ORIGINAL RESEARCH

Bismuth Toxicity Presenting as Declining Mobility and Falls

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ABSTRACT

A 77-year old woman presented with a history of falls. Known health problems included biopsy-proven collagenous colitis treated with bismuth subsalicylate. On examination, in addition to impaired balance and gait, she was found to have tremors and cognitive deficits. Investigations revealed a markedly elevated urinary bismuth level. Withdrawal of bismuth subsalicylate led to marked cognitive and physical improvement.

Key words: bismuth toxicity, falls, cognitive impairment, delirium, collagenous colitis

Introduction

In this short report we present an unusual complication from a commonly used medicinal compound.

CASE REPORT

A 77-year old woman was referred to the Calgary Fall Prevention Clinic with a history of falls and declining mobility since June of 2017. She had three non-injurious falls, and was seen in local urgent care and emergency departments for post-fall evaluations after two of them. Investigations done at the time included a CT scan of her head (no acute changes noted, mild white matter hypoattenuation) and routine laboratory studies (no significant abnormalities other than stage 3 chronic kidney disease with an estimated GFR of 44 ml/min; in June of 2016 her estimated GFR had been 56 ml/min).

She was seen in her own home on the 27th of September 2017 for an initial assessment. In addition to the presenting issues, she complained of intermittent "shaking' of her arms and legs. Her family reported a dramatic decline in her cognitive and physical status over the preceding 30 days. Known health problems included biopsy-proven collagenous colitis, hypertension, hyperlipidemia, osteoarthritis, and venous insufficiency. Medications were irbesartan-hydrochlorothiazide 300/25 mg daily, furosemide 20 mg daily, rosuvastatin 5 mg daily, bisoprolol 5 mg daily, and Pepto-Bismol® (bismuth subsalicylate 262.5 mg) one tablet three times daily (dose of 0.8 g/d). She was adherent with all including Pepto-Bismol®. Pertinent physical findings were a significantly decreased ability to maintain attention, Montreal Cognitive Assessment (MoCA version 7.1) score 13/30 (no prior cognitive concerns noted), timed "Up and Go" (TUG) 27.7 sec, and markedly impaired balance (unable to maintain Romberg stance for 10 sec with eyes open). These findings were immediately brought to the attention of her attending family physician. Laboratory investigations at this time showed no significant abnormalities other than a positive urine culture. Though she had no lower urinary tract symptoms, she was prescribed antibiotics without effect.

When discussed at interdisciplinary Clinic rounds on October 5th, she was felt to have a delirium. Bismuth toxicity was noted as a possible cause. The patient and her family were asked to discontinue Pepto-Bismol®, which they did stop on October 6th when salicylate and bismuth levels were obtained, and arrangements were made for her to undergo a more detailed evaluation in our Clinic.

When seen on the 12th of October she gave a three-to-four-year history of mildly impaired mobility, with a further decline over the preceding summer when she began having falls. Collagenous colitis was diagnosed in 2009 on a colonic biopsy, with persistent disease confirmed on repeat biopsies in 2013. In the summer of 2016 she was placed on daily Pepto-Bismol® (initially 3 tablets three times daily for eight weeks, then 2 tablets three times daily for an unspecified number of weeks, followed by 1 tablet three times daily from late September 2016 on), which controlled her watery diarrhea. On examination, she scored 14/30 on a repeat MoCA (version 7.2), but did well on tests of attention (i.e., correctly listed days of the week and months of the year backwards). There was a coarse tremor of both legs with standing, and a slight postural and kinetic tremor of her upper extremities, but no dysarthria, extra-pyramidal signs, or myoclonus. Specimens taken on the 6th of October showed a blood salicylate level of < 0.07 mmol/L (therapeutic range 0.70–1.80 mmol/L) and a urine bismuth level of 2117 nmol/L (reference range 0–20 nmol/L). Based on her clinical and laboratory assessment, she was diagnosed with bismuth neurotoxicity. The offending agent had already been

discontinued. Other than planning to monitor her, no additional measures were implemented at this time.

On the 26th of October she was placed on budesonide for recurrent diarrhea, with benefit. When seen in follow-up on November 8th, she and her family noted a "huge" improvement in her cognitive status and significant, but less impressive, changes in mobility. There had been no further falls. Subjectively her tremor had improved and was no longer evident on examination. She scored 25/30 (11-point improvement) on a MoCA (version 7.3), was able to maintain Romberg and semi-tandem stances for over 10 sec each, and chair stands in 30 sec had increased from four (when initially seen) to seven. Her TUG was essentially unchanged at 25.8 sec. Continued Clinic involvement was proposed to deal with the residual mobility challenges.

DISCUSSION

Short-term therapy with bismuth compounds is used for a number of gastrointestinal conditions including second-line therapy of collagenous colitis.[1-9] Though generally well tolerated, about a thousand cases of bismuth neurotoxicity from ingestion of predominantly bismuth subnitrate or subgallate occurred in France and Australia during the 1970s.[10-12] Bismuth subsalicylate appears less likely to cause problems than these two bismuth salts, but tissue accumulation has been demonstrated on usual dosages of this agent after six weeks of treatment. This has led to a recommendation that bismuth-containing oral compounds should be taken for no longer than six to eight weeks, followed by at least an eight-week bismuth-free interval.[12]

There are seven case reports documenting bismuth neurotoxicity with bismuth subsalicylate (see Table 1).[13-19] After oral administration, bismuth subsalicylate is nearly completely hydrolyzed in the gastrointestinal tract to bismuth and salicylic acid. Acute overdoses can lead to salicylate toxicity, and two additional cases of this form of toxicity from the use of bismuth subsalicylate have been reported.[20,21] As noted, our patient's salicylate level was undetectable. Less than 1 per cent of the bismuth in this particular compound is absorbed.[22,23] The metal is distributed throughout the body and slowly eliminated, primarily in urine. Abnormal bowel permeability (leading to increased absorption) and/or renal

Table 1.
Summary of neurotoxicity cases from ingestion of bismuth subsalicylate

Reference	*Age*	*Sex*	*Bismuth Dose*	*Bismuth Duration*	*Manifestations*	*Bismuth Level and Outcome*
Hasking & Duggan (1982)[13]	60	M	Unknown	"… some years"	Withdrawn, inappropriate & twitching x mth then dysarthria, disorientation, incontinence x2, twitches & primitive reflexes	High blood level; full recovery in mth
Mendelowitz *et al*. (1990)[14]	45	M	5.2-9.4 g/d (AIDS patient with diarrhea[24]	7 days	Lethargy, dysarthria, & myoclonic jerking that progressed to coma with myoclonus	High blood & urine levels; death
Jungreis & Schaumburg (1993)[15]	68	F	1.2 g/d	2 yrs	Intention/rest tremor, myoclonic jerks, unsteady gait, forgetfulness & episodic confusion	Blood level high 6 wks after stopping; recovery in 6 mths
Gordon *et al*. (1995)[16]	54	M	1-4 g/d with recent increase	Took for "… many years"	Progressive confusion, memory difficulty, myoclonic jerks, tremor & unsteady gait	Blood & urine levels high 35 days after stopping; improved over 12 wks
Reynolds *et al*. (2012)[17]	56	F	2.3 g/d with recent increase	2 mths	Psychomotor retardation, poor concen-tration, drowsy, visual hallucinations, tremor, myoclonic jerks, & postural instability	High blood & urine levels; recovery within several mths
Masannat & Nazer (2013)[18]	56	F	2.3 g/d	Unclear (abstract stated mths but text indicates several wks)	Progressive confusion, poor concentration, myoclonic jerks, tremors, gait instability, and visual hallucinations	High blood level days after stopping; complete recovery in 4 mths
Siram *et al*. (2017)[19]	25	F	Unclear but high dose – 8 tablets Q2 hr.	15-20 days	Tinnitus/ hearing loss (likely concurrent salicylate toxicity) progressing to altered sensorium	Elevated blood level 20 d after stopping; improved over 2 mths

M = Male; F = Female.

impairment (with decreased elimination) may predispose to bismuth toxicity. Our patient's mild renal impairment possibly played a minor role in her presentation or may have reflected subtle renal damage from bismuth toxicity. Cases of bismuth subsalicylate neurotoxicity reported to date have been marked by long-term, high-dose—or both—usage. We believe the long-term, uninterrupted consumption of bismuth subsalicylate was the primary factor in our patient.

Neurological manifestations of bismuth toxicity include impaired cognition (which can be severe), lethargy, somnolence, coma, insomnia, incoordination, balance and gait abnormalities, dysarthria, tremor, myoclonus, seizures, Parkinsonism, and neuropsychiatric symptoms (i.e., apathy, depressed mood, anxiety, irritability, psychotic features).[10-19] Falls as a manifestation have not been previously noted. Our patient's clinical presentation was compatible with the described symptoms and signs. As shown in Table 1, recovery takes place gradually after stopping the agent as the metal is cleared. This was seen in our patient.

To summarize, our patient's uninterrupted daily intake of bismuth for over a year, compatible clinical picture, high urinary bismuth level, lack of other explanation for her presentation, and improvement after discontinuing the offending agent, all support the diagnosis of bismuth neurotoxicity. This case highlights the diverse causes of falls in older patients, the need for a careful drug history in their assessment, and the potential risk of long-term use of bismuth subsalicylate.

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CONFLICT OF INTEREST DISCLOSURES

The authors declare that no conflicts of interest exist.

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