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BRIEF REPORT

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Acute renal failure after overdose of colloidal bismuth subcitrate

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Abstract Bismuth salts are widely used to treat peptic ulcers. Acute toxicity with colloidal bismuth subcitrate overdose causes nephrotoxicity. There have been numerous reports of encephalopathy after long-term consumption of bismuth salts, but only a few cases of nephrotoxicity (adult and pediatric) have been documented to date. This report presents a case of acute renal failure due to colloidal bismuth subcitrate overdose in adolescent. A 16-year-old girl presented with complaints of nausea, vomiting, and facial paresthesia. Ten days earlier she had tried to commit suicide by taking 60 tablets of De-nol (colloidal bismuth subcitrate 18 g). The physical examination findings on admission indicated minimal fluid overload but no signs of encephalopathy. Laboratory tests on admission showed blood urea nitrogen 102 mg/dl, serum creatinine 19.9 mg/dl, and serum bismuth level 495 μg/l. The patient was started on appropriate fluid therapy and penicillamine as a chelating agent and then began hemodialysis on alternate days. The patient's renal function gradually returned to normal over 9 weeks and by 64 days after the overdose her serum bismuth level had fallen to almost half the level detected 2 days after admission. The patient made a complete recovery. The case demonstrates that acute renal failure can develop as a manifestation of acute toxicity from colloidal bismuth ingestion, and that the prognosis may be favorable if the patient receives appropriate supportive treatment and dialysis

Keywords Acute renal failure · Colloidal bismuth subcitrate · Hemodialysis · Nephrotoxicity · Pediatrics

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Introduction

Bismuth salts, especially colloidal bismuth subcitrate and bismuth subsalicylate, are widely used to treat peptic ulcers, functional dyspepsia, and chronic gastritis [1, 2]. The reported toxic effects caused by overdose of bismuth compounds include encephalopathy, nephropathy, osteoarthropathy, gingivostomatitis, and colitis. These problems are rarely seen with normal use of bismuth salts because only small amounts of these compounds are absorbed from the gastrointestinal tract [3, 4, 5, 6, 7, 8, 9, 10, 11]. Colloidal bismuth has greater bioavailability than other bismuth salts; thus treatment with this form carries higher risk of toxicity. Chronic exposure to high levels of bismuth salts results in encephalopathy, whereas acute toxicity manifests as nephrotoxicity. To date only a few reports have documented nephrotoxicity after ingestion of colloidal bismuth [8, 9, 10, 11, 12, 13, 14]. We present the case of an adolescent girl who developed acute renal failure due to an overdose of colloidal bismuth subcitrate.

Case report

A 16-year-old girl presented to our hospital with complaints of nausea, vomiting, and facial paresthesia. Ten days earlier she had ingested 60 tablets (18 g) of colloidal bismuth subcitrate (De-Nol) in a suicide attempt. Six hours after ingesting the pills she had been taken to another hospital where she underwent gastric lavage, received intravenous fluid therapy, and was hospitalized for 24 h. However, for the next 9 days she continued to vomit 3 or 4 times daily at home and was thus brought to our center.

Evaluation at admission revealed that the patient (168 cm, 65 kg) had a pulse rate of 88 beats/min and blood pressure of 110/

Table 1 The patient's serum bismuth concentration and renal function parameters at different stages after the overdose (*BUN* blood urea nitrogen, *Cre* creatinine, *Bi* bismuth)

	Day after ingestion				
	10	12	18	26	64
Serum BUN (mg/dl)	102	57	29	22	16
Serum Cre (mg/dl)	19.9	14	5.6	2.1	1.1
Serum Bi before dialysis (μg/l)	–	495	470	366	260
Serum Bi after dialysis (μg/l)	–	450	320	317	–
Dialysate Bi (μg/l)	–	120	–	–	–
Urine Bi (μg/l)	–	162	–	–	–
Urine volume (ml/day)	875	900	1050	1500	–

70 mmHg. Physical examination revealed periorbital and pretibial edema and facial paresthesia but no signs of encephalopathy. Other systemic findings and urine output were normal. Blood biochemistry testing revealed blood urea nitrogen 102 mg/dl, serum creatinine 19.9 mg/dl, and normal serum levels of electrolytes and liver enzymes. Urinalysis showed specific density 1.005, pH 7.0, glucose 14 mmol/l, protein 0.74 g/l, sodium 79 mEq/l, and 4–6 leukocytes and 1–2 erythrocytes per high-power field (×400). The results of renal function tests were creatinine clearance 8.8 ml min^{-1} 1.73 m^{-2}, fractionated sodium excretion 6.6%, renal failure index 9.2%, and tubular phosphate reabsorption 63%. Abdominal ultrasonography demonstrated slightly increased kidney size bilaterally and slightly increased echogenicity in the renal parenchyma. Electrocardiography and echocardiography findings were normal.

Serum bismuth concentrations were measured by atomic absorption spectrophotometry, and the level 2 days after admission was 495 μg/l (Table 1). Appropriate fluid therapy was initiated and the patient started hemodialysis therapy, first on alternate days and then twice weekly. Oral treatment with a metal chelating agent (penicillamine 20 mg/kg per day) was also prescribed. The patient's serum blood urea nitrogen and creatinine levels decreased gradually over approx. 1 month. When serum creatinine reached 2.1 mg/dl, hemodialysis therapy was discontinued.

The patient made a good clinical recovery and was discharged after 16 days in hospital. Seven weeks after discharge her renal function had returned to normal, and her serum bismuth level had dropped to almost one-half the level detected 2 days after admission.

Discussion

Bismuth is absorbed from the gastrointestinal tract in very low amounts, less than 1% of oral dose. The remainder is excreted as insoluble salts in feces, and these change the stool color to black. The half-life of bismuth in blood varies from 3.5 min to 17–22 years. Absorbed bismuth binds to α_2-macroglobulin, immunoglobulin M, β-lipoprotein, and haptoglobulin in circulation, and is distributed to the spleen, liver, brain, heart, skeletal muscle, and kidneys. Distribution of bismuth in the organs is largely independent of the compound administered or the route of administration. The concentration of bismuth in the kidney, and its retention time is higher than in other organs (lung, liver, brain). Bismuth binds to a metal-binding protein in proximal renal tubule cells, and remains bound in this way for months. Elimination from blood displays multicompartment 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 [12]. In our case the patient's serum bismuth concentration 2 days after admission to our center (12 days after ingestion) was 495 μg/l. Over the first weeks of treatment we observed reductions in blood bismuth concentration after hemodialysis, but these were transient (Table 1), and it was thought that higher levels were likely being reestablished from tissue stores. Over a 9-week period the patient's serum bismuth level dropped to almost one-half the level that was detected in the initial days after admission.

Bismuth toxicity can develop due to excessive ingestion at one time or due to ingestion of large amounts over a prolonged period. Chronic bismuth intake can lead to toxicity in the form of encephalopathy, whereas acute toxicity manifests as nephrotoxicity [12]. Reports indicate that normal use of colloidal bismuth subcitrate or bismuth subsalicylate is not associated with neurotoxicity, and that these agents can be used safely at therapeutic doses for 4–8 weeks [1, 2, 7]. Specifically, encephalopathy has been associated with prolonged consumption of oral preparations of bismuth salts, and this condition can be reversed by discontinuing therapy [4, 5, 6, 7]. Our patient did not exhibit encephalopathy. Her only neurological sign was facial paresthesia, which was observed in the first 2 days of hospitalization and resolved spontaneously.

In acute bismuth nephrotoxicity renal blood flow and glomerular filtration rate are both decreased. Leussink et al. [15, 16] developed a rat model for bismuth induced reversible nephropathy. A large single oral overdose of colloidal bismuth subcitrate administered to Wistar rats led to damage to the proximal tubule, especially in the last segment (S_3). They observed that high overdose of bismuth induced cell death by necrosis, possibly by destabilization of the cell membrane in another study [17]. The same research group showed that bismuth nephrotoxicity is mediated by changes in the distribution of proteins involved in intercellular adhesion [18]. 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 glucouria, proteinuria, and decreased tubular phosphate reabsorption.

To date, acute renal failure after overdose of colloidal bismuth has been reported in five adults and two pediatric patients (Table 2) [8, 9, 10, 11, 12, 13, 14]. In three of these seven cases renal biopsy showed acute tubular necrosis [11, 12, 13]. One patient was succesfuly managed strictly with fluid therapy, furosemide, dopamine, and mannitol [12], whereas the other six were treated with dialysis (five hemodialysis and one peritoneal dialysis) [8, 9, 10, 11, 13, 14].

Hudson and coworkers [8] documented blood bismuth levels before and after hemodialysis in their adult patient. Similar to our case, they reported transient reduction in blood bismuth concentration after hemodialysis, and they attributed this to redistribution from tissue stores. Clear-

Table 2 Reported cases of overdose of colloidal bismuth subcitrate in the literature (*BS* bismuth subcitrate, *HD* hemodialysis, *PD* peritoneal dialysis, *DMPS* sodium-2,3-dimercapto-1-propanesulfonate)

Reference	Age	Sex	Ingestion form	Ingested bismuth	Therapy	Outcome	Kidney biopsy
Hudson et al. [8]	27	M	Acute one time, 4 h previously	12 g BS	HD, rehydration, colonic purging	Alive	Absent
Taylor [13]	76	M	Acute one time, 4 h previously	9.6 g BS	HD, colonic purging	Died from perforated duodenal ulcer	Acute tubular necrosis
Huwez [12]	21	M	Acute one time, 3 h previously	4.68 g BS	IV cristalloid, furosemid, dopamine, mannitol	Alive	Acute tubular necrosis
Stevens et al. [14]	21	M	Acute one time, 48 h previously	6–7.2 g BS	Charcol, bowel irrigation, chelating agent (DMPS), HD	Alive	Absent
Akpolat [11]	16	F	One time 1 week previously	1.2–1.8 g BS	HD	Alive	Acute tubular necrosis
Islek et al. [10]	2	M	Acute one time, 6 h previously	3.2 g BS	Gastric lavage, PD, IV cristalloid	Alive	Absent
Hruz [9]	22	F	Acute one time, 60 h previously	5.4 g BS	HD, chelating agent (DMPS)	Alive	Absent
Present case	16	F	Acute one time 10 days previously	18 g BS	HD, chelating agent (Penicillamine), IV cristalloid	Alive	Absent

ance of bismuth from tissues via hemodialysis was inadequate, and their patient had detectable blood bismuth levels 2 or 3 months after the agent was ingested. Islek and colleagues [10] reported a 2-year-old patient with colloidal bismuth overdose who was treated with peritoneal dialysis alone. They observed that removal of bismuth via this method was also slow. Although the dialysate/plasma ratio of bismuth was quite good in both our report (120/450) and that of Islek et al. (498/739), the removal of bismuth with hemodialysis and peritoneal dialysis was inadequate. Hruz [9] described the case of a 22-year-old woman who ingested 5.4 g colloidal bismuth subcitrate in a suicide attempt. These authors used intravenous sodium 2,3-dimercapto-1-propanesulfonate (DMPS) as a chelating agent in addition to hemodialysis. They noted that the patient's serum bismuth level decreased from 640 μg/l 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 chelation with DMPS is highly effective when used in conjunction with hemodialysis. It has been suggested that early treatment with intravenous DMPS and hemodialysis helps prevent the development of acute renal failure in cases of bismuth overdose [9]. 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 [8, 19], but penicillamine had no observable effect in our case.

Currently there is no established treatment regimen for bismuth intoxication. Gastric lavage, administration of activated charcoal, bowel irrigation or colonic purgation, hydration, and forced diuresis have been recommended, especially in the early stage after an overdose. Hemodialysis or peritoneal dialysis should be performed if acute renal failure develops. Adjunctive chelation with DMPS helps to eliminate bismuth from the body.

Bismuth intoxication is a rare cause of acute renal failure and is usually reversible if properly managed. Some of our patient's problems were related to late diagnosis of acute renal failure. Clinicians should be aware that acute renal failure could occur after bismuth intoxication. Therefore patients with bismuth intoxication should continue to be observed after first aid is performed and should be monitored with renal function tests. It should be kept in mind that early appropriate management is essential.

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