Bismuth Subsalicylate Coagulopathy in a Patient with Chronic Liver Disease

Catherine Yu¹ · Noel Eustaquio² · Diane P. Calello^{1,2} · Bruce E. Ruck² · Lewis S. Nelson^{1,2} · Cynthia Santos^{1,2}

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Abstract

Bismuth subsalicylate (BSS) is the active ingredient in over-the-counter antacid and antidiarrheal medications. Coagulopathy in the setting of acetylsalicylic acid toxicity is well documented but not in setting of bismuth subsalicylate overuse. We present a case report of coagulopathy from BSS poisoning in a patient with underlying cirrhosis. The patient's high prothrombin time suggests inhibition of vitamin K-dependent coagulation factors. The patient had decreased factor V activity, which is responsible for converting prothrombin to thrombin. Patients with cirrhosis often have hypoprothrombinemia which may be exacerbated by salicylate-induced coagulopathy. Given the widespread use of BSS products, physicians should recognize coagulopathy as a possible manifestation of toxicity especially in patients with underlying liver disease.

Keywords Salicylate · Bismuth · Coagulopathy · Liver disease

Introduction

For more than a century, bismuth salts have been used for gastrointestinal ailments. Bismuth is a metal with atomic number 83, and while the elemental form is non-toxic, bismuth salts are toxic. Bismuth salts can be categorized by their different properties and toxicities into four groups (see Table 1) [1]. Bismuth subsalicylate (BSS), an insoluble salt-containing bismuth and salicylic acid, is commonly the active ingredient in popular antacid and antidiarrheal medications.

Ninety-nine percent of ingested bismuth is passed fecally, and the little absorbed bismuth is eliminated from the body via renal or hepatic processes [2–4]. Despite the limited absorption, acute bismuth intoxication may manifest as abdominal

pain and kidney failure [1, 2]. More commonly, chronic bismuth toxicity occurs in patients with long-term excessive dosing and presents as a progressive myoclonic encephalopathy [5–8].

Overuse of BSS can also lead to salicylate toxicity [1]. The clinical manifestations and management of salicylate toxicity are analogous to that from other salicylate sources. Coagulopathy is one clinical manifestation that is not commonly reported in literature. The mechanism of platelet aggregation inhibition has been well-studied; however, there is evidence that salicylic acid also acts on thrombin-mediated coagulation factors that are synthesized in the liver [9]. Patients with underlying liver disease may be predisposed to further coagulopathy after salicylate poisoning. In this case report, we present a 62-year-old woman with chronic liver disease who develops coagulopathy in the setting of BSS toxicity.

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✉ Cynthia Santos
cynthia.d.santos@rutgers.edu

¹ Department of Emergency Medicine, Rutgers New Jersey Medical School, Newark, NJ, USA

² New Jersey Poison Information & Education System, Newark, NJ, USA

Case Report

The patient was a 62-year-old woman who presented to the emergency department with 1 week of watery non-bloody diarrhea and confusion. She denied nausea, vomiting, abdominal pain, sick contacts, and recent travel. She reported taking half a bottle a day of Pepto-Bismol® throughout the 5 days prior to admission in an unsuccessful attempt to control her diarrhea. The

Table 1 The Absorptive Characteristics of Bismuth Salts [1]

Group	Chemistry	Toxicity	Examples
I	Insoluble in water Inorganic	Minimal	Bismuth subnitrate Bismuth subcarbonate
II	Lipid soluble Organic	Neurologic	Bismuth subsalicylate Bismuth subgallate
III	Water soluble Organic	Renal	Bismuth triglycollamate
IV	Hydrolyzable Water soluble Organic	Minimal	Biotropeptide

patient was not sure whether she took regular strength or extra strength and was not sure of the size of the bottle. The patient was only able to recall that she took “up to a half bottle per day.” If she took one-half bottle of the largest and most concentrated type (473 mL ES) that would be 8.27 g of BSS per day (two times maximum daily dose). If she took just the regular strength then she would have ingested 4.14 g of BSS per day, which is just below the maximum daily dose.

Her medical history was significant for hepatitis C cirrhosis, osteoporosis, hypothyroidism, and hypertension. She had a transjugular intrahepatic portosystemic shunt (TIPS) procedure performed 14 years prior with a revision done 12 years prior. She was also on the liver transplant list with a model for end-stage liver disease (MELD) score of 11. Current medications included furosemide, spironolactone, propranolol, ergocalciferol, alendronate, zolpidem, levothyroxine, and rifaximin.

On initial evaluation, her blood pressure was 144/66 mmHg, heart rate 74 bpm, respiratory rate 18, temperature 98.4 F, and oxygen saturation of 100% on room air. Physical exam was significant for dry mucous membranes, blunted effect, and disorientation of place and date. Her gait was steady, cranial nerves II–XII intact, motor strength 5/5 throughout, sensation intact throughout, and deep tendon reflexes 2+ throughout. She did not exhibit any myoclonus.

Initial laboratory test results are listed in Table 2. Her initial coagulation studies resulted in PT of 61.2 s, PTT 46.2 s, and INR of 7.2. Her initial salicylate level was 50 mcg/dL. Computed tomography (CT) of the head and of the abdomen/pelvis did not reveal any acute abnormalities. Initial EKG revealed normal sinus rhythm with inverted T waves in the inferior leads: QRS 90 ms, QTc 462 ms.

The New Jersey Poison Information and Education System was consulted and recommended alkalization of the plasma/urine with sodium bicarbonate, the possible need for emergent hemodialysis, to trend the salicylate level and to obtain a bismuth level. The patient was admitted to the ICU with presumed chronic salicylate poisoning. Hepatology was consulted and recommended to check her factor V activity from her initial laboratory studies, which was low at 54% (normal 60–130%). Over the subsequent 48 h, treatment with intravenous sodium bicarbonate, N-

Table 2 Present case initial laboratory results

Hemoglobin	14.8 g/dL
Leukocytes	$7.5 \times 10^9/L$
Platelets	$274 \times 10^9/L$
PT	61.2 s (previous 14.1)
PTT	46.2 s (previous 31.3)
INR	7.2 (previous 1.4)
Factor V activity	54%
Sodium	133 mmol/L
Potassium	5.4 mmol/L (slight hemolysis)
Chloride	96 mmol/L
Bicarbonate	14 mEq/L
Calcium	9.6 mg/dL
BUN	42 mg/dL (previous 17)
Creatinine	1.7 mg/dL (previous 0.9)
Glucose	108 mg/dL
Anion gap	23
Lactic acid	2.3 mg/dL
AST	75 IU/L
ALT	26 IU/L
Alk phos	133 IU/L
Ammonia	33 $\mu\text{mol/L}$
Albumin	3.6 g/dL
Total protein	7.6 g/dL
Acetaminophen	< 15 mcg/mL
Salicylate	50 mg/dL
Bismuth (blood)	4 mcg/L
Bismuth (urine)	147.6 mcg/L

acetylcysteine (NAC) infusions, one unit of fresh frozen plasma, and two doses of 10 mg vitamin K IV were given. Two sessions of hemodialysis were performed for salicylate removal after which the concentration was < 10 mg/dL. Her INR also decreased to 2.9 by the end of day one, and by day two, it returned to her baseline of 1.9. Her diarrhea resolved by day two, and her mental status returned to baseline by day three. The patient was subsequently transferred to the medical floors and discharged to rehabilitation 11 days after presentation. Her bismuth levels were sent to an outside laboratory and came back with a urine concentration of 147.6 mcg/L (normal 0.3–4.6 mcg/L) and a serum concentration of 4 mcg/L (normal 0–9 mcg/L). Consent to publish the case report was obtained and provided to the journal.

Discussion

Coagulopathy has been reported in patients using salicylate and relevant publications are summarized in the [supplemental table](#), which provides a summary of eight case reports and two case series [10–18]. All cases had eventual resolution of coagulopathy before either being discharged from the hospital or

expiring. Note that several of the reported cases involved salicylate-related coagulopathy in patients with normal hepatic function. One other published case involved bismuth subsalicylate [12], six publications involved acetylsalicylic acid [10, 11, 14, 16–18], and two publications involved methyl salicylate [13, 15].

The other bismuth subsalicylate case published by Bingham in 2013 resulted in a peak INR of 3.54 in a patient who was on warfarin already for DVT prophylaxis [12]. In contrast, this present case resulted in a peak INR of 7.7 in a patient who was not taking any other anticoagulants but had underlying liver disease. In the present case, the patient's dose of bismuth subsalicylate (8.3 g/day for 5 days) was two times the maximum daily dose, and her presenting salicylate level of 50 mg/dL was well into the toxic range. In this case, there was a dramatic decline back to her baseline INR of 1.9 within 2 days using FFP, vitamin K, and the removal of salicylate using hemodialysis. The use of NAC may have also had a small contribution towards increasing the INR (generally by 0.5–1 unit) by slightly reducing vitamin K-dependent clotting factor activity (II, VI, IX, and X); however, this effect is modest and not clinically relevant [19, 20].

Of these reports, six cases, including the present case, presented with coagulopathy from salicylate as the sole source with no underlying explanations for the coagulopathy. As mentioned previously, there is growing evidence that salicylates act on coagulation factors in addition to their antiplatelet effects. One study evaluated the time course of various clotting factor activations before and after aspirin ingestion using quantitative immunoassays [21]. It was found that prothrombin and factor V activation levels decreased after aspirin administration, starting from the 30 s immediately following ingestion to after 7 days of use. These effects were demonstrated in the present case as evidenced by the prolonged prothrombin time and decreased factor V activity.

A study investigating the mechanism of salicylate-induced coagulopathy in rats suggests that salicylates do so by inhibiting vitamin K quinone reductase, an enzyme necessary in the biosynthesis of vitamin K-dependent coagulation factors, particularly prothrombin [22]. Patients with underlying liver disease and impaired metabolism of vitamin K, such as the present case, may be predisposed to coagulopathy from salicylates.

This mechanism is similar to that of coumarin on clotting factor synthesis. It is important to note that case studies describing dangerous bleeding complications from the augmentation of coagulation factor inhibition due to drug interactions between warfarin and salicylate have been reported in literature, including two cases and the case series (see [Supplemental Table](#)) [12, 13, 15].

Of the cases with salicylate as the sole source of coagulopathy, three were found to have disseminated intravascular coagulation (DIC) based on findings of thrombocytopenia,

increased prothrombin time, and increased fibrin split products [14, 16, 18]. Two of the three cases involved patients who already had transaminitis from disease-induced liver injury and developed DIC from further aggravation with aspirin use [16, 18]. While the patient in the present case did not have thrombocytopenia, she had cirrhosis as preexisting liver disease, and DIC may have been a potential complication for her.

Coagulopathy associated with salicylate poisoning has been long recognized although not in the setting of bismuth subsalicylate overuse. Our case adds to the small number of reported cases of coagulopathy from salicylate in patients with underlying liver disease. A major limitation of this case is the lack of a measured baseline factor V activity prior to BSS ingestion, which makes it difficult to assess whether the patient's decreased factor V activity was the result or the cause of her coagulopathy. Other limitations are the confounding effects from the patient's other medications and treatments which could have affected her coagulopathy as well. More studies assessing the risk of liver disease and coagulopathy is needed in a larger cohort of salicylate-poisoned patients. Although bismuth subsalicylate is used widely, there is a lack of published cases of coagulopathy from salicylate poisoning.

Conclusions

Coagulopathy associated with salicylate poisoning has been long recognized although not in the setting of bismuth subsalicylate overuse. Given the widespread use of BSS products, it is important for coagulopathy to be considered as a possible manifestation of toxicity especially in patients with underlying liver disease and preexisting prothrombinopenia.

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Compliance with Ethical Standards Consent for publication of this case was obtained and provided to the journal in accordance with JMT policy.

Ethics Committee Approval IRB exemption obtained from the Rutgers New Jersey Medical School.

Conflict of Interest None

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