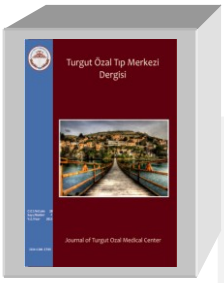

OLGU SUNUMU/CASE REPORT
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Acute Kidney Injury Associated with Rapid Treatment of Hemodiafiltration for Bismuth Intoxication: Update and Review of the Literature

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Abstract
A 16-years-old girl admitted to our emergency unit with complaints of nausea and vomiting. From her history, we learned that she had ingested 35 tablets (10.5 g) of colloidal bismuth subcitrate (CBS) (De-Nol) in a suicidal attempt 7 days ago. On admission, her physical examination findings were unremarkable. Her laboratory findings were blood urea nitrogen (BUN) 76.0 mg/dl, serum creatinine (Cr) was 19.2 mg/dl and serum bismuth level was 395 µg/L. Intravenous fluid and electrolytes, hemodialysis (HD) and penicillamine as a chelator agent was initiated. Then, continuous veno-venous hemodiafiltration (CVVHDF) was performed during 72 hours. On the 3rd day the CVVHDF treatment BUN and Cr values decreased to 14 mg/dl and 0.78 mg/dl, respectively. This case report showed that CVVHDF can be an alternative therapy for acute kidney injury due to CBS intoxication when complications observed in HD.
Key Words: Acute Kidney Injury; Children; Colloidal Bismuth Subcitrate; Hemodiafiltration.

Hemodiafiltrasyon İle Hızlıca Tedavi Edilen Bizmut Zehirlenmesine Bağlı Akut Böbrek Hasarı: Güncelleme ve Olgu Tartışması

Özet
On altı yaşında kız hasta bulantı ve kusma yakınmaları ile acil servisimize başvurdu. Öyküsünden, 7 gün önce intihar amaçlı 35 adet De-Nol tablet (10,5 gr kolloidal bizmut subsitrat) aldığı öğrenildi. Başvuru anındaki fizik muayene bulguları normal olarak değerlendirildi. Laboratuar tetkiklerinde; BUN 76 mg/dl, kreatinin 19.2 mg/dl ve serum bizmut düzeyi 395 µg/lt idi. Hastaya sıvı ve elektrolit tedavisi, hemodiyaliz tedavisi ve şelatör ajan olarak penisilamin tedavileri başlandı. Daha sonra, 72 saat süreyle sürekli venö-venöz hemodiyafiltrasyon tedavisi uygulandı. Üç günlük hemodiyafiltrasyon tedavisi sonunda BUN: 14 mg/dl ve serum kreatinin düzeyi 0.78 mg/dl'ye geriledi. Penisilamin tedavisinin 14. gününde serum bizmut düzeyi 32 µg/L'ye düştü. Bu vaka; kolloidal bizmut subsitrat intoksikasyonu sonucu gelişen akut böbrek hasarının tedavisinde hemodiyaliz yan etkileri gözlendiğinde hemodiyafiltrasyonun alternatif bir tedavi yöntemi olabileceğini göstermiştir.
Anahtar Kelimeler: Akut Böbrek Hasarı; Çocuklar; Kolloidal Bizmut Subsitrat; Hemodiafiltrasyon.

INTRODUCTION

Bismuth salts, especially colloidal bismuth subcitrate (CBS) and bismuth subsalicylate, have been widely used to treat nonspecific gastrointestinal diseases such as chronic gastritis, peptic ulcer, hemorrhoids, and dyspepsia (1,2). Very low amount of bismuth salts are absorbed from the gastrointestinal tract, therefore in normal doses side effects due to bismuth subcitrate are rare. The side effects such as encephalopathy, nephropathy, osteoarthropathy, stomatitis, gingivitis, and colitis after overdoses over bismuth salts have been widely documented in population (1-4). CBS has higher risk of toxicity than other bismuth salts because it has higher bioavailability. Encephalopathy is a well-known and a life-threatening complication of chronic exposure to high levels of bismuth salts, whereas acute toxicity manifests as nephrotoxicity as a result of destruction of proximal tubule epithelial cells. To date, acute kidney injury after overdose of CBS has been reported in only a few adult cases (5-12). Currently there is no established treatment regimen for bismuth intoxication. Gastric lavage, administration of activated charcoal, chelating agent (sodium-2.3-dimercapto-1-propanesulfone (DMPS) or penicillamine), bowel irrigation or colonic purgation, hydration, and forced diuresis have been recommended, especially in the early stage after an overdose of CBS. Hemodialysis (HD) or peritoneal dialysis (PD) should be performed if acute renal failure develops (5-12). To our knowledge, there is no information in the literature about continuous veno-venous hemodiafiltration (CVVHDF) treatment which is used for CBS intoxication. Therefore, we present the case of an adolescent girl who developed acute kidney injury due to an overdose of CBS and treated with CVVHDF.

CASE REPORT

A 16-years-old girl admitted to our pediatric emergency room with complaints of nausea, vomiting which had continued for 7 days. From her history, it was learned that she had ingested 35 tablets (10.5 g) of CBS (De-Nol 300 mg, 60 tablets, Genesis Pharmaceutical and Health Products Corporation, Turkey) in a suicide attempt. Evaluation at admission revealed that the patient (162 cm, 45 kg) had pulse rate of 90 beats/min and blood pressure of 120/70 mmHg. On admission, her physical

findings were unremarkable, there was no sign of encephalopathy and urine output was normal. Laboratory investigations revealed the following results: hemoglobin level 9.9 gr/dl, white blood cell count 6.4×10^3/µL, platelet count 250×10^3/µL, blood urea nitrogen (BUN) 76 mg/dl, serum creatinine (Cr) 19.2 mg/dl and serum uric acid level 8.2 mg/dl. Serum electrolytes and liver function tests were normal. Urinalysis showed specific density 1.007, pH 6.0, glucose 200 mmol/L, protein 0.30 g/L, ketone positive, bilirubin negative, with 1–2 leukocytes and 1-2 erythrocytes per high-power field (×400). The results of renal function tests were creatinine clearance 4.6 ml/min/1.73 m^2, fractional sodium excretion 5.1%, renal failure index 10.2%, protein excretion in 24-hours urine 21 mg/m^2/hour, and tubular phosphate reabsorption 68%. Abdominal ultrasound revealed that the kidney size was normal, and parenchyma echogenicity of kidneys bilaterally increased. Electrocardiography and echocardiography findings were normal. Serum bismuth concentrations were measured by atomic absorption spectrophotometer, and the level 3 days after admission were measured 395 µg/l.

Acute poisoning due to CBS was diagnosed and IV saline was initiated at 2000 ml/m^2 per day in the paediatric emergency service. The patient was started HD therapy and oral treatment with a metal chelating agent (penicillamine 20 mg/kg per day) was also prescribed. Because of hypotension and arrhythmia was observed during HD, HD therapy was discontinued. Then, CVVHDF with a Prismaflex dialyzer machine (Gambro, Sweden), Prismaflex M100 set and AN69 filter membranes (0.9 m^2) was performed during 72 hours (the blood flow rate was 5-10 ml/kg/minute (maximum 180 ml/min) and ultrafiltration coefficient with blood, 1-2 ml/kg/hour). After CVVHDF therapy, the patient's serum levels of BUN, Cr and uric acid decreased gradually over approximately 3 days. When Cr reached 0.78 mg/dl on the 3rd day of the therapy, CVVHDF therapy was discontinued. Penicillamine was continued and the patient was hospitalized for observation for 2 weeks. During the hospitalization BUN and Cr levels did not increase and on the 14th day of penicillamine therapy serum bismuth level decreased to 32 µg/L. The patient was discharged with complete recovery.

DISCUSSION

Less than 1% of an oral dose of bismuth is absorbed, the remainder is excreted as insoluble salts in the stool. Absorbed bismuth binds to α_2-macroglobulin, immunoglobulin M, beta-lipoprotein, and haptoglobin in blood and is distributed to spleen, liver, brain, heart, skeletal muscle, and especially the kidney (3,4). Distribution of bismuth in the organs is largely independent of the compound administered or the route of administration. Bismuth binds to a metal-binding protein in proximal renal tubule cells, and remains bound in this way for months. Elimination from blood displays multi-compartment pharmacokinetics. It is excreted in saliva, urine, and bile (2,3). At therapeutic doses serum bismuth concentrations range from 10–20 µg/l. It has been suggested that 50 µg/l signals possible toxicity [7]. In our patient's serum bismuth concentration 3 days after admission to our centre (10 days after ingestion) was 395 µ/l. Over the second week of the therapy we observed to 32 µg/L reductions in blood bismuth concentration after CVVHDF and penicillamine therapy.

In acute bismuth nephrotoxicity renal blood flow and glomerular filtration rate are both decreased. Leussink et al. (13,14) developed a rat model for bismuth induced reversible nephropathy. A large single oral overdose of CBS administered to Wistar rats led to damage to the proximal tubule, especially in the last segment. They observed that high overdose of bismuth induced cell death by necrosis, possibly by destabilization of the cell membrane in another study (15). The same research group showed that bismuth nephrotoxicity is mediated by changes in the distribution of proteins involved in intercellular adhesion [16]. When acute tubular necrosis occurs, this leads to defective reabsorption in the proximal tubule. In our case we observed findings of tubular dysfunction such as glycosuria, proteinuria, and decreased tubular phosphate reabsorption. To date, acute kidney injury after overdose of CBS has been reported in five adults and three pediatric patients (Table 1) (5-12).

In three of these eight cases, renal biopsy showed acute tubular necrosis (6,7,9). One patient was successfully managed strictly with fluid therapy, furosemide, dopamine, and mannitol [7], whereas the other seven patients were treated with dialysis (six HD and one PD) (5,6,8-12).

Hudson et al. (5) documented blood bismuth levels before and after HD in their adult patient. Similarly Cengiz et al. (12) documented blood bismuth levels before and after HD in their pediatric patient. They reported transient reduction in blood bismuth concentration after HD, and they attributed this to redistribution from tissue stores. Clearance of bismuth from tissues via HD was inadequate, and their patient had detectable blood bismuth levels 2 or 3 months after the agent was ingested. Islek et al. (10) reported a 2-year-old patient with colloidal bismuth overdose who was treated with PD alone. They observed that removal of bismuth via this method was also slow. In our case, we started HD therapy and oral treatment with penicillamine accordance with the literature. However, our patient did not tolerate HD because of the complications due to HD. Therefore, we used CVVHDF therapy. At the end of the 3rd day of CVVHDF therapy renal functions and clinical findings improved. Over the 3rd day of therapy we observed 32 µg/L reductions in blood bismuth concentration after CVVHDF. In the literature, the half-life of bismuth in blood is reported in various ranges. It can be as short as 3.5 min and as long as 17–22 years (3,17). We think that the half-life of bismuth in blood in our case may be short, suggesting rapid clearance of CVHDF.

Table 1. Reported cases of overdose of colloidal bismuth subcitrate in the literature

Reference	Age, Sex	Ingestion form	Ingested CBS	Therapy	Outcome
Hudson et al. (5)	27, M	Acute one time, 4 h previously	12 g	HD, rehydration, colonic purging	Alive
Taylor et al. (6)	76, M	Acute one time, 4 h previously	9.6 g	HD, colonic purging	Died
Huwez et al. (7)	21, M	Acute one time, 3 h previously	4.68 g	IV crystalloid, furosemid, dopamine, mannitol	Alive
Stevens et al. (8)	21, M	Acute one time, 48 h previously	6–7.2 g	Charcol, bowel irrigation, HD, chelating agent (DMPS)	Alive
Akpolat et al. (9)	16, F	Acute one time, 1 week previously	1.2–1.8 g	HD	Alive
Islek et al. (10)	2, M	Acute one time, 6 h previously	3.2 g	Gastric lavage, PD, IV crystalloid	Alive
Hruz et al. (11)	22, F	Acute one time, 60 h previously	5.4 g	HD, chelating agent (DMPS)	Alive
Cengiz et al. (12)	16, F	Acute one time, 10 days previously	18 g	HD, chelating agent (penicillamine), İV crystalloid	Alive
Present case	16, F	Acute one time, 7 days previously	10.5 g	CVVHDF, chelating agent (penicillamine), İV crystalloid	Alive

M; Male, F: Female, IV; Intravenous, CBS; Colloidal bismuth subcitrate, HD; hemodialysis, PD; peritoneal dialysis, CVVHDF; Continuous veno-venous hemodiafiltration, DMPS; sodium-2,3-dimercapto-1-propanesulfone

Hruz (11) described the case of a 22-year-old woman who ingested 5.4 g CBS in a suicide attempt. These authors used intravenous sodium DMPS as a chelating agent in addition to HD. They noted that the patient's serum bismuth level decreased to 15 µg/l within 6 days, and that she had normal renal function after 6 weeks of treatment. In patients with renal insufficiency due to bismuth intoxication chelating with DMPS is highly effective when used in conjunction with HD. It has been suggested that early treatment with intravenous DMPS and HD helps prevent the development of acute kidney injury in cases of bismuth overdose (11). Unfortunately, we were unable to obtain this drug but decided to try another metal chelator, penicillamine. The efficacy of penicillamine and dimercaprol in cases of bismuth overdose is controversial in bismuth overdose. Some authors have reported that these drugs may be effective in the early stages before tissue binding has occurred, which is similar to our findings (5,18). In our case, we observed that penicillamine may be effective in the early stages before tissue binding has occurred, which is consistent with previous studies.

In this case, we showed that with CVVHDF renal functions improved more quickly than HD. We thought that CVVHDF can be an alternative therapy for acute kidney injury due to CBS intoxication when complications observed in HD.

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