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The ACG Committee on FDA-Related Matters under the primary authorship of Barry J. Marshall, M.D.

The Use of Bismuth in Gastroenterology

INTRODUCTION

Bismuth preparations have been useful in a variety of gastrointestinal disorders for over two centuries. The most commonly used preparations are bismuth subsalicylate (BSS), available as Pepto Bismol, and colloidal bismuth subcitrate (CBS), available abroad as De-Nol, for the treatment of peptic ulcer disease. BSS is antibacterial against enterotoxigenic *Escherichia coli* and other enteropathogens, and is effective in the prophylaxis and treatment of travelers' diarrhea. The recent demonstration that bismuth is antibacterial against *Helicobacter pylori* has encouraged many studies utilizing BSS and CBS, alone or in combination with antibiotics, in patients with gastritis or peptic ulcer disease. Both compounds are effective in healing these conditions. The need for total eradication of *H. pylori* to prevent relapses has resulted in the use of bismuth/antibiotic combinations, with promising results. Utilized in recommended dosages, bismuth salts pose no safety hazards.

HISTORY

The use of oral bismuth for medical purposes dates back to Great Britain in the late 18th and early 19th centuries when bismuth subnitrate was reported as helpful in the treatment of "spasmodic pain of the stomach and bowels." "Complete cures" were reported in four out of six patients with "spasmodic affections of the stomach," and it was reported as effective in "pyrosis" and "cardalgia" (heartburn). In 1848, bismuth subnitrate was used in the United States for the treatment of "nervous disorders of the stomach," and in 1868, Kussmaul reported its usefulness in gastric ulcer (1). Bismuth subcitrate was advocated by Ogle for nonulcer dyspepsia in 1864 (2). In 1901, a bismuth subsalicylate preparation was advocated for the treatment of "cholera infantum." Subsequently, this preparation gained widespread use and popularity, and in 1918 was marketed under the name of "Bismosol" by Norwich Pharmacal Company. The name was subsequently changed to "Pepto-Bismol" (3), and it is now marketed by the Procter and Gamble Company.

The antispirochetal action of bismuth was demonstrated in 1916 (4), and in 1921, it was shown to cure experimental syphilis in the rabbit (5). Subsequent to clinical studies in human syphilis, over 100 bismuth compounds were synthesized, and by 1935 thousands of publications on the antispirochetal use of bismuth had appeared in the literature (6).

With the advent of penicillin and its antibiotic descendents, the potential antimicrobial properties of bismuth were forgotten. Bismuth use after 1950 was almost entirely limited to over-the-counter preparations. In 1950, Ivy and Grossman reported the ineffectiveness of bismuth as an antacid (7). During the 1970s, bismuth compounds were used sparingly in most countries, except in Australia, where bismuth subgallate was widely used as a stool deodorizer for patients with colostomies, and in France, where bismuth salts were widely used for a variety of gastrointestinal disorders. Little was known concerning the pharmacology of the bismuth salts.

CHEMISTRY AND PHARMACOLOGY OF BISMUTH

Bismuth is the heaviest nonradioactive element, with an atomic number of 83 and an atomic weight of 209. It has a valence of three and is in the same periodic table group as phosphorus, arsenic, and antimony.

The various bismuth salts are derived from bismuth nitrate which, in turn, is produced by the action of nitric acid on free bismuth or bismuth ores. After separation from the acid, bismuth nitrate is hydrolyzed to bismuth subnitrate, which can then react in solution with soluble basic salts to form bismuth subcarbonate, subgallate, subsalicylate, or subcitrate (Fig. 1).

Bismuth salts are essentially insoluble in water. Solubility increases slightly in hydrochloric acid, but almost all ingested bismuth is converted in the stomach to the insoluble oxide, hydroxide, and oxychloride

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forms. As a result, most bismuth salts form a precipitate, mainly of BiOCl in the stomach. Only trace amounts of bismuth are absorbed, probably via localization on the brush border glycocalyx of intestinal enterocytes and subsequent phagocytosis by the cells (8, 9). In the colon, bismuth salts are converted to black bismuth sulfide by the action of bacteria-produced hydrogen sulfide. This imparts a black color to the stools. These organisms are also found in the oral cavity.

Bismuth subsalicylate and bismuth subcitrate are currently the two most frequently used bismuth preparations.

Bismuth subsalicylate (BSS) is available in the United States primarily as Pepto-Bismol. It is used primarily for the acute treatment of diarrhea and upper gastrointestinal symptoms, and is available in liquid and chewable tablet forms. Two liquid strengths provide BSS in a 1.75% or 3.5% suspension in a vehicle containing magnesium aluminum silicate, methylcellulose, and food coloring. Each tablet contains 262 mg of BSS plus 350 mg of calcium carbonate. The usual dose is 525 mg of BSS (305 mg of bismuth), which is equivalent to 30 ml of the 1.75% suspension, 15 ml of the 3.5% suspension, or two tablets. Each dose contains salicylate equivalent to 258 mg of salicylic acid. The usual dosage for acute diarrhea or dyspepsia is one dose every ½ h up to 8 doses per day for 1–2 days (3, 10).

BSS disassociates in the stomach, allowing the salicylate moiety to be absorbed independent of the bismuth. In 1981, Feldman *et al.* (11) studied the levels of salicylate in plasma and urine in six healthy men who received a single dose of 15, 30, or 60 ml of Pepto-Bismol (262.5, 525, and 1050 mg of BSS, respectively). After 72 h, the percentage of salicylate recovered from the urine ranged between 91.3% and 95%, a finding indicating that the salicylate from BSS is almost completely absorbed from the gastrointestinal tract and excreted in the urine.

Pickering *et al.* (12) determined the peak plasma concentrations of salicylates in healthy adult males after eight doses of 525 mg of BSS administered every 30 min for a period of 3½ h. The peak level of salicylate was 137 ± 20 μg/ml, with a time to peak of 5 h after the first administration. This peak level of salicylate in plasma is significantly lower than the level of 400 μg/ml associated with acute salicylate toxicity.

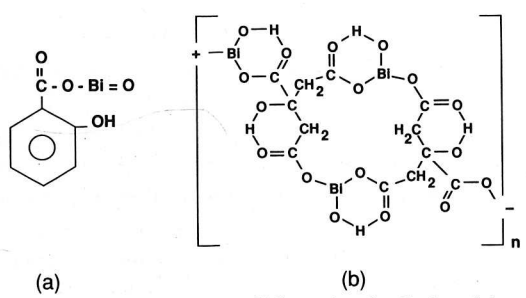

FIG. 1. Molecular structures of bismuth subsalicylate (*a*) and colloidal bismuth subcitrate (*b*).

Nwokolo *et al.* (13) measured plasma bismuth and salicylate concentrations before and after three 30-ml oral doses of BSS in 10 fasting healthy subjects. From 0 to 120 min after the first dose of BSS, the plasma bismuth concentration was less than 1 μg/L. The peak median bismuth concentration occurred at +240 min (1.7 μg/L, range 0.8–5.3 μg/L). Salicylate appeared in the plasma of all subjects at +30 min and reached peak levels at +120 min (median 61 mg/L, range 46–104 mg/L).

An assessment of the bioavailability of bismuth from BSS was done by administering eight 30-ml doses of Pepto-Bismol at 30-min intervals to 15 healthy men (3). 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 8 h and then once daily for 14 days. Urine and blood levels of bismuth were performed on all specimens using atomic absorption spectroscopy. All subjects had levels of bismuth in blood below the level of detection (5 μg/L) at all times measured. During the first 8 days following dosing, the total amount of bismuth excreted in the urine was 64 ± 25 μg. This corresponds to 0.003% of the ingested bismuth, and suggests negligible absorption of bismuth. These data indicate that the levels of salicylate and bismuth obtained with these dosages of bismuth subsalicylate are far below those considered to be toxic (14).

Bismuth subcitrate is widely used as a prescription product outside the United States for the treatment of peptic ulcer. On the addition of ammonia, bismuth subcitrate forms a colloidal solution by linkage of the trivalent bismuth to the trivalent citrate moiety. This colloidal suspension was the original formulation of De-Nol, but to improve palatability, it has been superseded by colloidal bismuth subcitrate (CBS) tablets, a spray-dried derivative of the liquid form.

The usual dose of CBS is one tablet four times daily (108 mg elemental bismuth), taken an hour before meals and at bedtime. Once ingested, the citrate moiety is easily metabolized, while the bismuth component converts to the poorly absorbed precipitable BiOCl so that, as in the case of BSS, bismuth absorption is minimal. After 8 wk of chronic administration of the above-mentioned dose of CBS, blood bismuth levels are rarely in excess of 35 μg/L. The recent conversion of the CBS formulation from "chewable tablets" to "swallowable tablets," which disintegrate within 5 min of entering the stomach, has been shown to cause transient high serum bismuth levels (50–500 μg/L) after acute administration (15). This does not appear to be clinically relevant, but further observation is necessary.

Concerns for bismuth toxicity, particularly in the

form of encephalopathy, arose due to experiences in France and Australia. In France, bismuth became a widely used gastrointestinal panacea during the 1970s. Bismuth subcarbonate, subgallate, and subnitrate were commonly consumed in doses up to 20 g of elemental bismuth per day (16). As a result, an epidemic of bismuth encephalopathy occurred in that country between 1973 and 1977, resulting in many fatalities.

In Australia, where high doses (3–20 g/day) of bismuth subgallate were widely used by patients with colostomies, 29 cases of encephalopathy were reported in patients who had taken the drug for between 6 months and 3 yr (17).

Evaluation of the French and Australian data revealed that prolonged use (months to years) of high doses (>1.5 g of bismuth metal/day) was necessary for bismuth toxicity to occur (18). Serum levels of bismuth in toxic patients often reached 150–4000 μg/L (150–4000 parts per billion of whole blood), while the usual therapeutic dose of bismuth (<1.5 g/day) in normal persons provided levels of 15–35 μg/L after 2 months of use.

Restrictions on the use of bismuth in France and the banning of the use of bismuth subgallate in Australia has virtually eliminated further cases of bismuth toxicity. There have been no documented cases of bismuth toxicity with the recommended acute dosages of either bismuth subsalicylate or colloidal bismuth subcitrate. A single case of encephalopathy associated with BSS has been reported from Australia (19). The patient, a diabetic, had been taking BSS continuously for over a year, much longer than the customary short duration of BSS therapy, and for a period of time for which there is little experience with BSS.

Mendelowitz *et al.* (20) recently reported a patient with AIDS suffering from severe debilitating diarrhea as a result of cytomegalic colitis. Therapy with tincture of opium, loperamide, diphenoxylate, acyclovir, and kaolin had been unsuccessful in controlling his diarrhea, which persisted in volumes of 2–3 L a day. The diarrhea was dramatically decreased by administration of Pepto-Bismol, 30–90 ml every 2 h as needed. The actual total dose of bismuth ranged from 5.2 to 9.4 g/day in divided doses. After the establishment of the diagnosis of cytomegalic colitis, treatment with gancyclovir (10 mg/kg of body weight per day intravenously) was initiated. After 7 days of BSS, the patient was noted to have lethargy, dysarthria, and myoclonic movements of the fact and extremities. The blood bismuth concentration was measured by atomic absorption spectrophotometry as 200 μg/L (safe level, 10–50 μg/L). A trial of chelation therapy with D-penicillamine was attempted; however, the patient died within 24 h. A postmortem examination was refused. The authors theorize that diffusely diseased mucosa may have led to increased bismuth absorption in a seriously ill patient.

CURRENT THERAPEUTIC USES OF BISMUTH SALTS

Bismuth subsalicylate in the treatment of diarrhea

There is a substantial amount of animal (21, 22) and clinical (23–30) evidence that BSS is effective in the treatment of a wide variety of diarrheal disorders. *In vitro* bactericidal activity of BSS against enterotoxigenic *E. coli* has been demonstrated (23, 31, 32), and its effectiveness in both prevention and treatment of travelers' diarrhea is well documented (24–26). Studies utilizing BSS in this disorder have demonstrated that it reduces the frequency of unformed stools, improves stool consistency, and decreases the accompanying symptoms of nausea, vomiting, and abdominal cramps.

DuPont *et al.* (25) observed a 65% protection rate in students in Mexico who received 525 mg BSS four times a day as prophylaxis against travelers' diarrhea. Students on placebo had a 40% chance of developing diarrhea *versus* a 10% chance on the BSS. In a study in volunteers challenged with enterotoxigenic *E. coli* (ETEC), Graham *et al.* (23) reported that the administration of 600 mg BSS (equivalent to about 35 ml of Pepto-Bismol) administered 8 and 2 h prior to the challenge and 2 and 4 h after the challenge, provided prophylactic efficacy in 75% of the subjects ($p < 0.03$).

Steffen (27) has compared the efficacy of BSS treatment of travelers' diarrhea with other antidiarrheal agents in a total of 2520 individuals involving four randomized studies. Other agents included loperamide, co-trimoxazole, doxycycline, mecillinam, and *Streptococcus faecium* SF 68. Subjects took medication only if diarrhea occurred, and a total of 530 individuals were evaluable. BSS relieved symptoms in 47% within 8 h. Other therapies ranged between 25% and 49% effective at 8 h, whereas placebo effectiveness was only 18%. Loperamide appeared to work faster and doxycycline was slightly more effective than BSS, but, in view of the contraindication for loperamide in dysenteric cases and the inadvisability of systemic antibiotics for unclassified diarrhea, BSS was considered a desirable therapeutic choice.

Steinhoff *et al.* (28) inoculated 59 volunteers with the Norwalk agent. Of this group, 34 developed an illness characterized by vomiting and diarrhea, and were randomly assigned to a course of BSS or placebo in double-blind fashion. There was a significant reduction in the severity and duration of abdominal cramps ($p < 0.01$) and in the median duration of gastrointestinal symptoms ($p < 0.05$) in the group treated with BSS.

BSS has proved safe and effective in the therapy of

childhood diarrheas. Gryboski *et al.* (29) reported that BSS was effective in the therapy of infants and children with chronic diarrhea of diverse etiologies. In this study, 29 children, age 2–70 months, were treated in double-blind fashion with BSS or placebo. The BSS-treated group had significantly fewer stools, with less water content, and had a significant improvement in clinical status compared with the placebo-treated group. BSS has also been reported as effective in the treatment of acute diarrhea, whether of rotavirus or bacterial origin, in children (30).

Several mechanisms apparently contribute to the effectiveness of bismuth subsalicylate in the treatment of diarrhea. Ericsson and colleagues (22, 31) have reported that BSS significantly reduced the secretory activity of *E. coli* and cholera toxins. They demonstrated that Pepto-Bismol binds cholera toxin *in vitro* and reduces accumulation of fluid in secretory and inflammatory diarrhea.

In vitro bactericidal activity of BSS against enterotoxigenic *E. coli* and other enteropathogens has been demonstrated by several investigators (23, 32, 33). In addition, Soriano-Brücher *et al.* (34) recently reported the beneficial effects of BSS in childhood diarrhea of diverse etiologies, and demonstrated that BSS effectively eradicated enterotoxigenic *E. coli* and other enteropathogens from the stools of the infected children. Chang *et al.* (35) have recently reported the beneficial effect of BSS in a hamster model of *C. difficile* colitis, and Cornick *et al.* (32) have reported that BSS has marked *in vitro* antibacterial action against *C. difficile* with a very low inhibitory concentration (MIC90 - minimum inhibitory concentration to kill 90% of organisms) of 128 μg/L. The same group reported low MIC90 values for *B. fragilis.* Marshall *et al.* (36) have reported relatively low MIC values for *C. difficile* with colloidal bismuth subcitrate. In other *in vitro* studies, Sox and Olson (37) demonstrated that BSS was able to bind bacteria of diverse species, and that these bound bacteria were subsequently killed. They reported that intracellular ATP decreased rapidly after exposure of *E. coli* to 10 mM BSS, and after 30 min, was only 1% of its original level. Extracellular ATP increased after exposure to BSS, but the accumulation of extracellular ATP was not sufficient to account for the loss of intracellular ATP. They postulate that the killing of bacteria exposed to BSS may have been due to cessation of ATP synthesis or a loss of membrane integrity.

The salicylate component of BSS may contribute to its effectiveness in diarrhea. Burke and Gracey (38) demonstrated that salicylates are capable of antagonizing toxin-induced intestinal secretion produced by a wide range of organisms including *E. coli*, *Shigella*, and *Salmonella.* Manhart (33) has demonstrated antibacterial activity of sodium salicylate, a hydrolysis product of BSS in the gut. The relatively low degree of antibacterial activity makes it unlikely that the salicylate plays a role in this regard.

Gorbach *et al.* (39) quantitated the fecal flora in two groups of healthy volunteers before and after the administration of BSS. In one group, 8 ounces of BSS were administered on two successive days. In the second group, 8 ounces of BSS was given over a 4-h period after a standard oral intestinal lavage preparation (GoLYTELY) was used to clean the colon. In neither group was there a significant effect on the normal microbial population in the fecal microflora.

Leon-Barua *et al.* (40) tested the *in vitro* effects of tripotassium dicitrato bismuthate (bismuth subcitrate), bismuth subsalicylate, and bismuth subnitrate on fermentation by colonic bacteria. All three were effective, but BSS showed the greatest activity, decreasing gas production by 74% ($p < 0.0001$). *In vivo* studies using bismuth subnitrate for a period of 8 days in six flatulent patients, showed significant reduction ($p < 0.01$) in colonic fermentation of ingested raffinose.

Treatment of upper gastrointestinal disorders

Prior to recognition of the etiological role played by *Helicobacter* (formerly *Campylobacter*) *pylori* in gastritis and peptic ulcer disease, studies utilizing BSS in disorders of the upper gastrointestinal tract had been limited. In 1976, in a placebo-controlled study, Goldenberg *et al.* (41) demonstrated that BSS had antiemetic properties in dogs, and was an antinauseant and antiemetic in humans. Subjects were given ipecac syrup, and a dose-related suppression of nausea and vomiting was observed with a BSS suspension. BSS relieved 80% of patients given a nauseant dose of ipecac. The same investigators demonstrated that Pepto-Bismol prevented alcohol, aspirin, and cold restraint stress-related gastric erosions in rats (42).

Hailey and Newsom (43) reported in 1984 that they had treated patients with chronic dyspepsia with BSS and found it more effective than placebo in relieving symptoms of nausea, heartburn, flatulence, sense of fullness, and abdominal distension. The dosage used was 30 ml of BSS or placebo at the onset of symptoms, followed by 30 ml every 30 min up to a maximum of eight doses.

Colloidal bismuth subcitrate (CBS)

A colloidal suspension of bismuth subcitrate (CBS) is available as De-Nol in many countries (but not the United States) for the treatment of peptic ulcer. Its efficacy and safety in ulcer healing have been well demonstrated in a number of studies. The introduction of chewable and swallowable tablets has improved patient compliance by masking the ammonia-like taste of the liquid formulation.

The pharmacology of CBS has been extensively re-

viewed (44, 45). In the stomach, bismuth subcitrate is rapidly converted to bismuth oxide and oxychloride, and combines with proteinaceous material at the ulcer base to form a mechanically stable coating.

CBS shares with other bismuth preparations an antibacterial action against *H. pylori*. In addition, there is *in vitro* evidence that CBS contributes to inhibition of hydrogen ion passage through the gastric mucus (45). CBS has also been shown to increase the prostaglandin content of rat gastric mucosa (46), and to increase mucosal bicarbonate secretion (47). These cytoprotective mechanisms are thought to contribute to the ability of CBS to heal peptic ulcers and to protect against mucosal damage from aspirin, alcohol, acetic acid, and cold-immobilization (48).

CBS, BSS, and H. pylori

The important role of *H. pylori* in the etiology of gastritis and peptic ulcer disease (49) has resulted in the development of a new and important role for bismuth in the therapy of these disorders. Marshall *et al.* (50) were the first to note the antibacterial effect of CBS and other bismuth compounds on *Helicobacters*, particularly *H. pylori*. This afforded a ready explanation for the effectiveness of CBS in peptic ulcer disease, as reported in earlier studies (51, 52), and for the reported effectiveness of BSS in upper gastrointestinal disorders (41–43).

Subsequent to the discovery of the role of *H. pylori* in the etiology of peptic ulcer disease and the antibacterial action of bismuth compounds on *H. pylori*, a number of studies appeared demonstrating the healing equivalence of CBS and the histamine H2-receptor antagonists (H2RA). In a review of seven studies comparing cimetidine with CBS, CBS was reported as superior to cimetidine in six and equivalent to cimetidine in one (53). Although for each individual study, this difference was not statistically significant, CBS had a significantly better healing rate when the data from all of the studies were combined. In a similar analysis in which ranitidine was compared with CBS, there was no difference between the two groups (53). In studies in which therapy was continued for 8 wk, healing rates with CBS and cimetidine were 93% and 86%, respectively, a difference not statistically significant (53).

Although ulcer healing rates are similar for CBS and the H2RAs, a difference in relapse rates following the use of the two agents has been observed. This was demonstrated with cimetidine by Martin *et al.* (54) and with ranitidine by Lee and Samloff (55). The significant factor in determining relapse rate appears to be whether or not *H. pylori* was eradicated or suppressed. When *H. pylori* persists, the relapse rate with any acute therapy is about 85%, whereas it is less than 20% when *H. pylori* has been cleared (56).

Rauws *et al.* (57) demonstrated a 30% eradication rate of *H. pylori* with CBS, and similar rates have been observed by Marshall *et al.* (58). In a prospective double-blind study reported by Coghlan *et al.* (59), the eradication rate for *H. pylori* was 45% with CBS *versus* zero for cimetidine alone. In a recent report by Rauws and Tytgat (56), the eradication rate was 8% in patients treated with the new CBS swallowable tablet formulation, suggesting that the obsolete chewable tablets were more effective in eradicating *H. pylori*.

McLean *et al.* (60) performed a cost-effectiveness analysis comparing therapies with a high relapse rate, *e.g.*, H2RAs, with therapies that have a low relapse rate. They demonstrated that when intermittent therapy with cimetidine was employed (relapse rate 17% per month), the number of treated patients with active ulcer disease at any one time was four times that of patients treated with intermittent courses of De-Nol (relapse rate 5% per month). Alternatively, if maintenance therapy with cimetidine were as effective as intermittent therapy with CBS, the decreased amount of drug used in the latter circumstance and its moderate cost (two-thirds that of H2RAs per month) made it more cost effective.

Bardhan *et al.* (61) compared maintenance therapy with CBS (120 mg) and ranitidine (150 mg) with a placebo, and found that both active therapies were equivalent in their prophylactic efficacy over periods of 6 and 12 months, and both were significantly superior to placebo.

CBS has been shown to be effective in the healing of gastric ulcers. Patty *et al.* (62) reported a healing rate of 68% with CBS at 4 wk *versus* 54% for cimetidine. After 8 wk, healing rates were 81% and 71% for CBS and cimetidine, respectively (NS). Parente *et al.* (63) observed 4-wk gastric ulcer healing rates of 70% and 63% with CBS and cimetidine, respectively. In an evaluation of various therapies for gastric ulcer *versus* placebo for 4 wk, Tytgat and Nio (53) obtained values of 47% for CBS, 33% for sucralfate, 33% for ranitidine, and 23% for cimetidine.

The finding that all bismuth salts appear to be antibacterial to *H. pylori* has served to focus attention on the upper gastrointestinal effects of bismuth subsalicylate, readily available as Pepto Bismol. Previous studies had reported its effectiveness as an antinauseant and antiemetic (41, 42), and Hailey and Newsom (43) reported relief of nausea, vomiting, heartburn, flatulence, and abdominal fullness in patients with chronic dyspepsia. In retrospect, these beneficial effects were probably related to the antibacterial action of BSS on *H. pylori*.

To assess the clearance of *H. pylori* by BSS and to determine whether this clearance is associated with improvement in histologic gastritis, Lanza *et al.* (64) randomized 20 patients with gastritis and antral biop-

sies colonized with *H. pylori* to treatment with 30 ml of BSS (525 mg) or placebo four times daily for 21 days. After both 2 and 3 wk of therapy, *H. pylori* was cleared in 70% (7/10) of BSS-treated patients compared with 10% (1/10) of patients on placebo ($p < 0.05$) at 2 wk, and 0% (0/10) of patients on placebo at 3 wk ($p < 0.01$). A significant improvement of histologic gastritis was noted after 2 and 3 wk of BSS treatment.

In a clinical and histologic study in 50 evaluable patients with *H. pylori* and non-ulcer dyspepsia, McNulty *et al.* (65) employed regimens of placebo, erythromycin ethylsuccinate syrup, or BSS (Pepto-Bismol)

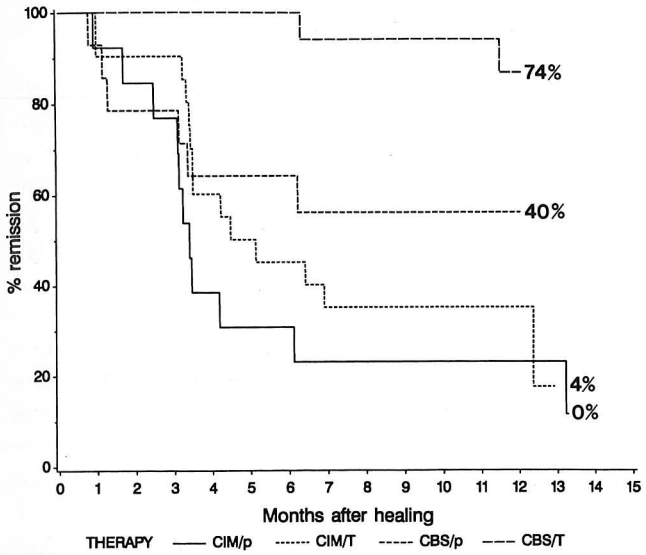

FIG. 2. Effects of treatments on relapse rates. *H. pylori* eradication rates are shown at *right* [from Marshall BJ *et al.* (58)]. *CIM/P*, cimetidine + placebo; *CIM/T*, cimetidine + tinidazole; *CBS/P*, colloidal bismuth subcitrate (De-nol) chewable tablets + placebo; *CBS/T*, CBS + tinidazole.

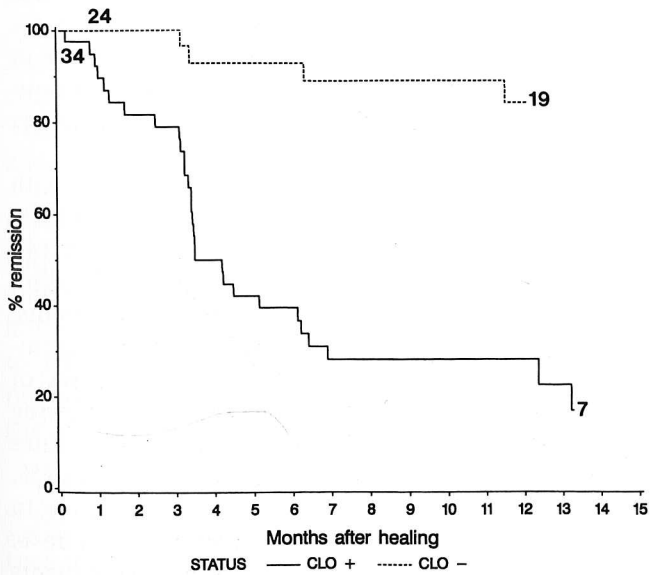

FIG. 3. Differences in relapse rates between *H. pylori*-positive and *H. pylori*-negative groups. Numbers of patients remaining are shown in both groups [from Marshall *et al.* (58)].

TABLE 1
*MICs (μg/ml) of Antibiotics and Anti-ulcer Agents against H. pylori**

Agent	No. of Strains	MIC 50	MIC 90	Range
Erythromycin	26	0.2	0.2	0.05–0.4
Clindamycin	26	0.2	3.1	0.2–12.5
Chloramphenicol	27	0.8	6.2	0.8–12.5
Sulfamethizole	27	100	100	100
Nitrofurantoin	25	0.8	1.6	0.2–3.1
Metronidazole	25	1.6	6.2	0.4–6.2
Gentamycin	27	0.2	0.4	0.1–1.6
Nalidixic acid	27	100	100	25–100
Carbenicillin	26	0.2	0.8	0.25–1.6
Doxycycline	27	0.8	3.1	0.2–6.2
Cephradine	25	1.6	3.1	0.2–6.2
Ciprofloxacin	26	0.2	0.4	0.1–0.8
Ampicillin	27	0.05	0.2	0.12–0.4
Cephalothin	26	0.4	1.6	0.1–1.6
Benzylpenicillin	25	0.025	0.1	0.12–0.4
Bismuth subsalicylate	27	12.5	25	12.5–25
Sucralfate	27	1600	3200	1600–>3200
Cimetidine	27	800	3200	400–3200

* From Andreasen and Andersen (70).

TABLE 2
*Antibacterial Action of Bismuth in Relation to H. pylori Colonization Inhibition of 12 Isolates by CBS, BSS, Cimetidine, and Ranitidine**

	No. of Isolates Inhibited by Drug Concentration (mg/L)					
	6.5	12	25	200	400	400
Colloidal bismuth subcitrate (CBS)	4	8	0	0	0	0
Bismuth subsalicylate	1	9	0	0	0	0
Cimetidine tablets	0	0	0	0	4	8
Cimetidine liquid	0	0	0	0	4	8
Ranitidine liquid	0	0	0	0	0	12

* Adapted from Marshall *et al.* (36) and Bayerdorffer and Ottenjam (73).

for 21 days. At the end of therapy, clearance of *H. pylori* was achieved in 78% (14/18) of patients taking BSS, in 7% (1/15) taking erythromycin, and in 0% (0/17) patients taking placebo. There was histological improvement of the gastritis in 81% (13/16) patients taking BSS, 23% (3/13) in patients on erythromycin, and in none of the placebo-treated patients. All differences between BSS and both erythromycin and placebo were highly significant. Symptomatically, 92% of the patients on BSS improved, but 66% on placebo also showed improvement, making the difference statistically nonsignificant.

Follow-up studies on some of these patients revealed that, at 4 wk, virtually all of the patients who had been initially cleared of *H. pylori* showed biopsy evidence of persistence of the organism and a return of the histology to baseline levels (66). Twelve to 18 months after treat-

TABLE 3
*Eradication Rate of H. pylori with Bismuth and/or Antibiotics**

Agents	Eradication (Rate %)	References
Bismuth subcitrate (CBS)	30–40	55, 56, 57
Bismuth subsalicylate (BSS)	<10	66
Amoxicillin	20	55
Erythromycin	20	63
Nitroimidazoles	0	70
Quinolones	0–20	71
CBS + amoxicillin	30–40	70
CBS + erythromycin	40–60	70
CBS + tinidazole	75	56
CBS + tetracycline + metronidazole	70–90	72
BSS + amoxicillin	40	69
BSS + erythromycin	30	69
BSS + tetracycline + metronidazole	90	73

Note: Data are from studies in which patients were reassessed no sooner than 14 days after completion of therapy.
* From Marshall (76).

ment, McNulty performed a follow-up examination on 10 of the 15 patients cleared of *H. pylori* (67). Eight patients had evidence of *H. pylori* infection; six of these patients also had histologically proven gastritis. Only two patients were still clear of *H. pylori*; neither had histologically confirmed gastritis.

When recrudescence of colonization with *H. pylori* occurs, the original *H. pylori* strain has been shown to be responsible for the recurrence. This has been demonstrated by restrictive endonuclease DNA analysis (68). The site and mechanism of the dormancy of the organism remain undetermined.

Eberhardt and Kasper (69) performed a controlled, open clinical trial to compare the effect of oral BSS (600 mg three times daily) with cimetidine (800 mg/day) on *H. pylori*, ulcer healing, and rate of ulcer relapse in 49 patients with peptic ulcer. The presence of *H. pylori* was determined by gastric antrum biopsies and culture at baseline and after 4 wk of treatment. The rate of ulcer relapse was determined by a 9-month follow-up examination. There was 4-wk ulcer healing in 73% of the BSS-treated group and 65% in the cimetidine-treated group. The number of *H. pylori*-positive patients pretreatment was identical in both groups (61%). After 4 wk of treatment, 75% of the previously culture-positive cases in the bismuth-treated group reverted to negative (a statistically significant change), whereas only 40% of the cimetidine-treated group reverted (not statistically significant). The rate of clearance of *H. pylori* was statistically significant for the 29 patients with healed ulcers and correlated strongly with the ulcer healing in the bismuth group only. The rate of relapse after 9 months of follow-up was 13% in the BSS-treated group, a figure significantly lower than the 54% rate of relapse seen in the group treated with cimetidine.

In a prospective, double-blind trial, Marshall *et al.* (58) studied 100 consecutive patients with duodenal ulcer and *H. pylori* colonization of the antrum to see whether eradication of the organism affected ulcer healing and relapse rate. Patients were randomly assigned to four groups and treated for 8 wk with cimetidine or CBS with tinidazole or placebo given concurrently from day 1 to day 10, inclusively. Endoscopy, biopsy, and culture were done at entry, in weeks 10, 22, 34, and 62 and whenever symptoms recurred. There was no maintenance regimen. *H. pylori* (HP) persisted in all of the cimetidine-treated patients (22/22) and in 96% (28/29) of those treated with cimetidine/tinidazole, but was eradicated in 27% (6/22) of the CBS/placebo group and in 74% (20/27) of the CBS/tinidazole group.

There were 70 patients with healed ulcers at the 10-wk endoscopy, 35 of whom had received cimetidine. The relapse rate for all cimetidine-treated patients was 86% in 12 months. In the CBS/placebo group 53% (8/15) relapsed. In those who were still HP positive, relapse occurred in 87% (7/8), whereas only 17% (1/6) of HP negative cases relapsed. Of 20 patients whose ulcers healed with CBS/tinidazole, only 25% (5) went into relapse. The observed differences in relapses between the four groups could be accounted for by *H. pylori*. The results of this study are depicted in Figures 2 and 3.

It appears, therefore, that the relapse rate of duodenal ulcer strongly correlates with the persistence of *H. pylori*. Conversely, permanent eradication of the organism might be expected to cure the disease (56).

In an attempt to accomplish this objective, many investigators, including Marshall *et al.* (58), have utilized antibiotics with and without bismuth in the treatment of upper gastrointestinal disorders associated with *H. pylori* colonization. MIC values for *H. pylori* for antibiotics and some antiulcer agents are shown in Table 1 (70), and Table 2 tabulates comparative antibacterial action of CBS, BSS, cimetidine, and ranitidine (36).

Marshall *et al.* (71) treated consecutive patients with peptic ulcer disease (30%) or non-ulcer dyspepsia (70%) who were positive for *H. pylori* colonization with 14–21 days of BSS, 520 mg qid. In addition, amoxicillin, 500 mg qid was administered to 25 of the patients, erythromycin 250 mg qid to 20 patients, and metronidazole to 19 patients during the 2nd and 3rd wk of therapy. Patients were reinvestigated 4 wk following completion of therapy. The *H. pylori* eradication rates for the three combinations were 28%, 25%, and 79%, respectively. When the initial isolate was sensitive to metronidazole *in vitro*, the eradication rate was 86%. There was no evidence of reinfection in seven patients who were followed for 4–28 wk (mean 14 wk) after eradication. Improvement in histology was noted in

those in whom there was eradication of *H. pylori*. The results were similar to those obtained by Goodwin *et al.* (72) using a combination of CBS and tinidazole. Rauws *et al.* (57) reported similar results with a 4-wk course of therapy with De-Nol and amoxycillin. Bayerdorffer has extensively reviewed the subject of bismuth and antibiotic combination therapy (73).

Recently, Borody *et al.* (74) reported a 94% "cure" rate, confirmed at 1-yr follow-up, using the combination of CBS, tetracycline, or amoxycillin, and metronidazole. Graham *et al.* (75) have had similar success using ranitidine 300 mg hs in combination with BSS as the bismuth salt, tetracycline 2 g, and metronidazole 750 mg for the first 2 wk of therapy. Table 3 lists eradication rates for *H. pylori* with bismuth and/or antibiotics (76).

Therapy with combined antibiotics is not without side effects; up to 30% develop diarrhea and an occasional case of *C. difficile* colitis has been reported (73).

CONCLUSION

Studies have demonstrated a significant role for bismuth in the treatment of both lower and upper gastrointestinal disorders. Both experimental and clinical data support the beneficial effects of bismuth subsalicylate in the treatment of a variety of diarrheal diseases, most prominently, traveler's diarrhea.

The antibacterial action of bismuth, both in the form of colloidal bismuth subcitrate (CBS) and bismuth subsalicylate (BSS), against *H. pylori*, also makes it a valuable adjunct to the therapy of peptic ulcer disease and gastritis. There is convincing evidence that unless *H. pylori* is eradicated from the gastric mucosa, there is a high incidence of ulcer recurrence and no essential change in the relapsing natural course of the disease. The addition of antibiotics to the therapeutic regimen adds to its effectiveness.

At the moment, it seems likely that the use of antibacterial therapy will be primarily for those patients with relapsing ulcer disease or symptomatic gastritis. Only further controlled studies carried out for prolonged periods of time will provide the necessary data to define the safest and most effective therapy that will provide a permanent cure for *H. pylori*-associated upper gastrointestinal disease.

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