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Bismuth Subsalicylate: History, Chemistry, and Safety

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Pepto-Bismol, which contains bismuth subsalicylate (BSS) as the active ingredient, has been marketed in the United States for more than 80 years. In the gastrointestinal tract, BSS is converted to salicylic acid and insoluble bismuth salts. The salicylate portion of BSS is extensively absorbed (>90%) and excreted in urine. The maximal daily dose of Pepto-Bismol (4.2 g of BSS) results in peak concentrations of salicylate in plasma considerably below the level of salicylate toxicity. In contrast, little bismuth from BSS is absorbed from the gastrointestinal tract (<.005%). Extended dosing of Pepto-Bismol (3.14 g of BSS/d) for up to 6 weeks produced a mean concentration of bismuth in blood of 16.1 ± 7.9 ng/g, considerably below concentrations in blood that have been reported to cause neurotoxicity. Neurotoxicity studies in animals and human safety data indicate that Pepto-Bismol can be used safely for its acute indications and for up to 3–4 weeks of extended dosing.

The first documented medical use of bismuth was in 1733, when its use in salves was described. While some internal use of bismuth may have occurred in Europe before the late 1700s, in 1799 the editors of a prestigious English medical journal described bismuth as a potent remedy for the relief of spasmodic pain of the stomach and bowels. Shortly thereafter, bismuth salts were reported by Chambers in the United Kingdom and Kussmaul in Germany to be an effective treatment for dyspepsia [1, 2].

The history of the use of bismuth subsalicylate (BSS) is actually the history of Pepto-Bismol. In the early 1900s approximately two of every 10 children died before the age of four, many from an illness called "cholera infantum." This disease was characterized by diarrhea and upset stomach. Although a variety of treatments were tried, none proved successful.

In 1900, on the basis of reports from Europe of the use of bismuth salts for the treatment of various ailments of the gastrointestinal tract, a physician in New York developed a liquid preparation that contained BSS and zinc salts for their astringency, salol (phenyl salicylate) for its antiseptic ability, oil extracts of the wintergreen plant for flavor, and a red dye to make the product pink in order to appeal to children. This preparation was called "Mixture Cholera Infantum" and, unlike previous preparations for cholera infantum, was successful for the treatment of this illness.

When demand for the product exceeded the capacity of the local druggist to make it, the physician contracted the newly formed Norwich Pharmacal Company (Norwich, N.Y.) for its manufacture; the product was first made in 20-gallon wooden tubs and sold directly to physicians.

As use of the product increased, physicians discovered that Mixture Cholera Infantum was effective against a condition called "summer complaint," which was characterized by a range of symptoms including acute gastroenteritis, diarrhea, stomach cramps, and vomiting. Although in 1918 Norwich Pharmacal began to market this product nationally as Bismosal, the name was changed to Pepto-Bismol when it was discovered there was another product marketed under the Bismosal name. Since its early development nearly a century ago, Pepto-Bismol has become a household name and can be found in ~60% of homes in the United States.

Chemistry of BSS in the Gastrointestinal Tract

BSS is a highly insoluble salt of trivalent bismuth and salicylic acid. Each molecule contains 58% bismuth and 42% salicylate by weight. Although the chemistry of BSS in the gastrointestinal tract is not completely understood, in vitro dissociation data and in vivo animal data have allowed us to speculate about the reactions that may take place after ingestion of BSS (figure 1). BSS is believed to be nearly completely hydrolyzed in the stomach to form bis-

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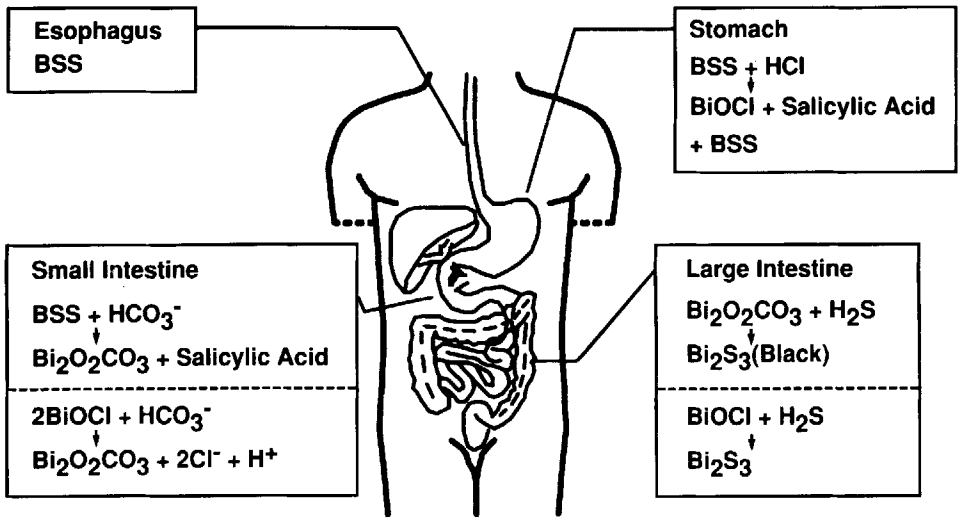

Figure 1. Schematic diagram of the postulated chemical fate of BSS in the gastrointestinal tract.

muth oxychloride and salicylic acid. Results of in vitro studies in which simulated gastric juice was used indicate that BSS is rapidly hydrolyzed at pH levels <3. Bismuth from BSS or nondissociated BSS appears to be strongly associated with the mucosal surface of the stomach. Studies in dogs indicate that bismuth is present in gastric mucosal samples for up to 6 hours after a single 30-mL dose of Pepto-Bismol, which contains 525 mg of BSS [3]. This association of bismuth with the gastric mucosal surface may be responsible in part for the cytoprotective properties of Pepto-Bismol.

While dissociation of BSS occurs primarily in the stomach, absorption of salicylate is believed to occur in the small intestine as peak levels of salicylate in plasma are reached 1–2 hours after dosing [4]. The rate of gastric emptying and the pH of the stomach are believed to determine how much nondissociated BSS enters the small intestine. In the small intestine nondissociated BSS is believed to react with other anions (bicarbonate and phosphate) to form bismuth subcarbonate and bismuth phosphate salts. Like their parent salt, these bismuth salts are highly insoluble; thus little bismuth is absorbed across the small intestine.

In the colon, nondissociated BSS and other bismuth salts are believed to react with hydrogen sulfide produced by anaerobic bacteria to produce bismuth sulfide, a highly insoluble black salt responsible for the darkening of the stool during use of BSS. This darkening of the stool is transient and harmless and does not interfere with standard tests for occult blood [5]. A similar mechanism in the oral cavity is also likely to be responsible for the occasional temporary darkening of the tongue during BSS therapy.

Salicylate Pharmacology and Toxicology

In 1981, Feldman et al. [4] characterized the absorption of salicylate from BSS. Levels of salicylate in plasma and urine were measured in six healthy men who received a single dose of 15, 30, or 60 mL of Pepto-Bismol liquid (262.5, 525, and 1,050 mg of BSS, respectively). After 72 hours the percentage of salicylate recovered in the urine from each dose ranged between 91.3% and 95.0%, a finding that suggests salicylate from BSS is almost completely absorbed from the gastrointestinal tract and excreted in the urine.

Table 1 shows a comparison of the bioavailability of salicylate by absorption from BSS with the absorption of salicylate from aspirin. At the highest dose of Pepto-Bismol (60 mL or 1,050 mg of BSS) evaluated, the peak plasma concentration of salicylate was 40.1 μg/mL, with a time to peak of 1.8 hours. The area under the concentration curve (AUC) was 365 (μg·h)/mL [4]. For comparison we measured the bioavailability of salicylate from aspirin after the ingestion of two 325-mg aspirin tablets (498 mg of salicylate) or two maximum-strength aspirin tablets (1,000 mg of aspirin or 767 mg of salicylate). Peak

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Table 1. Bioavailability of salicylate after an oral dose of Pepto-Bismol or aspirin.

	BSS (mg)	Salicylate (mg)	Peak salicylate concentration (μg/mL)	Time to peak (h)	AUC (μg·h/mL)
Pepto-Bismol*					
60 mL	1,050	526	40.1	1.8	365
Aspirin					
650 mg	. . .	498	34.3	1.9	344
1,000 mg	. . .	767	58.9	2.3	470

* Data are from [4].

plasma concentrations were 34.3 and 58.9 μg/mL, respectively, with the time required to reach the peak level from 1.9 to 2.3 hours. The AUC for salicylate from aspirin (344 [μg·h]/mL for 650 mg of aspirin; 470 [μg·h]/mL for 1,000 mg of aspirin) are within the range of the AUC for salicylate from 60 mL of Pepto-Bismol. These data support the conclusion that the pharmacokinetics of salicylate from BSS are similar to those of salicylate from aspirin. However, it should be noted that the pharmacologic actions of BSS and aspirin are different.

On the basis of measurements of the AUC for various doses of BSS, Feldman et al. [4] observed a nonlinear increase in the AUC, a finding that suggests that salicylate excretion becomes saturated and nonlinear at high doses of BSS and that at these doses there is the potential for salicylate to accumulate. Since the use of multiple doses of BSS is recommended for the treatment of diarrhea, Pickering et al. [6] determined the peak plasma concentrations of salicylate in healthy adult males after multiple dosing. In these studies, a dose of 525 mg of BSS (30 mL of Pepto-Bismol) was given every 30 minutes for a total of eight doses in 3½ hours. This regimen provided a total daily dose of 4.2 g of BSS. The peak level of salicylate in plasma was 137 ± 20 μg/mL, with a time to peak level of 5 hours after administration of the first dose. These peak levels of salicylate in plasma are significantly lower than the level of 400 μg/mL associated with acute salicylate toxicity and are also considerably lower than the levels of 200–390 μg/mL of salicylate that have been reported to produce hyperventilation, dehydration, and CNS effects (e.g., tinnitus) during chronic salicylate administration [7]. These data demonstrate that the maximal daily dose of Pepto-Bismol does not result in toxic levels of salicylate.

To evaluate the effect of extended use of Pepto-Bismol on plasma salicylate levels, we measured plasma salicylate levels in subjects who received a 30-mL dose four times a day for 3 weeks, for a total daily dose of 2.1 g of BSS. This is the same dosing regimen that DuPont et al. [8] found to be effective in the prophylaxis of travelers' diarrhea with Pepto-Bismol tablets. While peak levels of salicylate in plasma were not measured, steady-state levels of salicylate were reached after 2 weeks and averaged 24 μg/mL. For comparison, the steady-state level of salicylate in plasma following the maximal daily dose of aspirin (4 g/d) is 160 μg/mL—levels considerably above those reached with the daily dosing of 2.1 g of BSS. Thus, the extended dosing regimen for Pepto-Bismol (525 mg four times daily for 3 weeks) produces steady-state levels of salicylate that are well below those obtained with maximal daily aspirin therapy, which is considered safe.

Bismuth Pharmacology and Toxicity

In contrast to salicylate, little bismuth is absorbed from the gastrointestinal tract, presumably because of the insolubility of bismuth salts in biologic fluids in the stomach and intestine. More than 99% of the bismuth present in an oral dose of Pepto-Bismol is excreted in the feces. An assessment of the bioavailability of bismuth from BSS was done by administering eight 30-mL doses of Pepto-Bismol at 30-minute intervals to 15 healthy men. This dosing regimen corresponds to the maximal daily recommended dose for Pepto-Bismol and provides 4.2 g of BSS. Blood samples were collected hourly for the first 8 hours and then once daily for 14 days. Urine samples were collected for 24-hour periods for the 8 days after dosing. Bismuth in the blood and urine samples was measured by atomic absorption spectroscopy with a detection limit of bismuth of 5 ng/g in blood and 1 ng/g in urine.

At enrollment none of the participants had detectable levels of bismuth in blood or urine. After administration of Pepto-Bismol, all participants had levels of bismuth in blood below the level of detection (5 ng/g) at all time points measured. During the first 8 days following dosing, the total amount of bismuth excreted in urine was 64 ± 25 μg. This corresponds to 0.003% of the ingested bismuth dose and suggests negligible absorption of bismuth. The design of this study was not appropriate for determination of the total amount of bismuth absorp-

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tion, since any bismuth that may have accumulated in tissue could not be measured. Finally, the half-life of urinary bismuth excretion in this trial was ~33 ± 8 hours, a value consistent with the slow excretion of residual bismuth in the body after treatment with a slightly soluble bismuth salt.

Despite the extremely low level of bismuth absorption, concern has been expressed about the neurotoxic potential of bismuth salts. Between 1973 and 1980, ~1,000 cases of bismuth-related neurotoxicity were reported in France [9, 10], 40 in Australia, and 26 in Belgium, Switzerland, and Spain [11]. In most instances, patients had ingested large doses of bismuth subnitrate or bismuth subgallate (700 mg to 20 g/d) for long periods (from 4 weeks to 30 years) for the treatment of gastrointestinal ailments—mainly constipation or diarrhea—or for odor control in ostomy patients. An epidemiologist who studied the cases of encephalopathy in France found no significant differences in the amount of bismuth ingested or the duration of dosing among patients who had neurotoxic symptoms and those who did not [12].

Only one case of neurotoxicity associated with BSS has been published [13]. This occurred in a 60-year-old man in Australia. He ingested more than twice the acute daily recommended dose of BSS (4.2 g of BSS). Of note, the BSS preparation used by this individual was not Pepto-Bismol. Because the patient may have been taking other medications for coexisting medical conditions, it could not be conclusively established whether the neurotoxicity was caused by bismuth.

Since the epidemic in France and Australia, only a few cases of bismuth-related neurotoxicity due to chronic oral ingestion of bismuth salts have been reported, despite the continued use of bismuth salts worldwide. In the United States no cases of bismuth-related neurotoxicity from oral administration of bismuth salts have been reported, and no cases of neurotoxicity have been reported worldwide with the use of Pepto-Bismol. More than 10 billion doses of Pepto-Bismol have been consumed since its introduction.

To further examine the safety of BSS and Pepto-Bismol, we developed an animal model [14] to aid in determining the mechanism of the neurotoxic effects of bismuth seen in the cases of human encephalopathy. Swiss-Webster mice were given from one to three ip injections of bismuth subnitrate (1.25–2.5 g/kg) and observed for signs of bismuth neurotoxicity. Nine of 58 mice showed definitive neurotoxic signs similar to those observed in humans, including myoclonus, ataxia, tremors, and convulsions. Animals with evidence of neurotoxicity, treated animals that did not demonstrate neurotoxic signs, and matched controls were killed and bismuth levels in the blood and brain were measured.

Animals that showed neurotoxic effects had hydrocephalus and levels of bismuth in brain tissue that were ~8,000 ng/g—levels similar to those reported in the few fatal human cases of bismuth-associated encephalopathy in which bismuth concentration in the brain was measured [15, 16]. While animals with bismuth levels in the brain of ~4,000 ng/g did not show signs of neurotoxicity, all animals with this level had hydrocephalus. No other histologic lesions were seen in the brains. Subsequent studies in mice (author's unpublished data) suggest that the no-observable-effect level (NOEL) for hydrocephalus with bismuth subnitrate given by ip injection is ~1,000 ng/g.

Using the mouse as a model for human bismuth neurotoxicity, we conducted a 91-day feeding study with BSS in mice. Animals were given a daily dose of up to 5 g of BSS/kg body weight. At this high-dose level, BSS constitutes 2.5% of the diet and provides a 60-fold exaggeration of the maximal recommended daily acute dose of Pepto-Bismol (4.2 g of BSS). No neurotoxic effects were observed throughout the study, and no histopathologic lesions were seen in the brain.

Hillemand et al. [17] reviewed the relationship between bismuth levels in blood and encephalopathy in humans using data from the cases of encephalopathy in France. In the reported cases of bismuth encephalopathy the minimal level of bismuth in blood measured was 180 ng/g. These authors concluded that when blood bismuth levels are >100 ng/g, dosing with bismuth should be discontinued; when levels are 50–100 ng/g, dosing could be continued but the patient should be monitored for symptoms of neurotoxicity; and when levels are <50 ng/g, no monitoring is necessary.

Because the neurotoxic effects reported in France and Australia were associated with extended use of bismuth salts, we studied the effect of extended Pepto-Bismol dosing on blood bismuth levels in humans. In one study, 30 normal, healthy volunteers took 12 Pepto-Bismol tablets a day for 6 weeks to provide a total daily dose of 3.14 g of BSS. Blood samples were analyzed for bismuth when the volun-

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teers enrolled in the study; at the end of weeks 1, 2, 4, and 6 of dosing; and at 9 weeks after dosing (figure 2). With continued dosing, blood bismuth levels increased and reached a mean of 16 ± 7.9 ng/g at 6 weeks. The highest blood bismuth level was 34 ng/g. No participant had neurotoxic symptoms, and all blood bismuth levels decreased to the <5 ng/g detection limit at 9 weeks after treatment. These data suggest that extended dosing of Pepto-Bismol at 3.14 g of BSS/d for up to 6 weeks does not result in blood bismuth levels that are associated with neurotoxicity.

Discussion

BSS in Pepto-Bismol has been safely marketed in the United States for >80 years. Because BSS in the gastrointestinal tract is hydrolyzed to salicylate and bismuth salts, the pharmacology and safety of salicylate and bismuth should be considered separately. While the pharmacokinetics of salicylate from BSS are similar to those of salicylate from aspirin, the pharmacologic action of BSS is different from that of aspirin. One adult dose of Pepto-Bismol liquid (30 mL of original strength) provides 258 mg of salicylate, and one adult dose of Pepto-Bismol tablets (two tablets) provides 204 mg of salicylate. Each of these doses contains approximately the same amount of salicylate delivered by one regular-strength aspirin tablet (249 mg of salicylate). It should be noted that the liquid preparation contains 54 mg more salicylate per dose than does the tablet preparation because of the presence of other salicylate salts that are used as buffering agents. Maximum-strength Pepto-Bismol liquid contains 460 mg of salicylate per dose, which is less than the amount of salicylate from two regular-strength aspirin tablets. At the maximal recommended daily dose of Pepto-Bismol liquid (original or maximum strength) or tablets, the amount of salicylate provided is less than the maximum salicylate ingestion allowed under the Over-the-Counter Internal Analgesic Monograph (3,080 mg/d).

Results of both animal and human studies indicate that bismuth is poorly absorbed from the gastrointestinal tract. In mice BSS at levels 60 times the maximal recommended human daily dose did not produce any signs of neurotoxicity. In addition, human testing of BSS at doses 50% greater than those used in studies of diarrhea prophylaxis [7] resulted in blood bismuth levels considerably below those at which it has been recommended that bismuth therapy be discontinued. These animal and human safety data indicate that ingestion of Pepto-Bismol for acute usage and for extended dosing up to 2.1 g of BSS/d for 3–4 weeks, such as in the prophylaxis of travelers' diarrhea [7], would not result in bismuth-related neurotoxicity. However, because the epidemic of bismuth-associated neurotoxicity in France and Australia involved chronic dosing of bismuth salts and because many aspects of this epidemic still remain unexplained, chronic dosing of Pepto-Bismol is not recommended at this time.

Pepto-Bismol should not be used by patients taking medication for anticoagulation, diabetes, or gout because of the potential for salicylic acid from BSS to inhibit the active excretion of these organic acid drugs by the kidney. Since Pepto-Bismol tablets (but not Pepto-Bismol liquid) contain calcium carbonate, concomitant use of Pepto-Bismol tablets with tetracycline antibiotics is not recommended. If Pepto-Bismol tablets are used with these antibiotics, dosing with the different agents should be separated by 1–2 hours.

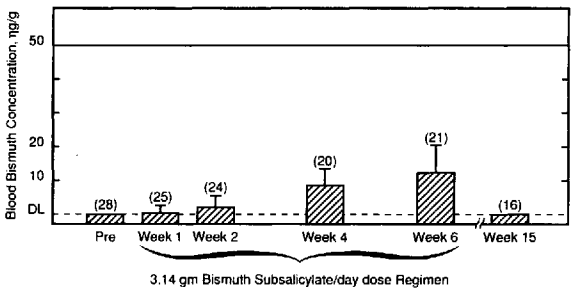

Figure 2. Bioavailability of bismuth after ingestion of 3.14 g of BSS/d in four divided doses. Each bar represents the mean ± SE; numbers in parentheses represent number of subjects.

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