered that toxic hemolysis due to copper sulfate had developed. Serum copper and methemoglobin levels had been found 210 µg/dl (N: 80-140) and 2.1% (N<1.5%), respectively. At ninth hour, BUN: 22 mg/dl, kreatinin: 1.8 mg/dl, uric acid: 4.8 mg/dl, total bilirubin: 2.45 mg/dl, indirect bilirubin: 2.19 mg/dl, LDH: 297 U/l, AST: 45 U/l, ALT: 21 U/l. He was followed for toxic acute tubular necrosis development caused by copper. The quantity of urine had been recorded as 70-100 ml/hour. The color of the urine had been dark green-brown. Urinary sediment was normal. Levels of glucose, uric acid, phosphorus, bicarbonate had been normal in the urine. The level of copper in the urine had been 98 µg/24 hours (N:<60). Metabolic acidosis was recorded (PaO2: 92 mm Hg, PaCO2: 30 mm Hg, PH: 7.32 and HCO3: 14 mmol/l). Findings associated with nitrogen retention and hemolysis were detected. Anemia was detected on the third day. Increase in the levels of AST and CK were observed on the fourth day. Acute erosive gastritis was shown by endoscopy. Nine units of erythrocyte transfusion were made due to severe anemia. Hemodialysis treatment was started as of day 5 in the patient whose nitrogen retention increased gradually. Hemodialysis was performed 9 times in twenty days. During the follow-up period, the quantity of urine had been 3-4 L/day. The color of urine turned normal gradually. The copper levels in the serum and urine and methemoglobinemia decreased on day 20. They were recorded as 92 µg/dl, 62 µg/24 hour, 1.6 %, respectively. The other values returned to normal within following days (indirect bi-

Table 1. Laboratory findings

Day	Hb (g/dl)	Hct (%)	Total bil. (mg/dl)	Ind. bil. (mg/dl)	LDH (U/l)	Creatinine (mg/dl)	AST (U/l)	CK (U/l)
After 5 hour from intake	16.6	52	1.8	1.4	222	1.2	30	63
After 16 hours from intake	16.7	49.5	2.45	2.19	297	1.8	45	72
3	7.8	24.0	6.26	5.28	1033	3.6	118	442
5	6.6	20.5	6.5	5.5	2100	5.2	226	677
6	5.3	15.0	6.12	4.78	1995	4.5	142	1383
7	5.4	15.6	1.3	0.80	1200	4.0	23	114
15	5.9	18.1	0.27	0.17	386	3.7	14	62
30	10.6	32.5	0.25	0.15	170	1.0	13	58

lirubin, AST and CK 7., LDH level 15.). Anemia improved on the day 30. Renal biopsy was performed since nitrogen retention continued at the end of week 3 as well. Findings compatible with acute tubular necrosis had been found in the biopsy (Figure-1). Kidney functions returned to normal on day 30.

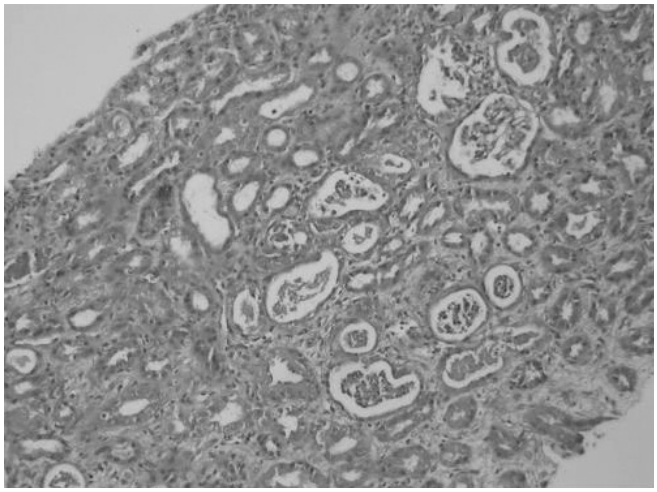

Figure 1. Normal glomeruli, flat epithelium of tubuli, desquamated cells and cylinders in lumen are seen (HEx125).

DISCUSSION

Copper sulfate is a compound, of which, even a very small quantity has a toxic effect. Hemolytic anemia, acute tubular necrosis, hepatotoxicity and rhabdomyolysis develop as a consequence of its acute toxicity. It is reported that mortality reaches up to 24.9 % (5, 22). In our case, at approximately 12th hour following the intake of copper sulfate, high levels of indirect bilirubine and LDH and nitrogen retention were detected. Then, these values increased gradually. Anemia was detected on day 3. Nine units of erythrocyte transfusion were made during the period that he was hospitalized. Organocopper compounds may cause prolonged hemolysis and methemoglobinemia through oxidative stress, especially among patients with G6PD deficiency (22). It was reported that hemolytic anemia had extended up to 18 days (18). In our patient, high level of indirect bilirubin caused by hemolysis returned to normal on day 7 and high level of LDH returned to normal on day 15. However, anemia improved after day 30. Hepatotoxicity and rhabdomyolysis had been also noted in copper sulfate intoxication (6). There has been an increase in the levels of AST and CK on day four in our patient but AST improved on day 8 and CK improved on day 9. Gastrointestinal injury is seen usually (12, 13, 22). Acute erosive gastritis was revealed by endoscopy in our patient.

It is known that renal tubular damage is predominant in chronic copper toxicity (11). It had been shown that chronic tubulointerstitial nephritis had developed as a consequence of parenteral copper sulfate (7). The significance of hemodialysis or hemoperfusion had been emphasized for treatment of acute tubular necrosis caused by copper (5, 10, 20, 9, 14). But according to some authors, copper is nondialysable and that hemodialysis is ineffective in the treatment of acute copper sulfate poisoning (3). In our case, hemodialysis indication developed on day five. Hemodialysis was performed nine times. However, nitrogen retention did not withdraw at the end of third week. Therefore, renal biopsy was performed. Acute tubular necrosis was detected in the biopsy. The fact that that copper was not shown with orsein may be explained with the elimination of copper by dialysis prior to biopsy. Nitrogen retention, increased copper levels in serum and urine and methemoglobinemia levels recovered on day 30.

It is known that a chelating agent (BAL, edetic acid, methylene blue, D-penicillamine, mercaptodextran, dimercaptopropane sulphonate, etc) may be useful in early stage (1, 2, 19). Using dimercaprol (BAL) and edetic acid rather than penicillamine are recommended (21). The haemolytic activity of copper sulfate (0.3 mM) in vitro was reduced in the presence of albumine (5-20g/l). The presence of D-penicillamine, triethylene tetramine or dimercaptosuccinic acid (0.3 mM) also reduced the copper-induced hemolysis, whereas 2,3-dimercaptopropane-1-sulphonate increased the cytolysis. N-ethylmaleimide (NEM) in appropriate concentrations (1 mM), as well as chromic chloride (0.3 mM), reduced the copper-induced hemolysis. Higher concentrations of NEM (2 mM) were ineffective (2) . D-penicillamine was started in our patient on first day.

Principle therapy in copper sulfate intoxication is removal of copper (hemodialysis, hemoperfusion or haemodiafiltration) together with the chelating agent (9, 14).

CONCLUSION

Copper sulfate is a material, of which, even a very small amount is toxic. In its acute toxicity, prolonged hemolytic anemia and renal failure is major presentation. Hepatotoxicity and rhabdomyolysis may also be added. Although renal function is normal, hemodialysis treatment together with chelating agent should be performed at an early stage. Because this approach may shorten the treatment period and is life rescuer.

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