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BRIEF REPORT

Successful management of acute bismuth intoxication complicated with acute renal failure, seizures and acute pancreatitis in a child

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ABSTRACT

Bismuth salts, including bismuth subcitrate, are commonly used for gastrointestinal disorders. Overdose of bismuth salts can lead to renal failure. Seizures and pancreatitis have not been reported as complications of bismuth overdose and/or chelator treatment up-to-date. An 8-year-old girl was presented with history of taking 18 grams of bismuth subcitrate, headache, agitations and anuria. She was hypertensive and her serum creatinine was 6.5 mg/dL with the estimated glomerular filtration rate of 9.61 ml/min/1.73 m^2. Antihypertensive drugs and hemodialysis were initiated. Fifteen hemodialysis sessions were performed during a month. At the sixth day of hospitalization dimercaptosuccinic acid (DMSA) treatment was initiated for chelating bismuth. Because of intense headache and seizures were observed after 7 days of DMSA therapy, DMSA was stopped and anticonvulsive drugs were given. Meanwhile pancreatitis was diagnosed based on ultrasound findings and increased serum lipase (maximum, 1363 IU/L) and amylase (maximum, 798 IU/L) levels. Following 10 days of anuria, polyuria developed. Clinical and laboratory findings of her returned to normal at the 35th day of hospitalization. In conclusion, seizures and pancreatitis may develop following chelator treatment for bismuth overdose. Chelation therapy should be used cautiously in bismuth intoxication.

Key Words: Bismuth intoxication, child, chelation therapy, complication, seizure, pancreatitis

INTRODUCTION

Bismuth salts are widely used for eradication of *Helicobacter pylori* in stomach and for some gastrointestinal complaints such as dyspepsia, nausea, and diarrhea without prescription. Bismuth toxicity is attributed to its affinity to combine with sulfhydryl groups of vital enzymes leading to destroying the functions of these enzymes. Nephrotoxicity is an early prominent finding of acute bismuth overdose, because bismuth is mainly excreted from kidneys. Bismuth can cause encephalitis with brain lesions. Diagnosis of bismuth intoxication is usually made by a history of taking bismuth containing drugs [1].

Normal therapeutic doses of bismuth generally do not lead to poisoning, due to very low gastrointestinal absorption of bismuth salts, except bismuth subcitrate, which has the higher intestinal absorption. Treatment of acute bismuth overdose include gastric lavage, activated charcoal, chelators agents [2-3dimercapto-1-propanesulfone (DMPS), dimercaptosuccinic acid (DMSA) or D-penicillamine], hydration, and even dialysis if severe acute renal failure developed [1,2]. In a search of English literature, we could not find a report on bismuth subcitrate intoxication leading to seizures and acute pancreatitis. In this report, we presented successful management of a child with bismuth overdose complicated with acute renal failure, convulsions and acute pancreatitis.

Case

An 8 years old girl with no history of a previous disease was referred to Dicle University hospital due to agitations, anuria and high levels of blood urea and creatinine. Medical history of the patient revealed that she had swallowed 60 tablets colloid bismuth subcitrate (De-Nol®,

each tablet containing 300 mg, totally 18 grams) throughout two days. She was referred after 5 days from taking bismuth tablets due to delay in apply to hospital. At hospital admission, her blood pressure was 150/90 mmHg, serum urea was 92 mg/dl and serum creatinine was 6.5 mg/dl. The estimated glomerular filtration rate (eGFR) was 9.61 ml/min/1.73 m^2. Urinalysis revealed blood trace, protein 2+, glucose 2+, density 1009, and leukocytes 50 per each field.

Intravenous fluid and electrolyte was initiated together with 2 mg/kg intravenous furosemid and anti-hypertensive drugs (amlodipine, doxazocin, and methyldopa). High blood pressure reduced to normal levels; however she remained oligo-anuric despite second dose of 2 mg/kg furosemid. Thus, intravenous fluids were limited to insensible fluid losses (400 ml/m^2/day) plus total amounts of daily urine output and hemodialysis decision was done. Afterwards, we performed 15-hemodialysis sessions during 30 days of hospitalization.

At the second day of hospitalization, agitations and headaches of the child more intensified, so we performed cranial computerized tomography (CT); however, cranial CT gave no abnormality. At the seventh day of hospitalization, we started 2,3-dimercaptosuccinic acid (DMSA) (30 mg/kg/day for 5 days followed by 20 mg/kg/day) because of anuric renal failure and continuous refractory headaches and agitations. We went on hemodialysis sessions daily or every other day based on her serum creatinine levels. At the 14th day of hospitalization more intensified headaches were reported by the patient and this followed by tonic-clonic convulsions. The seizure was stopped by midazolam infusion (25-50 µg/kg IV over 3 minutes), then diphenylhydantoin (15 mg/kg) was loaded and the patient was transferred to pediatric intensive care unit (PICU). Following repeated convulsions and development of impaired vision, brain magnetic resonance imaging (MRI) was performed. Cranial MRI showed widespread fine hyper-dense micro-areas in the cortex of brain parenchyma. Convulsion occurred once more and afterwards never repeated. DMSA was given 7 days and after seizures drug was discontinued. Meanwhile, increased serum lipase and amylase levels were noticed, and abdominal ultrasound disclosed increased peri-pancreatic fluid and increased anteroposterior diameter of pancreas on pancreas body, thus pancreatitis was diagnosed. Daily hemodialysis sessions were performed during hospitalization at PICU, intravenous parenteral nutrition was given for 8 days because of discontinuation of oral feeding due to pancreatitis. After that, oral feeding was re-instituted, based on clinical well-being of the child.

Following 10-day period of anuria, diuresis began and gradually increased to polyuria levels at the 15th day of hospitalization and polyuria (daily 1850-2100 cc urine) lasted nearly 3 weeks. During PICU hospitalization the patient received packed red cell and intravenous albumin infusion due to deep anemia and hypoalbuminemia. Serial measurements of blood chemistry and urine output are shown at Table 1.

Our patient had bismuth concentration of 219 µg/L in blood and 1245 µg/L in urine at hospital admission. These levels gradually decreased (Table 1) (Figure 1).

Table 1. Blood chemistry and urine output of the patient during hospitalization and follow up period

Date	Urine bismuth (µg/L)	Blood bismuth (µg/L)	Urea (mg/dl)	Creatinine (mg/dl)	LDH (IU/L)	Amylase (IU/L)	Lipase (IU/L)	Urine output (ml)	HD
Admission	1245	219	92	6,50	754	-	-	∅	+
3rd day	-	-	91	4.92	1294	-	-	∅	+
4th day	1025	184	52	3.52	720	-	-	∅	+
9th day	688	163	51	3.39	510	-	-	50	+
14th day	90	58	72	5.30	493	307	151	1200	+
18th day	-	-	82	2.78	400	508	259	2150	+
21st day	31	28	93	2.82	370	958	603	2050	+
23rd day	-	-	105	2.17	301	1363	798	2100	∅
28th day	-	-	70	1.50	256	564	235	1500	∅
35th day	15	20	39	0.69	170	339	123	1200	∅

LDH, Lactic dehydrogenase; HD, Hemodialysis

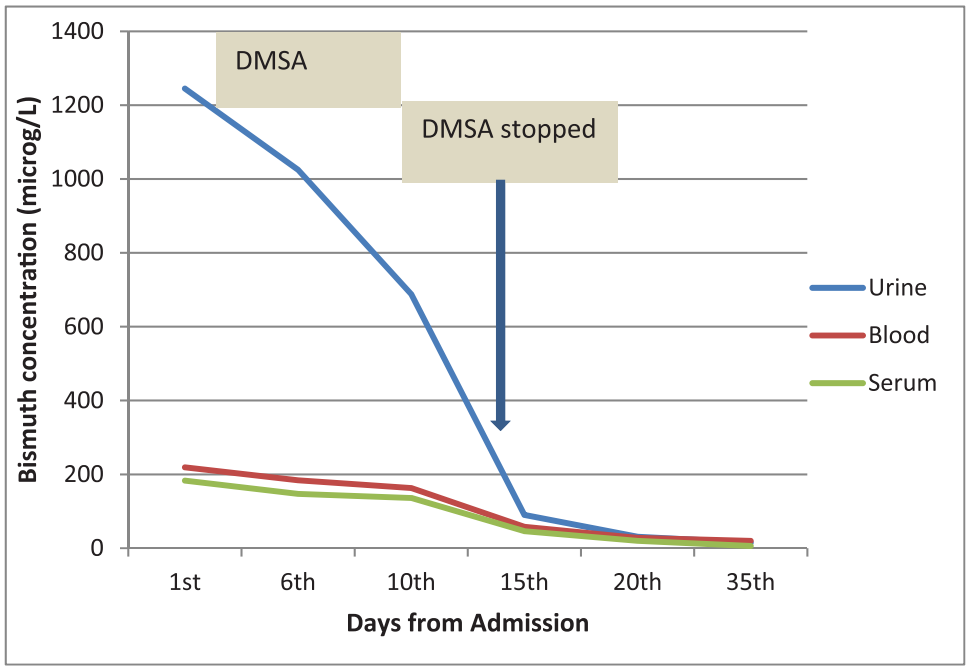

Figure 1. Change of bismuth concentrations in patient's urine, blood and serum during hospitalization

The patient discharged from the hospital at the 30th day of hospitalization. Follow up examination after two weeks from discharge revealed no clinical or laboratory abnormality. Now, the patient was under outpatient clinic controls without a health problem for 8 months. We obtained informed consent from the patient and her family.

DISCUSSION

Taking normal therapeutic bismuth doses can lead to serum bismuth concentrations of 10-20 μg/L and >50 μg/L may be a signal for possible toxicity and normal urine bismuth level should be less than 1 μg/L [1]. Serum and urine bismuth concentrations of our patient were very high at hospital admission and gradually decreased following 15 hemodialysis sessions and use of DMSA (Table 1).

Severe overdose of acute bismuth induces reversible proximal tubular damage leading to acute tubular necrosis (ATN). Acute tubular necrosis results in proximal tubular dysfunction, which clinically presents by low urine density, glycosuria, tubular proteinuria and decreased tubular phosphate reabsorption [3]. Our patient also presented with typical findings of ATN, such as anuria followed by polyuria, high serum creatinine, mild proteinuria, glycosuria and low density urine at admission. Clinical course of our patient also show three clinical phases of ATN, including anuric phase lasted 10 days followed by 4 weeks of polyuria, then returned to normal at last. This course of renal failure is typical for ATN.

The primary treatment is removal of the bismuth compounds from the body. Slikkeveer et al. [2] reported that dithiol compounds (DMPS, DMSA and BAL) were effective in most organs especially in kidney and liver resulting in higher elimination of bismuth via urine. Although chelation therapy is often recommended for severe acute poisoning, many experts prefer to treat conservatively and expectantly allowing bismuth to be excreted gradually. In support of this view, there is evidences of chelation therapy solubilizes the bismuth leads to increased concentration in the brain and lead to central nervous system complications [1,3]. One case report described clinical deterioration with DMPS and eventual discontinuation of the chelators like our case with DMSA [3]. In our case, we had to use DMSA because of anuric renal failure and severe irritability and headache of the patient, however when we observed seizures, we thought that bismuth would be accumulated in the brain secondary to more solubilization of the bismuth and discontinued the drug immediately. Brain MRI findings of our patient also supported this accumulation by reporting hyperdense microareas in brain cortex.

Acute pancreatitis has not been reported as a complication of bismuth overdose previously. Our case is the first reported pancreatitis case following bismuth overdose. Severe upper abdominal pain radiated to back was present in our patient. Acute pancreatitis also healed parallel to improvement of acute renal failure following hemodialysis treatment. Because findings of pancreatitis were observed following DMSA use, we speculated that pancreatitis also resulted from redistribution of more soluble bismuth due to DMSA.

In conclusion, we think severe central nervous system findings, seizures and pancreatitis might have occurred secondary to very high dose bismuth ingestion and redistribution of bismuth by DMSA use. Therefore only life-threating cases of bismuth poisoning should receive chelation therapy.

Declaration of interest: The authors report no conflicts of interest.
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