Reversible Acute Renal Failure After Colloidal Bismuth Subcitrate Intoxication: Case Report

Kolloidal Bizmut Subsitrat İntoksikasyonu Sonrası Gelişen Geri Dönüşümlü Akut Böbrek Yetmezliği: Olgu Sunumu

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ABSTRACT

Bismuth salts are widely used to treat peptic ulcers. Colloidal bismuth subcitrate has been reported in the literature to be nephrotoxic in humans when taken in high doses. In this case report, we present of acute renal failure on account of colloidal bismuth subcitrate overdose in a 23-year-old young woman. In general, acute renal failure after colloidal bismuth subcitrate intoxication is reversible if appropriately managed. Treatment with the chelating agent dimercaptosuccinic acid particularly in combination with hemodialysis is an effective treatment in reducing serum bismuth levels in the patient with acute renal failure.

KEY WORDS: Acute renal failure, Bismuth salt, Hemodialysis, Intoxication, Nephrotoxicity

ÖZ

Bizmut tuzları peptik ülser tedavisinde yaygın olarak kullanılmaktadır. Literatürde, kolloidal bizmut subsitratın yüksek dozda alındığında nefrotoksik olduğu bildirilmiştir. Bu olgu sunumunda, yüksek doz kolloidal bizmut subsitrat kullanımı sonrası gelişen akut böbrek yetmezliği olan 23 yaşında kadın hasta tanımlanmaktadır. Genellikle, kolloidal bizmut subsitrat intoksikasyonu sonrası ortaya çıkan akut böbrek yetmezliği doğru yönetilirse geri dönüşümlüdür. Akut böbrek yetmezlikli hastalarda serum bizmut düzeyinin azaltılmasında şelasyon ajanı dimerkaptosüksinik asit ile birlikte hemodiyaliz uygulanması etkin tedavi yöntemidir.

ANAHTAR SÖZCÜKLER: Akut böbrek yetmezliği, Bizmut tuzu, Hemodiyaliz, İntoksikasyon, Nefrotoksisite

INTRODUCTION

Bismuth salts, especially colloidal bismuth subcitrate (CBS) and bismuth subsalicylate are commonly used to treat patients with peptic ulser and non-ulcer dyspepsia (1,2). Toxic effects are rarely seen with the treatment dose of bismuth salts due to the low amounts of absorption from the gastrointestinal tract (3,4). The most common side effects of high dose bismuth intake have been declared as encephalopathy, nephropathy, osteoarthropathy, gingivostomatitis, and colitis. Chronic exposure to high levels of bismuth salts result in encephalopathy, whereas acute toxicity manifests as nephrotoxicity. In a few case reports, acute renal failure (ARF) was described after an overdose of CBS (5,6,7). In this case report, we present a 23-year-old woman with ARF after CBS intoxication.

CASE PRESENTATION

A 23-year-old woman presented to the emergency department of another hospital one hour after taking 40 tablets (De-nol, Zentiva, Kırklareli, Turkey) (12 g) of CBS in a suicide attempt. Each tablet included 300 mg of CBS. There was no medical history of previous intoxication or any other health problems. On admission, the patient was agitated but other physical examination findings were unremarkable. Her blood pressure was 110/60 mm Hg, pulse rate

Received : 08.07.2015
Accepted : 26.10.2015

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was 80 beats/minute, respiration rate was 16 breaths/minute, and body temperature was 36.5°C. Laboratory investigation revealed white blood cell count (WBC) 8.6 X 10^9/L, hemoglobin (Hb) 14.4 g/dL, platelet count (Plt) 263 X 10^9/L, blood urea nitrogen (BUN) 11.6 mg/dL, blood serum creatinine 1 mg/dL, and normal serum levels of electrolytes and liver enzymes. In the emergency department, the patient underwent gastric lavage with administration of activated charcoal and received intravenous fluid therapy. After consultation with the Turkey National Poison Information Center, they started oral treatment with the chelating agent dimercaptosuccinic acid (DMSA, succimer), using the following regimen: 10 mg/kg/dose every 8 hours for 5 days, followed by 10 mg/kg/dose every 12 hours for 14 days. At the end of the third day, her serum BUN and serum creatinine levels increased to 25 mg/dL and 2.6 mg/dL, respectively. Therefore, she was brought to the intensive care unit in our center.

Evaluation at admission observed that the patient's blood serum creatinine level increased to 4 mg/dL, while BUN was 25 mg/dL. Other laboratory tests were as follows: WBC, 8.8 X 10^9/L; Hb, 11.8 g/dL; Plt, 204 X 10^9/L; serum sodium, 137 mEq/L; serum potassium, 3.3 mEq/L; serum calcium, 9 mg/dL; serum phosphorus, 3 mg/dL; serum uric acid, 2.8 mg/dL; serum glucose, 96 mg/dL; serum aspartate aminotransferase, 49 U/L; serum alanine aminotransferase, 23 U/L; serum lactate dehydrogenase, 518 U/L. Urinalysis showed a density of 1012, pH of 5,5, protein of 500 mg/dL, glucose of 150 mg/dL, and 2 leukocytes and 2 erythrocytes per high-power field. Arterial blood gases showed metabolic acidosis with pH 7.27, PCO_2 21.8 mmHg, PO_2 130 mmHg, HCO_3 12.6 mmol/L, and BE -15 mmol/L. As the patient remained oliguric (<500 ml/day) and had persistent renal failure with metabolic acidosis, hemodialysis was started at the fifth day of DMSA administration also aiming to eliminate the CBS. Hemodialysis was conducted daily for the first three days and then alternate days. Avarage hemodialysis time was four hours. After six sessions, hemodialysis therapy was discontinued.

Table I: The patient's serum bismuth concentration and renal function parameters at different stages after the overdose of CBS.

Day after ingestion	Serum BUN (mg/dL)	Serum creatinine (mg/dL)	Serum bismuth (µg/l)	Urine volume (ml/day)
3	25	4		400
7	16	4.1		2500
10	17	5.2	69	2400
11	24	6.7	48	2600
13	21	6.6	36	2300
19	23	5.6	1.8	2450
25	15	1.6		
30	19	1		

After three hemodialysis sessions, the patient was transferred to the department of nephrology. Serum bismuth concentrations were measured by atomic absorption spectrophotometry (8) after admission to our department. The first measurement of serum bismuth level was 69 µg/l (10 days after ingestion) (Table I).

To exclude any additional pathology, ultrasonography and immunological parameters were performed. There was no any pathological finding. The clinical course was favorable. After the oliguric phase of the ARF, diuresis increased four days after admission in our center. Arterial blood gases and urinalysis returned to normal while the serum creatinine levels remained high. Therefore, hemodialysis was continued three times a week. Her serum creatinine levels decreased after six hemodialysis sessions, and hemodialysis therapy was stopped. On the 23rd day of admission to our center, the patient was discharged from the hospital. At discharge, her serum BUN and creatinine levels were 15 mg/dL and 1.6 mg/dL, respectively. At follow up one month after intoxication, the patient's renal function had returned to normal.

DISCUSSION

We have described the case of a patient with ARF after ingestion of CBS (40 tablets of De-nol include 12 g CBS) in a suicide attempt. The absorption of bismuth salts depends on the bismuth compound applied, dissolution of tablets, gastric and duodenal pH, and gastric emptying. Bismuth from CBS was at least 10% soluble and ultrafilterable and was absorbed in volunteers (>0.5%), whereas that from bismuth subnitrate was insoluble and not absorbed (<0.01%) (9). Distribution of bismuth in the organs is largely independent of the compound administered or the route of administration: the concentration in kidney is always highest and the substance is also retained there for a long time. It is bound to a bismuth-metal binding protein in the kidney, the synthesis of which can be induced by the metal itself. Elimination from the body takes place by the urinary and faecal routes, but the exact proportion contributed by each route is still unknown. Elimination from blood displays multicompartment pharmacokinetics with the the shortest half-life described in humans being 3.5 minutes, and the longest 17 to 22 years (10).

At therapeutic doses, bismuth concentrations range from 10 to 20 µg/l. It has been suggested that 50 µg/l signals possible toxicity (11). In our case, the patient's serum bismuth concentration was 69 µg/l, 7 days after admission to our center (10 days after ingestion). The first measurement of serum bismuth concentration was performed after the fourth hemodialysis session; because we were unable to take blood samples before the patient's transfer to our clinic. We thought that the serum

bismuth concentration was higher before treatment with hemodialysis and chelation with DMSA.

Hruz and colleagues showed that the treatment with the chelating agent sodium 2,3-dimercapto-1-propanesulfonate (DMPS), which is related structurally to 2,3-dimercapto-1-propanol (dimercaprol), combined with hemodialysis is an effective treatment in reducing the serum bismuth levels (6). In another case report, Cengiz et al (7). tried another metal chelator, penicillamine. DMSA (succimer) is an analogue of dimercaprol and has replaced dimercaprol as one of the main antidotes used in the management of poisoning by lead and other heavy metals. The advantages of succimer are that it is effective by oral administration because of its water-soluble pattern, it is well-tolerated, it has relatively low toxicity, and it can be given at the same time as iron supplements to treat iron deficiency anemia (12). In this regard, a study has shown that both DMSA and DMPS effectively increase the elimination of bismuth in the human urine and both chelators may be of benefit in the treatment of patients with bismuth intoxication (13). In our case, ARF occurred despite starting the treatment with DMSA as a chelating agent at the first day of ingestion. We suggest that early treatment with hemodialysis and DMSA helps to prevent the development of ARF in cases of bismuth overdose.

Leussink et al (14,15) developed a rat model for bismuth-induced reversible nephropathy. Histological examinations showed that the necrosis of the epithelial cells of the S3 segment of the proximal tubule occurs as early as 3 hours after CBS administration and is followed by a similar event in the S1/S2 segment 3–12 hours later. When acute tubular necrosis occurs, this lead to defective reabsorption in the proximal tubule. Acute tubular necrosis was the most encountered pathology in several case reports (11,16). Initially, In our case, we observed findings of proximal tubular dysfunction (Fanconi's syndrome) such as glucosuria (despite normal blood glucose levels), hypouricemia, hypophosphatemia, and metabolic acidosis. Because of the clear history of heavy metal intoxication and recovery of kidney failure, biopsy was not performed.

In summary, bismuth intoxication is a rare cause of ARF and is usually reversible if appropriately managed. Clinicians should be aware that AFR can occur after bismuth intoxication. Treatment with the chelating agent DMSA combined particularly with hemodialysis is an effective treatment in reducing serum bismuth levels.

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