Nonantimicrobial Agents in the Prevention and Treatment of Traveler’s Diarrhea

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Among the nonantimicrobial agents that are available and useful for the prevention of traveler’s diarrhea are bismuth subsalicylate–containing preparations, which can provide a rate of protection of up to 65% when taken 4 times daily. In one study, the probiotic *Lactobacillus GG* was found to provide 49% protection against traveler’s diarrhea, but results with this agent and other probiotics have been highly variable and geographically inconsistent. Tannin albuminate plus ethacridine lactate provided 36% protection, but it is not widely available.

Among the nonantimicrobial agents that are available and useful for the treatment of traveler’s diarrhea are bismuth subsalicylate–containing preparations, which reduce the passage of loose stools by 16%–18%. The antisecretory and antimotility agent loperamide reduces the passage of loose stools by ∼50% and has been especially useful, in combination with antimicrobial agents, in reducing the total duration of posttreatment diarrhea to a matter of hours.

The management of traveler’s diarrhea includes the use of agents that treat symptoms of diarrhea without directly killing the microorganisms that cause the syndrome [1–3]. These agents can be organized by their mechanisms of action (tables 1 and 2). One agent, bismuth subsalicylate (BSS), is unique in that it has multiple modes of action, including antimicrobial activity. This review will concentrate specifically on the data that have been generated in studies of populations of travelers and will briefly review agents that have not been studied in travelers but that might be effective against traveler’s diarrhea, owing to their mode of activity.

**PREVENTION OF TRAVELER’S DIARRHEA**

Chemoprophylaxis of traveler’s diarrhea is potentially appealing, because exposure to diarrhea-causing organisms is common in developing countries, and because travelers find it difficult to adjust their eating and drinking habits to avoid exposure to the organisms. Nevertheless, a consensus development conference in 1985 concluded that chemoprophylaxis with antimicrobial agents, including BSS, could not be recommended because of the potential for adverse reactions, compared with the self-limiting nature of the syndrome [4]. In practice, many practitioners do recommend chemoprophylaxis for high-risk travelers after discussion of the relative risks and benefits.

Various nonantimicrobial agents (table 1) have been studied with regard to the prevention of traveler’s diarrhea [5]. On the basis of studies with negative findings, many agents cannot be recommended, including antimotility agents, certain adsorbents (e.g., polycarbophil and activated charcoal), and halogenated hydroxyquinoline [5]. Although they have not been studied with regard to the prevention of traveler’s diarrhea, calmodulin inhibitors (e.g., zaldaride), enkephalinase inhibitors (e.g., racecadotril), antisecretory agents (e.g., SP-303; Provir; Shaman Pharmaceuticals), and anticholinergics have no logical role in chemoprophylaxis of traveler’s diarrhea.

BSS, the active ingredient in the over-the-counter product Pepto-Bismol (Procter and Gamble), is the most active of the chemoprophylactic agents in the “nonantimicrobial” category, but it is probably active as a preventive agent because of its antimicrobial ac-
Adsorbents and probiotics, which have enjoyed modest success in clinical trials, were not addressed by the 1985 consensus development conference [5]. The absorbent tannin albuminate plus ethacridine lactate has been championed in the German literature. In a randomized placebo-controlled trial involving Western tourists on a 16-day cruise in Egypt, 81% of 43 subjects receiving placebo developed diarrhea, compared with 53% of 34 subjects receiving verum. This was a modest 36% protection against diarrhea [14].

A number of probiotics have been popular, particularly in Europe [15, 16]. Conceptually, an avirulent organism is intentionally introduced into gut flora in the hope that it might successfully compete somehow with the later introduction of pathogenic flora and prevent disease. In the case of Lactobacillus GG, the organism not only has a propensity to adhere to the intestinal lining, but it also produces an antibacterial substance [17].

Enterococcus faecium did not prevent traveler’s diarrhea [18]. Saccharomyces boulardii was studied in 3000 Austrian travelers in a placebo-controlled trial [19]. A statistically significant, but clinically modest, benefit was noted in a dose-dependent fashion. That trial did not explain the regional differences in efficacy, with the highest benefit seen in North Africa and Turkey. S. boulardii was considered to be safe to use. Given the unpredictable efficacy of and geographic results for the probiotics that have been studied, other probiotics (e.g., Saccharomyces cerevisiae) should not be assumed to be efficacious without further study.

In a placebo-controlled trial, Lactobacillus GG was studied in 245 US adults traveling to a wide range of developing countries [20]. Travelers were given diary cards to complete during their trips, but the authors indicate that they also contacted subjects after they returned to ascertain whether diarrhea occurred and to record details of disease and treatment; thus, it appears that some recall bias may have been introduced into the design. Because the travelers’ journeys lasted for 1–3 weeks, the authors compared the average incidence of diarrhea per the number of days at risk. The placebo group experienced a 7.4% incidence of diarrhea per day at risk, compared with 3.9% for the Lactobacillus GG group. This calculates to a protection rate of 47% (i.e., [74 – 3.9]/74). No other study has reported data in this way, which obviates comparison with rates of diarrhea in other studies.

**Table 1. Agents for the prevention of traveler’s diarrhea, by mode of action.**

<table>
<thead>
<tr>
<th>Mechanism, agent</th>
<th>Effective in preventing traveler’s diarrhea?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimotility</td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>No</td>
</tr>
<tr>
<td>Difenoxin/diphenoxylate plus atropine</td>
<td>No</td>
</tr>
<tr>
<td>Tincture opium</td>
<td>No</td>
</tr>
<tr>
<td>Adsorbence</td>
<td></td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>No</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>No</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>62%–65% protection</td>
</tr>
<tr>
<td>Tannin albuminate plus ethacridine lactate</td>
<td>36% protection</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>62%–65% protection</td>
</tr>
<tr>
<td>Halogenated hydroxyquinoline</td>
<td>No</td>
</tr>
<tr>
<td>Probiotic</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus GG</td>
<td>11.8%–47% protection</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>No</td>
</tr>
<tr>
<td>Saccharomyces boulardii</td>
<td>Clinically modest but statistically significant protection, with marked regional differences</td>
</tr>
</tbody>
</table>

**References**

[1] Loperamide is absorbed in very low and clinically insignificant quantities from BSS. The insoluble bismuth salts, however, are black. A discolored tongue can be a nuisance, but black stools can be confused with melena. Unlike bismuth gallate or citrate, from which enough bismuth can be absorbed to cause encephalopathy, BSS can be taken for 2–3-week periods with resultant bismuth serum levels that remain well below the threshold associated with CNS symptoms. Finally, the vehicle of liquid Pepto-Bismol contains bivalent cations (magnesium aluminum silicate) that prevent the absorption of doxycycline [11, 12]. A formulation of BSS without the vehicle did not reduce the bioavailability of tetracycline [12]; however, other drugs were not studied. Persons taking doxycycline for malaria prophylaxis should avoid taking liquid Pepto-Bismol for the prevention of diarrhea. Because many travelers imbibe ethanol when they might be taking BSS for prophylaxis, it is reassuring that a recent study suggests that BSS is protective against chemically induced mucosal injury by scavenging reactive oxygen species implicated in the genesis of such injury [15].

Adsorbents and probiotics, which have enjoyed modest success in clinical trials, were not addressed by the 1985 consensus development conference [5]. The absorbent tannin albuminate plus ethacridine lactate has been championed in the German literature. In a randomized placebo-controlled trial involving Western tourists on a 16-day cruise in Egypt, 81% of 43 subjects receiving placebo developed diarrhea, compared with 53% of 34 subjects receiving verum. This was a modest 36% protection against diarrhea [14].

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Table 2. Agents for the treatment of traveler's diarrhea, by mode of action.

<table>
<thead>
<tr>
<th>Mechanism, agent</th>
<th>Effective in treating traveler's diarrhea?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimotility</strong></td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>Yes</td>
</tr>
<tr>
<td>Difenoxin/diphenoxylate plus atropine</td>
<td>Yes, but diphenoxylate was not studied in travelers</td>
</tr>
<tr>
<td>Tincture opium</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td><strong>Antisecretory</strong></td>
<td></td>
</tr>
<tr>
<td>Loperamide</td>
<td>Yes</td>
</tr>
<tr>
<td>SP-303 (i.e., Provir)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>Yes</td>
</tr>
<tr>
<td>Calmodulin inhibitor, zaldaride</td>
<td>Yes</td>
</tr>
<tr>
<td>Anticholinergic, mepenzolate bromide</td>
<td>No</td>
</tr>
<tr>
<td><strong>Adsorbent</strong></td>
<td></td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>No</td>
</tr>
<tr>
<td>Polycarbophil</td>
<td>No</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>Yes</td>
</tr>
<tr>
<td>Tannin albuminate plus ethacridine lactate</td>
<td>Yes</td>
</tr>
<tr>
<td>Kaolin/pectin</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td>Hydrated magnesium aluminum silicate (i.e., attapulgite)</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td>Dioctahedral smectite and other claylike compounds</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>Yes</td>
</tr>
<tr>
<td>Probiotic</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td>Enkephalinase inhibitor, racecadotril</td>
<td>Effective against diarrhea but not studied in travelers</td>
</tr>
<tr>
<td>Antimicrobial, bismuth subsalicylate</td>
<td>Yes</td>
</tr>
</tbody>
</table>

In an earlier placebo-controlled study [21] conducted among 756 Finnish travelers to 2 different destinations in Turkey, the incidence of diarrhea among placebo-treated subjects was 46.5%. The rate was 41.0% among Lactobacillus GG–treated subjects, yielding a modest rate of protection (11.8%). However, the rate of protection was 39.5% at one location and practically nil at the other. In both trials, Lactobacillus GG was considered to be safe to use.

It appears that some probiotics, particularly Lactobacillus GG, may have some benefit in preventing traveler’s diarrhea safely. Geographic differences in benefit remain unexplained; unless comparative studies indicate equivalence of efficacy, one probiotic should not be substituted for another. Although the modest benefits of Lactobacillus GG are intriguing, more work needs to be done before this approach can be recommended for prophylaxis of traveler’s diarrhea [22].

**TREATMENT OF TRAVELER’S DIARRHEA**

Several drugs have proven to be of no benefit in the treatment of traveler’s diarrhea, as outlined in table 2. Use of the anticholinergic agent mepenzolate bromide was studied in 70 US students in Mexico in a placebo-controlled trial [23]. The rates of recovery from diarrhea were similar for subjects receiving the drug (24%) and those receiving placebo (31%). Importantly, the incidence of anticholinergic-related adverse effects was 51% among subjects in the active drug group, compared with 14% among subjects in the placebo group. The authors concluded that anticholinergic agents could not be recommended for the treatment of traveler’s diarrhea.

As a class, the adsorbents have had mixed results in the treatment of traveler’s diarrhea. Activated charcoal and polycarbophil were not effective (H. L. DuPont and C.D.E., personal communication). Kaolin/pectin preparations, on the other hand, have had some modest and beneficial activity in the treatment of nonspecific diarrhea, but published studies involving travelers are lacking. An unpublished study conducted among travelers >20 years ago showed that kaolin/pectin had a modest effect on the form of stool but did not otherwise affect the clinical course of disease (H. L. DuPont and C.D.E., personal communication). Hydrated magnesium aluminum silicate (attapulgite) was compared with administration of loperamide according to the over-the-counter dose in travelers [24]. Loperamide performed better than attapulgite, with an average duration of diarrhea of 14.2 h in the loperamide group, compared with 19.5 h in the attapulgite group. The exact role of attapulgite could not be ascertained from this study, because a placebo group was not included in the study design, and because enrollment included only subjects with relatively mild illness. Attapulgite was safe, however, and is probably appropriate for the treatment of mild illness. In one study of 186 German travelers in Turkey, tannin albuminate plus ethacridine lactate was found to be better in...
alleviating symptoms of traveler’s diarrhea than was activated charcoal [25]. The available English abstract indicated only that stool frequencies returned to normal significantly earlier and that complaints of moderate-to-severe abdominal pain were recorded less frequently (50% vs. 82%) in the tannin albuminate plus ethacridine lactate–treated group. According to the available data, some adsorbents may have a modest benefit in the treatment of traveler’s diarrhea, and they are safe; however, more-efficacious alternatives exist.

Probiotics have enjoyed some success in the treatment of a number of enteric syndromes, but they have not been studied in the treatment of traveler’s diarrhea. They are also not widely available and cannot be recommended [16].

Several agents have been found to be effective in the treatment of diarrhea but either were not studied in travelers or were studied in traveler’s diarrhea but have not become widely marketed. The enkephalinase inhibitor racecadotril was found to be effective in the treatment of diarrhea in 945 adults from 14 developing countries [26]. Racecadotril compared favorably with loperamide, with the duration of treated diarrhea (55 h) equivalent in both groups. Racecadotril appeared to relieve abdominal pain and distension better and faster than loperamide. However, loperamide was given as a scheduled dose (2 mg 3 times daily) rather than as the recommended 4-mg loading dose followed by 2 mg after each loose stool. Furthermore, racecadotril failed to treat severe cholera any better than placebo [27], and a review of the comparative activities of racecadotril and loperamide suggests that further research on racecadotril is necessary before its role in diarrhea treatment can be determined [28]. In view of this assessment in the literature and the fact that racecadotril has not been studied in travelers, the drug cannot be recommended for the treatment of traveler’s diarrhea at this time.

SP-303, the active ingredient of which appears to be an oligomeric proanthocyanidin extracted from the bark latex of the Croton tree, is a potent inhibitor of chloride secretion that acts at the level of the cystic fibrosis transmembrane conductance regulator Cl-channel in human colonic T84 cells [29]. Provir was studied in 184 US adults in Mexico or Jamaica and was found to be effective in the treatment of traveler’s diarrhea, providing a 21% reduction in the duration of diarrhea [30]. In the placebo group, the average duration of posttreatment diarrhea was only 38.7 h. A limitation of the usefulness of this herbal extract is that it does not have approval from the US Food and Drug Administration as a drug and is now marketed on the Internet as a botanical food supplement (Normal Stool Formula; Shaman Pharmaceuticals).

The calmodulin inhibitor, zaldaride, was compared with loperamide in 2 studies of travelers [31, 32]. In the first placebo-controlled study [31], 179 US adults in Mexico received zaldaride (20 mg 4 times daily), loperamide (a loading dose of 4 mg, followed by 2 mg after each loose stool), or placebo. In the zaldaride group, the number of unformed stools passed during the first 48 h after treatment was reduced by 30%, and the duration of diarrhea was reduced by 23%, compared with that noted for the placebo group. Although loperamide appeared to be more efficacious than zaldaride during the first 48 h of observation, thereafter, the drugs appeared to be equivalent, implying that the 2 drugs might have been entirely equivalent if zaldaride had been given with a loading dose. When a 40-mg loading dose of zaldaride was given in a subsequent placebo-controlled study of 436 European travelers who developed acute diarrhea during Nile cruises, zaldaride and loperamide were equivalent in their benefits [32]. The problem is simply that the drug has not yet been marketed.

**BSS**

In a number of trials [33–37], compounds containing BSS have shown to be beneficial in the treatment of traveler’s diarrhea. Classifying the mode of action of BSS is difficult, because BSS has antimicrobial, antisecretory, and adsorbent properties [6, 38]. In a sentinel study [34], 169 students in Mexico received either BSS or placebo every half hour for 4 h. The reported study had a complex design and was really 2 different studies. Student groups included US adults who had recently arrived in Mexico (i.e., “summer students”), full-time US adult students who had resided in Mexico for an unspecified period, and Latin American students. In one study, 111 students with passage of ≥3 unformed stools during the preceding 24 h were randomized to receive 30 mL of BSS every half hour, for a total of 8 doses (4.2 g of BSS). In the other study, students with passage of ≥5 unformed stools during the preceding 24 h received 60 mL of BSS every half hour, for a total of 8 doses (8.4 g of BSS). In the lower-dose study, US students treated with BSS (n = 27), compared with students treated with placebo (n = 16), passed, on average, fewer unformed stools during the 4–24-h period (2.3 vs. 4.4 stools) and the 24–48-h period (2.1 vs 4.8 stools). However, only statistics calculated for the 4–48-h period reached significance (P < .025). Full-time US students realized no benefit from BSS treatment. Although Latin American students appeared to benefit statistically from BSS treatment, their numbers were small (only 6 were treated with active drug), and the data were heavily influenced by this group passing only 1 unformed stool during the entire 48 h of the study. In the higher-dose study, US students treated with BSS (n = 19), compared with students treated with placebo (n = 17), passed, on average, fewer unformed stools during the 4–24-h period (1.3 vs. 2.6 stools) and the 24–48-h period (0.4 vs 1.7 stools). Significant differences were seen for the 0–48-, 4–24-, and 4–48-h periods. Significant differences were not seen
among the 17 full-time or 5 Latin American students, but the numbers were very small. The benefit appeared to accrue, especially for subjects with diarrhea caused by enterotoxigenic Escherichia coli. Shigella species infection was not prolonged by use of BSS. With regard to the total number of unformed stools passed during the 48-h study by the 43 recently arrived US students who were treated with what is now the usually recommended dose (8 oz or 4.2 g of BSS over 4 h), only a 4% reduction in the passage of unformed stools was observed (i.e., [172 − 165]/172). A 16% reduction in the passage of unformed stools among recently arrived US students was observed when both dosing regimens were combined.

A study comparing BSS treatment (4.2 g for 4 h) with placebo among 133 European tourists in West Africa and 112 US students in Mexico confirmed a modest and statistically significant benefit of BSS at both sites [37]. Similar to the earlier study in Mexico, reduction in the passage of unformed stools during the 48-h study was 18% and 16% for subjects in West Africa and Mexico, respectively.

The modest benefit of BSS treatment was underscored in a study [39] involving adult US summer or full-time students or Latin American students in Mexico, as well as high school and college students volunteering at 7 sites widely dispersed across Latin America. Ill students (n = 219) were randomly assigned to receive loperamide (4-mg loading dose, followed by 2 mg after each loose stool, not to exceed 16 mg per day) or BSS (30 mL every half hour for 8 doses; 4.2 g of BSS). Significant differences in the passage of unformed stools occurred only in the 156 US summer students and volunteers but not in full-time US or Latin American students. Differences favoring loperamide occurred even during the first 4-h period, while BSS was still being taken (median number of unformed stools, 0.8 vs 1.3). Differences persisted in both the 4–24-h (1.2 vs. 2.4 stools) and the 24–48-h (0.8 vs. 1.1 stools) periods. The total numbers of unformed stools were not reported in that study, but, by use of the medians reported, loperamide provided a further 42% reduction in the passage of unformed stools beyond the benefits of BSS, which, by use of data from the other studies, can be assumed to have provided a 16%–18% reduction if it had been compared with placebo. From these and previous data, one can estimate that loperamide would have provided a reduction of a little more than 50% in the passage of unformed stools, if it had been compared with placebo.

BSS has been available since the turn of the century and has a generally safe track record. Although the drug is not as effective as loperamide, it can be recommended for the treatment of mild-to-moderate traveler’s diarrhea. One limitation is lack of availability in some regions of the world, such as Europe, New Zealand, and Australia.

LOPERAMIDE AND OTHER ANTIMOTILITY AGENTS

An early study published in the German literature suggested that the antimotility agent difenoxin, a drug closely related to diphenoxylate, may have a role in the treatment of traveler’s diarrhea [40]. Another study documented the benefit of difenoxin in persons with acute and chronic diarrhea [40, 41]. Although a number of studies [42–44] supported the use of diphenoxylate (the active ingredient in Lomotil [G. D. Searle]) in the treatment of nonspecific diarrhea, the agent was never studied in travelers, and one review [45] suggested that loperamide provided better relief of diarrhea than did diphenoxylate.

The benefits of loperamide were confirmed in a study of the use of loperamide and trimethoprim-sulfamethoxazole in the treatment of acute traveler’s diarrhea among US students in Mexico. The study design included 46 subjects treated with loperamide alone (4 mg, followed by 2 mg after each loose stool) and 45 subjects treated with placebo. The duration of diarrhea after treatment was 34 h and 59 h in the loperamide and placebo arms, respectively, for a 42% reduction in the duration of diarrhea. This benefit was similar to the benefits of treatment with an antimicrobial agent (trimethoprim-sulfamethoxazole) in the same trial; however, 17% of subjects treated with loperamide alone took an antimicrobial agent because of inadequate response to loperamide alone. In that same study, subjects treated with loperamide plus trimethoprim-sulfamethoxazole had an average duration of diarrhea of only 1 h. The benefits taking loperamide according to the over-the-counter dose were confirmed in a later study in Mexico in which loperamide provided substantially more relief of diarrhea than did over-the-counter Pepto-Bismol [35].

COMBINATION THERAPY WITH LOPERAMIDE AND AN ANTIMICROBIAL AGENT

The study of loperamide plus an antimicrobial agent confirmed an earlier study of BW942C, an enkephalin-like pentapeptide, which had demonstrated modest benefits of combining an agent that relieves symptoms with an antimicrobial agent for a benefit that exceeded that associated with the use of either drug alone. Several subsequent studies of loperamide plus an antimicrobial agent in Mexico confirmed the benefits of dual treatment for traveler’s diarrhea, whether the antimicrobial agent was trimethoprim-sulfamethoxazole or the fluoroquinolone ofloxacin [46–49]. However, in a study of 142 military personnel in Thailand, where the prevalent causes of diarrhea were Campylobacter species (41%) or Salmonella species (18%), the addition of loperamide to ciprofloxacin appeared to provide no additional benefit [50]. Loperamide was determined to be safe in this setting. Another study of 104 US military personnel
in Egypt, where enterotoxigenic *E. coli* was the prevalent pathogen (57%), found differences favoring the addition of loperamide to antimicrobial therapy, particularly among subjects with enterotoxigenic *E. coli* infection [51]. The authors pointed out the modest differences in the average number of stools passed during the 24 h after initiation of therapy: 1.9 stools for subjects receiving loperamide plus ciprofloxacin, versus 2.6 stools for subjects receiving ciprofloxacin alone. A recent study of azithromycin, with or without loperamide (C.D.E., personal communication), sheds light on how adding loperamide to an antimicrobial agent in the treatment of traveler’s diarrhea provides benefits that might not be evident if the average number of stools passed during a 24-h period is analyzed. During the first 24 h after treatment, an average of 1.2 uniformed stools were passed by subjects in the azithromycin plus loperamide arm of the study, compared with 3.3 uniformed stools pass by subjects in the azithromycin-only arm. On the surface, this appears to be only a difference of 2 uniformed stools during a 24-h period. However, the benefit appears to accrue substantially to a subset of subjects. During the same 24-h period, only 1.7% of subjects in the combination treatment arm passed >5 uniformed stools (average, 8.7 stools), compared with 20% of subjects in the antimicrobial agent-only arm (average, 8.0 stools).

Although a study by Murphy et al. [52] did not involve travelers, it did find that 88 Thai adults with dysentery who were hospitalized in Thailand with invasive endemic diarrhea due to infection with *Shigella* species or enteroinvasive *E. coli* benefited when loperamide was added to ciprofloxacin for treatment. The duration of diarrhea was 42 h for subjects treated with ciprofloxacin alone and 19 h for subjects treated with combination therapy. The results of that study underscore the safety of loperamide, even in the treatment of bacillary dysentery; however, the subjects were likely partially immune, so the applicability of the findings to travelers is limited.

The benefit of combination therapy is limited by the activity of the antimicrobial agent against enteric flora. Despite earlier studies showing the benefit of loperamide plus trimethoprim-sulfamethoxazole, this combination can no longer be recommended owing to the high level of resistance to trimethoprim-sulfamethoxazole among enteric flora around the world. Likewise, owing to the prevalence of fluoroquinolone-resistant *Campylobacter jejuni*, the combination of loperamide plus a fluoroquinolone cannot be recommended in Southeast Asia, where the combination of loperamide plus azithromycin would be preferred.

Unlike opiates or difenoxin/diphenoxylate, loperamide is not habit forming and is approved for use in children ≥2 years of age. The drug is generally well tolerated. The worsening of diarrheal illness by treatment with loperamide, which has been reported on occasion, has often been accompanied by either overdose of the drug or continuation of the drug well past recommended durations of treatment. Reviews of the excellent safety profile associated with the use of loperamide have been published elsewhere [5, 45]. Given the favorable safety profile and consistent benefit documented in numerous studies of diarrhea in travelers, loperamide can be recommended as a drug of choice from among the currently available therapeutic options involving the use of nonantimicrobial agent for the treatment of traveler’s diarrhea.

**SUMMARY**

When chemoprophylaxis of traveler’s diarrhea is considered, nonantimicrobial options that can be recommended include BSS preparations and *Lactobacillus* GG. BSS prevents a modest 65% of episodes of diarrhea, and chewing tablets 4 times a day is not convenient. Practitioners must be aware that substantial salicylate is absorbed, and travelers must anticipate black tongue and stools. *Lactobacillus* GG prevents even fewer episodes of diarrhea (40% protection) but is safe to use.

For the treatment of traveler’s diarrhea, adsorbents, such as kaolin preparations, confer minimal benefits but are safe. BSS preparations provide a modest reduction in the number of loose stools passed and should probably be reserved for the treatment of mild diarrhea. The antisecretory and antimotility agent loperamide reduces the total number of loose stools passed by ∼50%. Combining loperamide with an appropriate antimicrobial agent is especially effective and limits the average duration of traveler’s diarrhea to a matter of hours. Other antisecretory agents, Provir (SP-303) and zaldaride, are active in the treatment of traveler’s diarrhea, but Provir is only available as a botanical preparation, and zaldaride has not been marketed.

**Acknowledgments**

I thank H. L. DuPont for the excellent critique of the preparation of this review.

**Potential conflicts of interest.** C.D.E. has received funding for research from Pfizer and Salix Pharmaceuticals, has received speaking honoraria from Pfizer, Salix, and Elan Pharmaceuticals, and is a consultant to Salix Pharmaceuticals.

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