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BRIEF REPORT

İsmail İşlek· Serap Uysal · Faysal Gök
Ruşen Dündaröz · Şükrü Küçüködük

Reversible nephrotoxicity after overdose of colloidal bismuth subcitrate

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Abstract Although toxicity due to acute and chronic use of bismuth salts is well known, nephrotoxicity after ingestion of colloidal bismuth has been reported in few cases so far. Here we report the first case of acute renal failure (ARF) due to colloidal bismuth subcitrate overdosage in childhood. A 2-year-old boy was admitted to the hospital 6 h after ingestion of 28 De-Nol tablets (colloidal bismuth subcitrate 8.4 g). On admission, physical examination was unremarkable and he showed no signs of encephalopathy. Initially gastric lavage was performed then appropriate fluid therapy was started. ARF associated with uremia and oliguria developed on day 2 and peritoneal dialysis therapy was prescribed on day 4 for 10 days. Blood and urine bismuth levels were 739 µg/l and 693 µg/l, respectively, 10 days after the pills had been taken. His urine volume gradually increased and plasma BUN and creatinine levels decreased during peritoneal dialysis. On day 20 post-admission, plasma BUN and creatinine were 14 mg/dl and 0.7 mg/dl, respectively. Blood bismuth levels were 96 µg/l on day 60 and 12 µg/l on day 105. Now the patient is well and has no problem. This case suggests that ARF may develop in children following colloidal bismuth subcitrate overdosage; the prognosis is good, and peritoneal dialysis may be useful in these cases.

Keywords Bismuth subcitrate overdose · Acute renal failure · Peritoneal dialysis · Child

İ. İşlek (✉) · S. Uysal · Ş. Küçüködük
Ondokuz Mayıs University, School of Medicine,
Department of Pediatrics, Samsun, Turkey
e-mail: iislek@omu.edu.tr
Tel.: +90-362-457-6000/2456, Fax: 90-362-457-6041

F. Gök · R. Dündaröz
Gülhane Military Medical School, Department of Pediatrics,
Ankara, Turkey

Introduction

Bismuth salts have been traditionally used in the treatment of functional dyspepsia, hemorrhoids and other non-specific gastrointestinal disorders. Despite numerous reports of encephalopathy after long-term consumption of insoluble bismuth salts, colloidal bismuth subcitrate (CBS) became popular for therapy of peptic ulcers and chronic gastritis in the previous decade since the awareness of the bactericidal effect on *Helicobacter pylori*. Toxic effects due to bismuth compounds have been widely documented in humans: encephalopathy, nephropathy, osteoarthropathy, gingivitis, stomatitis and colitis [1, 2, 3, 4, 5, 6]. Today, CBS and bismuth subsalicylate (BSS) have been promoted for the treatment of peptic ulcer disease and diarrhea. Toxic effects are rarely seen in normal use of these newer agents because bismuth is absorbed in very low amounts from the gastrointestinal tract [1, 2, 4, 5, 6, 7, 8]. To date, nephrotoxicity after overdose of CBS has been reported in only a few adult cases [9, 10, 11, 12, 13]. Here we present the first pediatric case of acute renal failure (ARF) due to overdose of CBS.

Materials and methods

A 2-year-old boy was admitted to the hospital 6 h after taking 28 De-Nol tablets (colloidal bismuth subcitrate 8.4 g). His mother stated that she was taking De-Nol tablets for treatment of peptic ulcer. She had bought a new box of 60 tablets and had used only two of them. The parents saw the patient eating De-Nol tablets and when the remaining ones were counted, they found that 28 of them were missing. The parents observed that their son vomited three times and found three degenerated tablets in gastric aspirate.

On admission, the boy was somnolent but other physical examination findings were unremarkable. His pulse rate was 90/min and blood pressure was 100/60 mm Hg. His height and weight were 83 cm and 12 kg, respectively. Laboratory investigations revealed the following results: Hb 11.5 g/dl, WBC 21,700/mm^3, 72% neutrophils, plasma BUN 17 mg/dl, plasma creatinine 0.7 mg/dl. Serum electrolytes and liver function tests were normal. Urinary examination showed pH 5.5, density 1010, protein nega-

tive, glucose negative, bilirubin negative, with 1–2 erythrocytes and 1–2 leukocytes per HPF (×400). An abdominal X-ray film demonstrated opacification of the intestine and the colon by ingested bismuth about 6 h after ingestion on the admission day. Abdominal ultrasound revealed that the kidney size was normal, and paranchymal echogenicity increased minimally on day 3. ECG and ECHO were normal on days 2 and 14 post-admission, respectively. An EEG was unremarkable on day 25 post-admission. Bismuth concentrations were not measured in the first 10 days.

Results

Acute poisoning due to colloidal bismuth subcitrate was diagnosed and the patient was given gastric lavage in the pediatric emergency service. Gastric lavage material was white in color. He was hospitalized for observation, as he had ingested large amounts of bismuth. IV saline was initiated at 2000 ml/m^2 per day. Bowel irrigation or colonic purging with aggressive use of laxatives or enemas could not be performed, as these approaches may cause fluid and electrolyte imbalances. Unfortunately, whole bowel irrigation, using polyethylene glycol electrolyte solution (PEG-ES), could not be performed because we could not obtain PEG-ES during the treatment of the patient. He was somnolent and lethargic on days 2 and 3. Urine output decreased at <0.5 ml/kg per hour, 140 ml/day, and plasma BUN and creatinine increased to 36 mg/dl and 1.5 mg/dl, respectively, on day 2. Mannitol (IV 0.5 g/kg per 30 min) and furosemide (IV 2 mg/kg) were then administered only once, and furosemide was given IV 2 mg/kg per day. Six hours after mannitol and furosemide administration, urine output was insufficient. At the end of day 2, IV saline was commenced in an amount equal to estimated fluid loss plus urine output. Urine output decreased to 50 ml/day (<0.5 ml/kg per hour), plasma BUN and creatinine increased to 56 mg/dl and 3.4 mg/dl, respectively, on day 3. Oral feeding was discontinued because the patient was lethargic and vomited. He became increasingly more hypoactive and lethargic, facial edema developed, and plasma BUN and creatinine increased to 75 mg/dl and 4 mg/dl, respectively, on day 4.

An intraperitoneal swan-neck catheter was placed and automated peritoneal dialysis (APD) therapy was prescribed with cycler. APD was prescribed as intraperitoneal filling volume (IFV) 350 ml and 24, 1-h cycles a day. Each cycle comprised 10 min inlet, 35 min contact and 15 min outlet during the first 3 days. The dialysis fluid (PD4 Dianeal %1,36) contained Na 132 mmol/l, Ca 1,25 mmol/l, Mg 0.25 mmol/l, Cl 95 mmol/l, and lactate 40 mmol/l. Osmolarity was 344 mOsm/l. During peritoneal dialysis, we observed no complication related to peritoneal dialysis. We observed no bowel movement during the first 3 days after admission and the stool was black in color on day 4. APD was changed to 12 cycles in a day, and each cycle comprised 10 min inlet, 90 min contact, and 20 min outlet during the next 3 days. The patient underwent APD for a total of 6 days. On day 2 of APD, the patient became active, started eating, and the facial edema resolved. His urine volume gradually increased (210 ml on day 5 and 500 ml on day 8). Plasma BUN and creatinine decreased to 37 mg/dl and 2.6 mg/dl, respectively, at the end of APD therapy. APD was changed to daytime ambulatory peritoneal dialysis (DAPD). DAPD was prescribed with IFV of 350 ml, and intraperitoneal dwell time took 10 min, one cycle took 20 min, and was repeated successively six times, making a total of 120 min/day with a full peritoneal cavity (400 ml) during the night. The patient underwent DAPD for a total of 10 days. Fortunately, we were able to detect bismuth levels on day 10 post-admission. Bismuth levels were 739 µg/l in the blood, 693 µg/l in 24-h collection of urine, and 498 µg/l in the night-time dialysate.

At the end of DAPD, plasma BUN was 14 mg/dl and creatinine 0.7 mg/dl. A control abdominal X-ray film

Table 1 Pertinent clinical and laboratory data of the patient. *PD* peritoneal dialysis, *APD* automated peritoneal dialysis, *DAPD* daytime ambulatory peritoneal dialysis

Day	Plasma BUN (mg/dl)	Plasma creatinine (mg/dl)	Blood bismuth[a] (µg/l)	Dialysate bismuth[b] (µg/l)	Urine bismuth[a,c] (µg/l)	Urine volume ml/day
1	17	0.7	–	–	–	330
2	36	1.5	–	–	–	140
3	56	3.4	–	–	–	50
4 APD	75	4.0	–	–	–	120
9 APD	37	2.6	–	–	–	750
10 DAPD (removed bismuth)	42	3.2	739	498 (199 µg/night)	693 (506 µg/day)	730
15 DAPD (removed bismuth)	45	1.6	614	372 (149 µg/night)	554 (471 µg/day)	850
20 DAPD	14	0.7	440	–	–	715
30	14	0.5	208	–	–	
60	16	0.6	96	–	–	
105	13	0.7	12	–	–	

[a] Measured by atomic absorption
[b] In the morning, in the first dialysate
[c] 24-h collection

Table 2 Reported cases of overdose of colloidal bismuth subcitrate in the literature

Case no [Ref.]	First author (year)	Age (year)	Sex	Ingestion form	Ingested bismuth	Therapy	Outcome	Kidney biopsy or necropsy
1 [9]	Hudson (1989)	27	m	Acute one-time ingestion 4 h previously	100 tablets, 12 g Bi_2O_3	Hemodialysis, colonic purging, rehydration	Alive	Absent
2 [10]	Taylor (1990)	76	m	Normal use in 4 weeks and acute one-time ingestion 4 h previously	80 tablets, 9.6 g Bi_2O_3 (one-time ingestion dose)	Hemodialysis, colonic purging,	Died from perforated duodenal ulcer	Acute tubular necrosis
3 [11]	Huwez (1992)	21	m	Acute one-time ingestion 3 h previously	39 tablets, 4.68 g Bi_2O_3	IV crystalloid, furosemide, dopamine, mannitol	Alive	Acute tubular necrosis
4 [12]	Stevens (1995)	21	m	Acute one-time ingestion 48 h previously	50–60 tablets, 6–7.2 g Bi_2O_3	Charcoal, bowel irrigation, chelator (DMPS), hemodialysis	Alive	Absent
5 [13]	Akpolat (1996)	16	f	One-time ingestion 1 week previously	10–15 tablets, 1.2–1.8 g Bi_2O_3	Hemodialysis	Alive	Acute tubular necrosis
6	Our case (2000)	2	m	Acute one-time ingestion 6 h previously	27 tablets, 3.2 g Bi_2O_3	Gastric lavage, peritoneal dialysis, IV crystalloid	Alive	Absent

demonstrated no opacification on day 6. The patient recovered clinically and was discharged on day 20 after admission. He was followed up monthly. At this time, the patient is well and problem free. Blood bismuth levels were 96 µg/l and 12 µg/l on days 60 and 105, respectively. Pertinent clinical and laboratory data are given in Table 1. Renal biopsy was not performed for ethical reasons.

Discussion

Bismuth salts have been traditionally used for therapy of various gastrointestinal diseases, stomatitis, and upper respiratory infections. Today, CBS and BSS are promoted for the therapy of peptic ulcer disease and diarrhea [1, 2, 3]. Toxic effects related to bismuth compounds are encephalopathy, nephropathy, osteoarthropathy, gingivitis, stomatitis, and colitis. Each adverse effect is due to certain bismuth compounds [2, 5, 6]. Toxic effects are rarely seen in normal use of CBS and BSS, because bismuth is absorbed in very low amounts [1, 4, 5, 6, 7, 8]. Less than 1% of an oral dose of bismuth is absorbed, the remainder is excreted as insoluble salts in the feces. 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. It is excreted in saliva, urine, and bile [5, 6].

Bismuth toxicity may develop due to excessive ingestion, or misuse when taken in very large quantities and for prolonged periods [8]. Bismuth encephalopathy was observed in France as an epidemic in 1973. This complication was associated with the prolonged consumption of oral preperations of bismuth subnitrate, subcarbonate, and subgallate. Encephalopathy was reversible after discontinuation of the drug [5, 8, 14]. Encephalopathy is rare in CBS and BSS use because they are less absorbed (<0.28% of oral dose) from the gastrointestinal tract [1, 2, 4, 7, 15, 16, 17]. It is reported that normal use of CBS and BSS is not associated with clinical neurotoxicity and can be used safely for up to 4–8 weeks of extended dosing [1, 4, 18]. We observed only somnolence and lethargy in our patient in early post-admission days. These findings are not specific for bismuth encephalopathy and EEG was unremarkable.

Although salicylate does not reach toxic levels after BSS ingestion, few cases of acute fatal salicylate toxicity and chronic salicylate toxicity have been reported due to bismuth subsalicylate which has a modest effect in treatment of traveler's diarrhea and acute and chronic diarrhea in children [1, 20, 19].

As an additional complication, respiratory distress has been reported due to bismuth subgallate when used to control hemostasis during tonsillectomy and adenoidectomy [21].

About 0.28% of an oral dose of CBS is absorbed from the gastrointestinal tract. The remainder is excreted as bismuth sulphide in feces. It turns the stool color black. A small amount is excreted in the urine [2, 5, 7]. We also observed black feces in our patient on day 4. The normal

concentration of blood bismuth is between 1 and 15 µg/l, but it increases 51–1483 times after the intake of CBS. The half-life of bismuth in blood may be as short as 3.5 min and as long as 17–22 years [5, 22]. Bismuth concentration is highest in the kidneys, where it binds to a bismuth-metal binding protein [5]. Bismuth is also retained for a long time. It may decrease glomerular filtration rate and renal blood flow, and cause proximal tubular reabsorption defects [23]. Patients with severe renal insufficiency should receive half dosages to avoid possible toxicity [7].

So far, the literature has reported five adult cases with ARF after overdose of colloidal bismuth subcitrate [9, 10, 11, 12], one of them a 16-year-old female patient [13] (Table 2). Acute tubular necrosis was demonstrated in two of the patients. Hudson et al. [9] documented blood bismuth levels before and after hemodialysis in their case. They reported that reductions in blood bismuth concentration after hemodialysis were transient because of redistribution from tissue stores, and the tissue clearance of bismuth by hemodialysis was uncertain. Blood bismuth levels were still detectable 2 or 3 months after ingestion [9]. Taylor and Klenerman [10] detected the highest blood bismuth level (1600 µg/l) in their case.

The treatment of bismuth overdose is not well established, and is still developing. The management includes gastric lavage, activated charcoal, bowel irrigation or colonic purgation, early hydration and forced diuresis [5, 9, 10, 11, 12, 13]. We performed gastric lavage and prescribed early hydration; however, bowel irrigation or colonic purgation using a laxative or enema could not be performed because of possible fluid and electrolyte imbalances in the patient. Whole bowel irrigation using PEG-ES has been used for the treatment of potentially toxic ingestion. This approach reduces drug absorption by decontaminating the gastrointestinal tract by physically expelling intraluminal contents. However, PEG-ES causes neither net absorption or secretion of ions, nor significant changes in water and electrolyte balance. Therefore, PEG-ES may be preferred for whole bowel irrigation [24]. Hudson [9] and Taylor [10] used colonic purgation in their patients (cases 1 and 2, Table 2); however, Stevens et al. [12] used PEG-ES for whole bowel irrigation. The use of the metal chelator dimercaprol is controversial in the treatment of bismuth overdose [25, 26, 27]. However, a new heavy-metal chelating agent, 2,3 dimercapto-1 propane sulphonic acid (DMPS), given by mouth or IV, has been demonstrated to increase the renal bismuth clearance and elimination of bismuth by hemodialysis significantly [12, 16]. Thus, it is suggested that early treatment with IV DMPS and hemodialysis with a highly porous membrane is useful to prevent developing ARF and neurotoxicity in bismuth overdose [12]. Unfortunately, we could not give a chelating agent because we were unable to obtain bismuth blood levels earlier.

The abdominal X-ray findings were also interesting in our patient. The patient did not receive any contrast material. As reported before, this roentgenographic finding may serve as an important clue to the diagnosis of potential bismuth toxicity in patients admitted to an emergency service with unknown drug poisoning. Also, abdominal X-ray may be a useful tool to show the effectiveness of bowel irrigation [19]. Although we did not perform bowel irrigation, we observed the patient's stool was black in color on day 4, and control abdominal X-ray revealed no opacification on day 6. Bismuth in the intestine may provide an additional source for high blood concentrations of bismuth in the first 4 days.

Fortunately, we were able to determine bismuth concentrations on day 10 after overdose in our patient. Blood bismuth concentrations continued to be high after 11–16 days of peritoneal dialysis. Although bismuth concentration in dialysate fluid suggests that bismuth may be transferred through peritoneal membrane to dialysate, obviously the removal of bismuth with peritoneal dialysis was slow, possibly because of its high intracellular concentrations. This might be the reason for high concentrations of bismuth 30 and 60 days after the overdose. The management of this patient suggests that peritoneal dialysis is effective in children with bismuth intoxication.

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LITERATURE ABSTRACTS

M. Agraharkar · P. Klevjer-Anderson · E. Rubinstien M. Galen

Use of cefazolin for peritonitis treatment in peritoneal dialysis patients

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For over two decades, intraperitoneal administration of vancomycin and an aminoglycoside has been an accepted regimen for the empiric treatment of peritonitis in the peritoneal dialysis patient, until definite identification of the organism has been made. The recent emergence of vancomycin-resistant organisms has been of great concern in many centers. The current treatment recommendation therefore is to use cefazolin in place of vancomycin. We analyzed peritonitis data from January 1, 1996 to June 30, 1997, prior to switching over to cefazolin. Seventy-five percent (27 episodes) in 1997 as compared to 78% in 1996 were due to gram-positive organisms. Twenty-two percent (8 episodes) were due to gramnegative organisms in 1997, 21% in 1996, and 3% (1 episode) due to yeast in 1997, 3% in 1996. Staphylococcus epidermidis (SE) caused 33% of the gram-positive peritonitis episodes in 1997 as compared to 37% in 1996. Twenty-two percent of the gram-positive episodes were due to Staphylococcus aureus (SA) in 1997 and 46% in 1996. Enterococcal infections were 26% in 1997 and 1% in 1996. All of these were confined to only 1 patient. The antibiogram revealed 100% sensitivity of both SA and SE to vancomycin and 100% sensitivity of SA to cefazolin, but only 11% sensitivity of SE to cefazolin. The same patient population had a 48% sensitivity of SE to cefazolin in 1996, showing a sudden and substantial increase in resistance to SE. Even though SE is thought to be a less virulent organism, treating patients with a high probability of being infected by SE with an antibiotic showing 89% resistance is not warranted.

M.H. Polenakovik · L. Grcevska

Treatment and long-term follow-up of patients with stage II to III idiopathic membranous nephropathy

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Many important aspects of the therapeutic approach to patients with idiopathic membranous nephropathy are still controversial. There are several reports that the effectiveness of therapy depends on histological staging and severity of interstitial mononuclear cell infiltration. We used several different treatments in 39 patients with stage II to III primary membranous nephropathy with proteinuria more than 2.5 g/d, without hypertension and chronic renal failure at biopsy. Ten patients were not treated, 13 were treated with only steroids, 13 with alternate use of steroids and chlorambucil, and three with cyclosporine A. The follow-up period was 5 to 10 years. Statistics included Kruskall-Wallis and one-way ANOVA analysis. A significant decrease in proteinuria was noted in patients treated with steroids ($P<0.01$), from 8.45±1.04 g/d (mean±SEM) to 1. 42±0.45 g/d after follow-up of 5 years and in patients treated with steroids and chlorambucil (12.9±2.4 g/d [mean±SEM] to 2. 46±1.38 g/d). Compared with patients treated with steroids (15.3%) and patients treated with steroids and chlorambucil (15.3%), untreated patients had a high frequency of chronic renal failure after 5 years of follow-up (70%) and had a significant increase in mean serum creatinine ($P=0.008$). We conclude that steroid therapy alone, or associated with chlorambucil, is effective in patients with stage II to III membranous nephropathy. Patients responded with a decrease of proteinuria and stable renal function during the long-term follow-up period. The group of patients treated with cyclosporine A was too small to analyze.