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Prevention of Traveler's Diarrhea by the Tablet Form of Bismuth Subsalicylate

ROBERT STEFFEN,[1]* HERBERT L. DuPONT,[2] ROLF HEUSSER,[1] ANDRÉE HELMINGER,[1] FELIX WITASSEK,[3] MICHAEL D. MANHART,[4] AND MEINRAD SCHÄR[1]

Institute of Social and Preventive Medicine, University of Zürich, CH-8006 Zurich,[1] and Institute for Parisitology, University of Zürich, CH-8057 Zurich,[3] Switzerland; University of Texas Health Science Center at Houston, The Medical School, Houston, Texas 77225[2]; and The Procter and Gamble Co., Cincinnati, Ohio 45241[4]

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In a randomized double-blind study, Swiss adults traveling to tropical countries for 12 to 28 days took a solid formulation of bismuth subsalicylate (1.05 or 2.1 g/day on a twice-daily regimen) or placebo. Efficacy was evaluated in 231 volunteers. Diarrheal incidence was reduced by 41% in persons taking the high dose (P = 0.007) and by 35% in those taking the low dose (P = 0.03) with excellent compliance. No serious adverse reactions occurred, but objectionable taste, constipation, and nausea were seen more frequently with active medication (P = 0.04). Twenty patients provided stool samples: no bacteria were detected in the 8 volunteers who were on active medication, but various bacteria were found in 5 of the 12 patients who had taken placebo (P = 0.04).

Traveler's diarrhea is the most frequent health problem of persons residing in industrialized nations when they visit Third World or tropical countries (12). Among the many chemotherapeutic agents used, bismuth subsalicylate (BSS) has been shown to be an effective agent for prophylaxis (3, 6) and treatment of traveler's diarrhea. So far, field studies have been performed with the liquid formulation (2, 3), which contains a vehicle that contributes to the inactivation of toxins (5). The minimal effective dosage has been repeatedly questioned (2, 6).

To test the efficacy of various dosages of the tablet form of BSS and to determine the minimal effective dosage for prophylaxis of traveler's diarrhea in tourists, we conducted a randomized, double-blind study.

MATERIALS AND METHODS

Upon approval by institutional review boards in Switzerland and at the University of Texas, 390 travelers 16 to 70 years of age were recruited between February and June 1984 at the Zurich University Vaccination Center before departure to a developing country for a stay of 12 to 28 days. Pregnant or nursing women and persons who were polyallergic or specifically allergic to salicylates were not included in the study. Ingestion of other medication during the period, except malaria prophylaxis or contraceptive drugs, caused exclusion from participation in the study.

Three treatment regimens were tested: two 525-mg BSS tablets taken twice daily and half that dosage, that is, two 262.5-mg tablets taken twice daily. A placebo was also used. Medications were taken from the day before departure continuously until day 2 after return home. Test medication was discontinued if diarrhea occurred. Trial drugs were prepared, randomized by computer, and labeled with serial numbers by the Procter and Gamble Co., Cincinnati, Ohio. Tablets were identical in size, color, and odor, and they were given a cherry flavor not found in the commercial product so that they tasted the same.

After giving consent, the travelers were allocated the test medication with consecutive trial numbers. Detailed verbal and written instructions were given about procedures and safety measures relevant to the trial medication, as well as the way to treat diarrhea should it occur. The volunteers were asked to complete a diary-type questionnaire indicating tablet consumption, stool frequency and consistency, possible illness, adverse reactions, and characteristics of the journey. After returning home, the participants sent the questionnaire and any remaining tablets to the Zurich University Vaccination Center.

Additionally, the volunteers were invited to take vials (Cary Blair and buffered glycerol saline [Remel, Lenexa, Kans.], to be analyzed in Houston; MIF [merthiolate iodine formaline; Institute for Parasitology, University of Zurich], to be analyzed in Zurich) to collect stool samples in case of diarrhea for the determination of etiology (10). Eleven persons were invited to come to the Zurich vaccination center within 5 days after their return for determination of bismuth levels in serum. Bismuth concentrations in whole blood or serum were determined at Procter and Gamble by a modification of the hydride generation-atomic absorption spectroscopy method, which has a limit of sensitivity of less than 1 ppb (μg/liter) (1, 11). For this study, samples of less than 5 ppb were considered equivalent.

Diarrhea was defined as three or more unformed stools or any number of such bowel movements per day when accompanied by fever, abdominal cramps, or vomiting. Excluded from efficacy evaluation were people who had taken the tablets for fewer than 4 days due to adverse reactions. All subjects for whom the actual and calculated pill count differed by 21 or more, indicating that more than 10 doses were missed, were defined as noncompliant and evaluated only for side effects. All persons missing 7 to 20 tablets were rated as being in fair compliance. Those missing no more than six tablets (three doses in the entire surveyed period, but none in the 36 h before the onset of diarrhea) were judged as showing excellent compliance.

The allocation to the various treatment groups was revealed only after all questionnaires were evaluated. Statistical tests were performed by the χ^2 method with Yates correction for continuity.

* Corresponding author.

RESULTS

Medication was distributed to 390 subjects, but 52 took no tablets (volunteer later refusing to take coded tablets or forgot medication at home, trip canceled, etc.), and 28 failed to comply with study requirements (e.g., because tablets were lost or stolen en route). A total of 310 subjects were evaluated for side effects. An additional 79 persons had to be excluded from efficacy evaluation for being noncompliant or because of adverse reactions before day 4, leaving 231 subjects for evaluation.

In the total evaluable population (112 in the high-dose active group, 98 in the low-dose group, 100 in the placebo group), 54% were men, the mean age was 36.5 years, and the mean duration of stay abroad was 17.8 days; 26% visited Kenya, 23% visited West Africa, 13% visited other parts of Africa, 23% visited Asia east of India, and 15% visited South America. In the three treatment groups, there were no significant differences with respect to sex, age distribution, duration of stay abroad, destination, purpose and type of the journey, previous stays in the tropics or in the same region, places of food consumption, or the type of malaria prophylaxis used. The volunteers took placebo for a mean of 15.5 days or low- and high-dose medication for a mean of 16.1 days.

The occurrence of diarrhea is presented by treatment group in Table 1. The incidence of diarrhea in the high- and low-dose groups was significantly reduced compared with the placebo group, both in the subgroup with excellent compliance and in the total group. The three treatment groups with diarrhea did not significantly differ in the rate of concomitant symptoms (fever, abdominal cramps, or blood or mucus admixed with stools), except for vomiting, which was highest in the low-dose group ($P = 0.03$). In the 58 volunteers with fair compliance, the proportion with diarrhea was 57% in the high-dose group, 47% in the low-dose group, and 60% in the placebo group.

Overall side effects were reported more frequently in the high-dose ($n = 34$, 30%) and low-dose ($n = 28$, 28%) groups than in the placebo ($n = 13$, 13%; $P = 0.04$) group. Objectionable taste, constipation, and nausea were noted in both treatment groups more frequently than in the placebo group. Additionally, one male traveler reported new onset of grand mal seizures. Another participant was airlifted home from the Philippines for presumed pancreatitis. Both individuals had been receiving low-dose medication. Follow-up examination provided evidence that both illnesses were preexistent. The former patient had a history of petit mal staring spells; the latter was hospitalized in 1982 in Switzerland with the same diagnosis. One person on placebo complained of anxiety-like symptoms. Blood bismuth levels in 10 of 11 (5 high-dose, 4 low-dose, 2 placebo [all but one on excellent compliance for over 14 days]) volunteers were <5 ppb; in the one person with seizures, the level was 10 ppb.

TABLE 1. Prophylactic efficacy of BSS (twice a day)

Compliance group and daily dose (g)	Participants (*n*)	No. of participants with traveler's diarrhea and incidence (%)	Significance
Fair and excellent (±20 tablets)			
2.1	88	38 (43.2)	$P = 0.014$
1.05	71	31 (43.7)	$P = 0.024$
Placebo	72	46 (63.9)	
Excellent only (±6 tablets)			
2.1	67	26 (38.8)	$P = 0.007$
1.05	54	23 (42.6)	$P = 0.031$
Placebo	52	34 (65.4)	

TABLE 2. Microbiological results in the three groups[a]

Serial no.	Group	Bacteria detected[b]	Parasites detected
28	Placebo	*Shigella dysenteriae* 4	
104	Placebo		*Entamoeba histolytica*, *Entamoeba hartmanni*
106	Placebo		
132	Placebo	ETEC, ST+	
134	Placebo	ETEC, LT+	
169	Placebo	ETEC, ST+, LT+	
187	Placebo		
215	Placebo		
242	Placebo	ETEC, ST+	
287	Placebo		
335	Placebo		
387	Placebo	*Salmonella enteritidis* (C2), ETEC, ST+, LT+	
262	Low dose		
364	Low dose		
24	High dose		*Entamoeba histolytica*[c]
34	High dose		*Endolimax nana*
35	High dose		*Entamoeba histolytica*, *Entamoeba hartmanni*, *Endolimax nana*[c]
135	High dose		
186	High dose		
193	High dose		

[a] No *Campylobacter*, *Cryptosporidium*, or *Yersinia* organisms were found.
[b] ST, Heat stable; LT, heat labile.
[c] Volunteer forgot to take some tablets in the 36 h before the onset of diarrhea.

Compliance was inequally distributed (Table 1). This was due to the fact that only 18 high-dose volunteers did not start the trial, compared with 32 in the low-dose and 30 in the placebo group ($P = 0.07$). Additionally, 22, 29, and 28 volunteers in the three above-mentioned groups had to be excluded from efficacy evaluation ($P = 0.6$).

Only 20 of 115 travelers who had experienced diarrhea sent in stool samples for evaluation. Analysis in Houston took place 8 to 52 days after the diarrheal episode. Leukocytes were detected in eight of the patients, equally distributed in all treatment groups. The microbiological results are given in Table 2. Bacteria were found only in the placebo group ($P = 0.04$, Fisher's two-tailed exact test).

DISCUSSION

In a previous study, BSS reduced the occurrence of traveler's diarrhea by 62% when 4.2 g of the liquid formulation was ingested daily by U.S. students in Mexico (3). The protection rate was 77% after adult volunteers were given a large dose of a single strain of enterotoxigenic *Escherichia coli* (ETEC) and 2.4 g of a solid preparation per day (6). In both of the previous studies, the test drug was given four times a day. In the present study, the percent protection rate was lower. On a twice-daily regimen with a daily dosage of 2.1 g, the rate of protection was 41% in the subgroup with excellent compliance and 32% in the group as a whole, which included those with fair compliance. The respective values were 35 and 32% in the low-dose-group volunteers who took

1.05 g/day. The high rate of diarrhea in the placebo groups in comparison with those reported in epidemiological studies (12) may be explained by the fact that persons prone to suffer from diarrhea enrolled more frequently in the trial. Similar to results from former studies (3, 6), microbiological assessment revealed significantly less bacteria in the active-drug groups (0/8), compared with the placebo group (5/12). There are limitations on interpreting this, as only a minority of the patients collected a stool sample, partly because they did not have vials at hand when diarrhea occurred outside their hotels.

One gram of BSS taken in two doses appears to be the minimum efficacious dosage. Doubling this dosage showed an only marginally diminished incidence of diarrhea, and the comparison of results of earlier studies with ours suggests that frequency of dosing plays an important role in efficacy. The lack of differences in diarrheal incidence in the subgroup with fair compliance suggests that irregular medication was not protective.

The active ingredient, BSS, was quite well tolerated by the study population. The most frequent complaint in all groups was the cherry flavor not found in the commercial product. This complaint, as well as constipation and nausea, was slightly more frequent in the active groups compared with the placebo group. We considered the increased incidence of vomiting in the low-dose group as due to chance, because it was not seen in the high-dose group. There were no serious adverse reactions attributable to BSS in this trial.

Bismuth toxicity nonetheless is a potential problem if an excessive dosage is used. More than 1,000 cases of bismuth-related encephalopathies have been reported in Europe and Australia. Almost all cases were linked to ingestion of bismuth subnitrate or bismuth subgallate taken in high doses over a prolonged time. The only case of encephalopathy linked to BSS occurred after unknown amounts of a noncommerical preparation were consumed by a patient with numerous gastrointestinal ailments (7).

In none of the published cases of encephalopathy were the bismuth levels in blood less than 100 ppb. It has been concluded that values above this are toxic and that a concentration below 50 ppb should not be associated with toxicity (8). The nine participants tested who were on active medication showed values up to 10 ppb, which is similar to the findings in six subjects of an earlier trial with liquid BSS in which bismuth levels in serum were below what was at the time the state-of-the-art detection limit of 50 ppb (4).

To our knowledge, no cases of encephalopathy, gastrointestinal bleeding, or Reyes syndrome have been attributable to the use of the commercial BSS product Pepto-Bismol in North America, despite its widespread use since 1904. Thus, the agent appears to be safe. However, to prevent serum levels of bismuth from reaching the margins of safe values (8), we recommend not administering the commercial medication prophylactically for over 3 weeks at a dosage of 1.575 g of BSS per day (see below). The calcium carbonate ingested in this regimen would be 2.1 g/day and therefore below that associated with the production of hypercalcemia and the milk-alkali syndrome (9). The U.S. Food and Drug Administration has set a safe limit of 8 g of calcium carbonate in its review of over-the-counter antacid ingredients that may be consumed daily. The amount of absorbed salicylates would correspond to approximately six aspirin per day.

Considering the safety of BSS, we believe that this agent may continue to play a role in travel medicine. An effectiveness of 40%, however, is not sufficient. In view of the fact that a protection rate exceeding 60% (3, 6) was achieved when medication was distributed in four instead of two daily doses, we suggest that two tablets containing 262.5 mg of BSS each (i.e., Pepto-Bismol), taken by adults three times per day with meals, would offer satisfactory protection, while still being acceptable to tourists. This remains to be evaluated in subsequent studies.

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