The Turkish Journal of Pediatrics 2019; 61: 292-296
DOI:10.24953/turkjped.2019.02.024

Case Report

Bismuth intoxication resulting in acute kidney injury in a pregnant adolescent girl

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Received: 18th December 2017, Revised: 11th February 2018, 8th April 2018, Accepted: 14th May 2018

SUMMARY: Çelebi-Tayfur A, Yaradılmış RM, Ulus F, Çaltık-Yılmaz A, Özayar E, Koşar B, Büyükkaragöz B, Horasanlı E. Bismuth intoxication resulting in acute kidney injury in a pregnant adolescent girl. Turk J Pediatr 2019; 61: 292-296.

Bismuth intoxication is a rare cause of acute kidney injury (AKI) and is usually reversible by appropriate therapeutic measures. We present here a case of an adolescent pregnant girl who developed AKI due to an overdose of colloidal bismuth subcitrate (CBS, total amount of 6 g). She received parenteral chelating agent dimercaprol for 14 days. Continuous venovenous hemodiafiltration (CVVHD) with high-flux membrane was carried out in the first 3 days of chelating therapy and intermittent hemodialysis for 11 days, thereafter. The patient recovered clinically and was discharged after 21 days. She gave birth to a healthy term boy. At the last visit, the baby was 6 months old with normal growth and development as well as normal kidney functions. Neither deterioration in renal functions nor emergence of proteinuria was recorded in the patient during follow-up care after hospital discharge. In cases of AKI due to an overdose of CBS, treatment with dimercaprol combined with high flux hemodiafiltration and subsequently hemodialysis appears to be both useful and safe for bismuth elimination.

Key words: bismuth intoxication, acute kidney injury, dimercaprol, teratogenicity.

Bismuth is a heavy metal with the symbol Bi and atomic number 83 and molecular weight 208.98 Da. Bismuth salts are insoluble and especially colloidal bismuth subcitrate (CBS) and bismuth subsalicylate, are widely used to treat peptic ulcers, functional dyspepsia, and chronic gastritis.[1,2] Only small amount of bismuth (approximately %1) is absorbed following oral administration.[2] CBS has greater bioavailability than other bismuth salts; thus treatment with this form carries a higher risk of toxicity.[2,3] To date, only a few reports have documented nephrotoxicity after ingestion of colloidal bismuth. We present here a case of an adolescent pregnant girl who developed acute kidney injury due to an overdose of CBS.

Case Report

A 16-year-old adolescent pregnant girl was admitted to the emergency department 30 hours after taking 20 tablets of CBS (De-Nol) in a suicide attempt. Each tablet included 300 mg of CBS, which is equivalent to 120 mg of bismuth oxide (Bi_2O_3). She had symptoms of nausea and vomiting and looked anxious on admission. Intermittent vomiting was present for 24 hours prior to admission to hospital. Physical examination upon admission was unremarkable: blood pressure 110/70 mm Hg, pulse 82 beats/minute, respiration rate 16 breaths/minute, and body temperature 36.5°C. Laboratory tests were as follows: white blood cell count 18,300/mm^3, hemoglobin, 15.4 g/dl, platelet count 290,000/mm^3, blood urea nitrogen (BUN) 24 mg/dl, serum creatinine 1.92 mg/dl, sodium 136 mEq/L, potassium 3.69 mEq/L, chloride 111 mEq/L, calcium 8.5 mg/dl, phosphorus 3.1 mg/dl, magnesium 2.5 mg/dl, glucose 98 mg/dl, aspartate aminotransferase (AST) 17 U/L, alanine aminotransferase (ALT)

7 U/L, lactate dehydrogenase (LDH) 276 U/L, albumin 4.1 g/dl. Arterial blood gases showed metabolic acidosis (pH 7.31, $PaCO_2$ 22,4 mmHg, PaO_2 52.7 mmHg, base excess -17 mmol/L, and HCO3 14.6 mmol/L). The blood bismuth level on admission was 102.1 μg/L (normal <0.8). The quantification of Bi in the blood was determined by atomic absorption spectrophotometry (AAS/ICP-MS). Beta human chorionic gonadotropin level in the blood was high (150.07 mIU/ml; normal<5). Abdominal ultrasonography (US) demonstrated severely increased echogenicity on both renal parenchyma. Transvaginal US detected an early pregnancy at 5 weeks, 4 days. Urine dipstick testing and microscopy revealed proteinuria (+3), hematuria with red blood cells of normal morphology and pyuria. Decontamination of Bi was performed by gastric lavage and appropriate fluid therapy. The patient rapidly became oliguric (500 ml/day) and blood creatinine level increased to 4.34 mg/dl (BUN 31 mg/dl) during the first 48 hours of admission. Fractional Na excretion, renal failure index or tubular phosphate excretion could not be measured in the patient due to oliguria. After consultation with Turkish National Drug and Poison Information Center, a chelation therapy with parenteral dimercaprol, also known as British anti-Lewisite (BAL; 2,3-dimercapto-1-propanol) was started and continued for 14 days. Continuous venovenous hemodiafiltration (CVVHD) with high-flux membrane was carried out in the first 3 days of chelating therapy in the intensive care unit. We stopped CVVHD after 72 hours and then intermittent hemodialysis (HD) was prescribed daily (4 hours/day) for the first 4 days and then three times (4 hours/day) weekly for one week. The patient's urine output progressively increased and renal function tests comprising arterial blood gas analysis gradually improved. We could not measure Bi level in any body fluid or dialysate fluid except in the blood sample received before initiation of extracorporeal renal replacement therapy (RRT) as the patient's insurance did not pay for the testing. The patient recovered clinically and was discharged at 21 days of hospitalization. Her gradual improvement in renal functions continued after discharge. Her serum creatinine and BUN levels 45 days after discharge were 0.69 mg/dl and 12.2 mg/dl, respectively. At this time the urinalysis results were also normal. The council of perinatalogy and obstetrics counselled the pregnancy at 9 weeks and recommended termination of the pregnancy due to potential teratogenic effects of high dose bismuth exposure and parental dimercaprol treatment; but the the patient and her partner preferred continuation of the pregnancy. The pregnancy proceeded well within normal limits. The patient gave birth to a term healthy baby boy with vaginal delivery. We could not measure the Bi level either in blood or urine sample as the baby's insurance did not pay for the testing. At the last visit, the baby was 6 months old with normal growth and development as well as normal kidney functions. Neither deterioration in renal functions nor emergence of proteinuria was recorded in the patient during follow-up care after hospital discharge. Informed consent was obtained from the participant and the family included in the study.

Discussion

The absorption of bismuth salts depends on the bismuth compound applied, dissolution of tablets, gastric and duodenal pH, and gastric emptying.[3,4] In blood, bismuth is thought to be primarily present in red blood cells possibly binding to glutathione inside the cells, and the remaining portion is transported bound to transferrin, albumin, alpha-2-microglobulin, immunoglobulin M, beta-lipoprotein, and haptoglobin and distributes widely throughout tissues.[5,6] Bismuth accumulates in kidney, liver, spleen, bone (metaphysis), lung, heart, and muscle. Bismuth forms strong covalent bonds with sulfhydryl groups of cellular proteins including vital enzymes[4]. The half-life of bismuth in blood varies from 3.5 minutes to 17–22 years. This extreme variation is because of bismuth's accumulation and resecretion from tissues.[3] The most common side effects of high dose bismuth intake are encephalopathy, nephropathy, osteoarthropathy, gingivostomatitis, and colitis.[4,7-11] The possible toxicity occurs at serum bismuth concentrations above 50 μg/L.[10] CBS is a complex bismuth salt of citric acid which is soluble in water but precipitates at pH less than 5.[3] After receiving CBS, the bioavailability of bismuth ranges from 0.16 to 0.28%. and the blood clearance of bismuth ranges from 50 to 95 ml/min.[6] The bismuth concentration typically increased to a

maximum within the first hour after ingestion of CBS (215 mg bismuth) and decreased with half-lives of approximately 1.6±0.7 h in a study conducted in 20 volunteers. The authors suggested that some bismuth absorption may occur in the stomach and the upper sections of the intestine. A total of 0.03 to 1.2% (0.06–2.51 mg) of the ingested bismuth was eliminated via the kidneys, at the most in the first 12 h after ingestion in that study.[12] The 91 to 93% of the ingested bismuth is eliminated via the feces within 5 days after ingestion of CBS and a few percent are stored in the human body or are eliminated via alternative pathways.[12]

Bismuth intoxication is a rare cause of AKI and is usually reversible if appropriately managed. Bismuth binds to a metal binding protein in proximal renal tubule cells and remains bound in this way for months. In acute nephrotoxicity, renal blood flow and glomerular filtration rate are both decreased. In experimental studies, 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.[8] Acute tubular necrosis has been the most encountered pathology in several case reports which also occurred in our patient.[4,7-11] Both reversible and irreversible Fanconi's syndrome were described in patients with bismuth intoxication.[7,8] In such patients acute tubular damage may proceed as the release of bismuth continues from deposited tissues even if normal blood level is achieved. Accordingly, there are case reports describing patients with prolonged duration of acute renal injury in whom appropriate conventional extracorporeal methods and chelation therapy were applied and normal bismuth blood levels were achieved in a few days.[7,11] Plasmapheresis is effective in elimination of substances which remain highly bound to plasma proteins and low distribution volume.[13] Disel et al.[14] described a patient with bismuth intoxication who was treated with plasmapheresis along with HD and achieved a quick recovery of AKI. The authors suggested that the quick recovery might be relevant to plasmapheresis that cleared circulating bismuth compounds. As bismuth tightly binds to plasma proteins, plasmapheresis may be an alternative method for extracorporeal elimination in patients with bismuth intoxication and AKI. We did not perform plasmapheresis in our patient because of limited experience of its usage in heavy metal intoxication and of also non-availability of the machine in our hospital.

Continuous renal replacement therapy (CRRT) is a blood purification technique used to treat the most severe forms of AKI. In CVVHD, diffusive transport of molecules is combined with convective removal in order to mainly improve the clearance of small solutes. CRRT as a preferable modality in hemodynamically unstable patients with AKI. The membranes used in CRRT are typically more permeable compared to standard intermittent HD membranes. CRRT membranes allow for the clearance of molecules as large as 20,000–40,000 Da. Another advantage of CRRT is the ability to avoid rebound of toxins removed from intravascular space, due to continuous nature of the procedure and slower rate of clearance, leading to less dramatic decreases in plasma drug levels and slower reequilibration of toxins between intracellular and intravascular spaces[15]. The molecular weight of bismuth is 208.98 Da and conventional intermittent HD or peritoneal dialysis combined with chelating agent seems to be an appropriate therapeutic measure for the treatment of AKI developed due to bismuth intoxication. Hence, many of reported cases with bismuth intoxication and AKI benefited from these treatment modalities [8,11,16]. Elmas et al.[17] also reported recovery of renal functions in a 16 year-old girl who developed AKI after ingestion of CBS. She had received 10.5 g CBS (35 tablets De-Nol), 7 days before admission. She was treated with HD, CVVHD (for 72 hours) and penicillamine as a chelator agent. The authors suggested that CVVHD could be an alternative therapy for AKI due to CBS intoxication. We performed CVVHD in the first 72 hours of hospital stay in our patient because she had to be hemodinamically stable due to pregnancy and of concern of rebound of toxicity. High-flux, non-celluloses membrane used for HD has increased permeability and is capable of removing moderate-sized molecules between 10000 to 15000 Dalton, including many of the inflammatory proteins, $ß_2$ microglobulin and lipoproteins. Some authors suggest the use of high−flux membranes will improve the adequacy of dialysis.[18] We stopped CVVHD after 72 hours and then intermittent HD was prescribed. The dialysis frequency in our

patient was determined according to treatment schedules described in case reports with bismuth intoxication in whom chelation therapy and HD were performed for the treatment of AKI.[7,8,11,14,17]

Although the placenta is permeable to bismuth, no teratogenicity has been reported in humans. On the other hand, bismuth is considered as possibly unsafe during lactation[19]. Neither major nor minor congenital malformation was observed in the baby described here. Normal developmental milestones were reached by the baby according to his age during every visit. The patient did not stop breastfeeding her baby, either.

There are few case reports describing the effectiveness of chelating agents including dimercaprol, sodium 2,3-dimercapto-1-propanesulfonate (DMPS) or dimercaptosuccinic acid (DMSA; succimer) when combined with HD in the management of poisoning by bismuth[7,8,20]. Succimer is administered orally because of its water-soluble pattern. It is well-tolerated, it has relatively low toxicity[20]. It would be unsafe to treat our patient with oral medication as she was very anxious and irritable in the first day of administration. Also, we could not achieve any drug other than dimercaprol in the limited adverb of time, either.

Dimercaprol (British anti-Lewisite (BAL) in Oil) is used to treat acute poisoning by arsenic, mercury, gold, and lead. There are also case reports reporting the effectiveness of dimercaprol in antimony, thallium, or bismuth poisoning. The sulfhydryl groups of dimercaprol form complexes with certain heavy metals thus preventing or reversing the metallic binding of sulfhydryl-containing enzymes. The complex is excreted. The sustained presence of dimercaprol promotes continued excretion of the metallic poisons. Common side effects include high blood pressure accompanied by tachycardia, pain at the site of injection, vomiting, and fever.[21]

Its pregnancy category is C. Dimercaprol is teratogenic in mice and has been associated with increased mortality, growth restriction, cleft facial features, cerebral herniation and abnormal digit.[22] It is not known whether BAL in Oil can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity.[23] It should be given only if the potential benefit justifies the potential risk to the fetus. Despite the described potential side effects regarding bismuth intake in a toxic dose and also to parenteral dimarcaprol treatment, we did not observe any of these in our patient.

The American Association of Poison Control Centers and the European Association of Poisons Centres and Clinical Toxicologists have issued a joint statement that gastric lavage should not be employed routinely, if ever, in the management of poisoned patients[24]. However, in the case of recent and potentially lethal ingestion, the procedure may be considered after carefully weighing the well-documented risks against the unclear benefits. Nevertheless the time interval when to perform gastric lavage in intoxication may be extended to 24 hours after intoxication according to some authors' opinion.[25] It is a challenge why we performed gastric lavage 30 hours after CBS ingestion despite its low yield, the doubt about the accuracy of an pregnant adolescent's report of drug use led us to perform this procedure.

We have described the first case of an adolescent pregnant patient with AKI after ingestion of CBS in a suicide attempt. In cases of AKI due to an overdose of CBS, treatment with dimercaprol combined with high flux hemodiafiltration and subsequently HD appears to be both useful and safe for bismuth elimination. Clinicians should be aware that AKI can occur after bismuth intoxication.

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