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Pink Prescribing

Bismuth Subsalicylate; History, Actions, Risks, and Future Use

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Recently, there seems to be more creative advertising regarding bismuth subsalicylate (BSS) for lots of gastrointestinal issues. I have found during medication reconciliation that some patients overuse and believe use of BSS products is without risks. From an advertising perspective, there seem to be many happy persons consuming BSS with no mention of restrictions or safety recommendations. What are the risks associated with its use? How effective is BSS? What about drug interactions?

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First identified as an effective treatment for gastric spasm, pain, and acidity in a 1799 London medical journal, bismuth subsalicylate (BSS) has been prescribed for a variety of gastrointestinal (GI) issues for over 200 years.[1] In 1897, bismuth was prescribed for chronic ulcers, alcoholic gastritis, and diarrhea to decrease pain, reduce vomiting, and enable patients to tolerate food as well as via injection for early stages of gonorrhea (which proved not effective).[2]

Bismuth subsalicylate is an insoluble salt with a trivalent heavy metal and salicylic acid. In the stomach, BSS undergoes hydrolysis in stomach acid–releasing salicylate, which is absorbed in the blood stream. Bismuth in the GI tract forms other salts including bismuth oxychloride (BiOCI). Antimicrobial properties of BSS and BiOCI inhibit growth or kill bacteria. Antiviral activity suggests that BSS and BiOCI prevent viral invasion of host cells and inhibit viral replication. Studies in the 1980s and 1990s exposing bacterial enteric pathogens in culture or human fecal material to BSS provided early evidence that BSS has antimicrobial properties against a wide range of diarrhea-causing pathogens.[3]

Bismuth subsalicylate active ingredients for many over-the-counter antacid and antidiarrheal agents include (list is not exhaustive) *Bismarex*, *Bismatrol*, *Bismatrol Maximum Strength*, *Childrens Kaopectate*, *K-Pek*, *Kao-Tin Bismuth Subsalicylate Formula*, *Kaopectate*, *Kaopectate Anti-Diarrheal Upset Stomach Reliever*, *Kaopectate Extra Strength*, *Kapectolin (New Formula)*, *Kola-Pectin DS*, *Maalox Total Relief*, *Maximum Strength Stress*, *Peptic Relief*, *Pepto-Bismol*, *Pepto-Bismol InstaCool*, *Pepto-Bismol Maximum Strength*, *Pepto-Bismol Original Strength*, *Percy Medicine*, *Pink Bismuth*, *Stomach Relief*, *Stress Maximum Strength*.[4,5] Nearly 99% of ingested bismuth is passed fecally, and absorbed bismuth is passed via renal and hepatic processes.[4,6]

Bismuth subsalicylate decreases flow of fluids into the bowel and reduces inflammation in the intestine with antimicrobial activity.[7] Antibacterial and antiviral activity occurs within 24 hours of dosing.[8] Tissue accumulation has been reported after 6 weeks of standard BSS doses. Interestingly, some recommend taking BSS no more than 6 to 8 weeks followed by 8 weeks of bismuth-free interval.[9]

Coagulopathy with acetylsalicylic acid toxicity is well documented. However, coagulopathy with BSS overuse is not. Exercise caution using BSS in liver and kidney disease, which increases risk of BSS toxicity.[9] Coagulopathy may be an indicator of BSS toxicity in patients with liver disease and preexisting prothrombinopenia. Patients with cirrhosis often have hypoprothrombinemia that can be exacerbated by salicylate-induced coagulopathy. Overuse of BSS can also lead to salicylate toxicity.[4]

Bismuth neurotoxicity is associated with uninterrupted long-term and/or high-dose usage.[9] Neurological symptoms can include impaired thought, lethargy, somnolence, coma, insomnia, dysarthria, seizures, and tremor. Patient may also display apathy, sadness, irritability, anxiety, and even psychotic symptoms. Additional early symptom may be falls. Symptoms slowly decrease once the BSS is stopped and the metal clears the body.[4,9]

Although very rare, consider encephalopathy related to BSS use in patients presenting with subacute encephalopathy and myoclonus and even stroke signs. If related to BSS use, cessation can result in resolution over a period of weeks. Bismuth subsalicylate (Pepto-Bismol®) appears less likely to cause neurotoxicity than other bismuth compounds (bismuth subnitrate or subgallate), and bismuth levels can be assessed in

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urine, cerebral spinal fluid, and blood.[10] Bismuth sometimes blackens the tongue and mucous membranes and discolors stool with use. This is the result of bismuth interacting with trace amounts of sulfur in saliva and GI tract and is temporary and harmless.[2,7]

As for drug interactions and polypharmacy, patients receiving blood thinners or daily aspirin or allergic to salicylate pain should exercise extreme caution in use of BSS. Do not combine BSS with other agents containing salicylates. Persons taking tetracycline antibiotics should take the antibiotic 1 hour before or 3 hours after taking BSS. Patients on insulin or oral diabetes medications should carefully follow dosing recommendations because large doses of BSS can provide false urine glucose results, and salicylates can decrease blood sugar. Diabetic medications should not be taken at the same time as BSS agents.[6,7] Finally, exercise caution in use of BSS when taking probenecid because aspirin and other salicylates should be avoided when receiving this agent for gout.[5,7]

Safety has not been established during pregnancy; therefore, use of BSS is not recommended. Although the risks for toxicity are small, significant fetal adverse effects have resulted from chronic exposure to salicylates. Because of this, the use of BSS during gestation should be restricted to the first half of pregnancy and then only in amounts that do not exceed the recommended doses.[11] Excretion of large amounts of bismuth into breast milk is not expected related to poor absorption of bismuth into the systemic circulation. Salicylates, however, are excreted in breast milk and are eliminated more slowly from milk than from plasma. Because of the potential for adverse effects in the nursing infant, BSS should be avoided during lactation.[4,12]

Promising evidence has emerged in the last decade supporting bismuth in the treatment of *Helicobacter pylori* infection; a primary cause of gastritis, gastric and duodenal ulcers, and gastric cancer. Bismuth remains one of few antimicrobials in which resistance has not developed and appears to provide a synergistic effect for several antibiotics independent of clarithromycin and/or metronidazole resistances.[13]

Commonly used therapies for *H pylori* of proton pump inhibitor (PPI) and antibiotics have demonstrated significant failure rates. In an analysis of a multisite European registry data from 1141 treatment-naive patients from 27 countries beginning in 2013, the efficacy and safety of bismuth plus standard clarithromycin triple therapy as treatment for *H pylori* were evaluated. Researchers found the addition of bismuth to a 14-day standard triple therapy with clarithromycin and amoxicillin eradicated *H pylori* infection in more than 90% of patients, based on intention-to-treat analysis and had an acceptable safety profile and patient adherence (ClinicalTrials.gov no. NCT02328131). In regions with known significant resistance without routine susceptibility testing, the addition of bismuth to triple therapy offers a significant and favorable alternative for lifesaving therapy.[13]

In another study, a prospective randomized controlled trial (RCT) evaluated *H pylori* eradication using standard triple therapy with bismuth and with or without probiotics for 7 to 14 days. A 7-day standard triple therapy (double-dose PPI, amoxicillin, long-acting clarithromycin with bismuth and probiotic) resulted in 100% efficacy for *H pylori* eradication in an area with high prevalence of metronidazole resistance and low prevalence of clarithromycin resistance. Results suggest that the addition of bismuth and probiotic apart from increasing the dosage and duration of PPI may improve *H pylori* eradication, thus reducing risks for gastric cancer.[14]

Finally, whether bismuth is an effective intervention for collagenous colitis remains under study. In a recent analysis of randomized controlled trials evaluating agents for collagenous colitis, results suggest that more study is necessary to clear up the uncertainty regarding the benefits and risks of therapy with BSS with and without cholestyramine, prednisolone and probiotics.[15]

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