SUPPLEMENT ARTICLE

Prophylactic Antimicrobials for Traveler's Diarrhea: An Early History

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The prevention of traveler's diarrhea by use of pharmacologic agents has been of great interest since the early 1960s. It was not until the discovery of enterotoxigenic *Escherichia coli* as the dominant causative organism of travelers' diarrhea, however, that rational antimicrobial therapy could be studied. Selected antimicrobials have proven to be highly efficacious, but, by consensus, are not widely used.

Traveler's diarrhea occurs, by definition, in visitors to developing countries. To be more specific, however, it occurs only (a) in areas where diarrhea is endemic among the children of that population and (b) when the travelers are from developed countries, where water quality and sanitation standards are high. Studies to find ways of preventing traveler's diarrhea by use of antimicrobial agents have been in progress since the early 1960s. This article will attempt to summarize the studies conducted through the middle of the 1980s, when a National Institutes of Health Consensus Conference was held [1]. More details of those studies can be found in the original articles cited or in many other review articles [2–13].

STUDIES PRECEDING THE RECOGNITION OF ENTEROTOXIGENIC *ESCHERICHIA COLI* (ETEC) AS A MAJOR ETIOLOGIC AGENT OF TRAVELER'S DIARRHEA

As short-term international travel to developing countries increased, particularly among students, it was recognized that diarrhea was a considerable hazard to the traveler, and B. H. Kean [14] began studies to characterize the disease and its etiology, treatment, and prevention. The only preventive measure known at that time was the use of discriminative food ingestion, because the association between food intake and diarrhea was readily recognized. It seemed that the use of pharmaceutical agents for prevention might be useful, even though nothing was known of the etiology of traveler's diarrhea at that time. In 1963, Kean said that "neither the cause nor the cure of traveler's diarrhea has been discovered" [14, page 613].

During the time preceding that statement, a number of studies of prophylactic medications had been done, although most were poorly controlled studies. Two of the early drugs studied by Kean and Waters [15] were enterovioform (iodochlorhydroxyquinoline, also called "clioquinol") and neomycin. Enterovioform was being used widely as a prophylactic against diarrhea at that time. However, neither enterovioform nor neomycin gave any protection. The relationship between the use of enterovioform and subacute myelo-optic neuropathy was later shown [16], and the drug was taken off the market.

The first controlled studies, published in 1962 by Kean et al. [17], involved healthy students from the United States traveling to Mexico for short periods of time (2 weeks). The 2 drugs used were neomycin sulfate and phthalylsulfathiazole, and both provided a significant rate of protection (25%–50% against any traveler's diarrhea and 60%–70% against severe disease). Kean's recommendation at that time was that phthalylsulfathiazole could be used for brief periods [14].

Another partially controlled study, performed by Turner [18], involved personnel of British Airways (then known as "BOAC") and their families who were traveling for up to 3 weeks to destinations all over the world. Study subjects (~350 subjects/group) were given

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either neomycin-trisulphamide, streptotriad (i.e., streptomycin, sulphadimidine, sulfadiazine, and sulfathiazole), or placebo. Both medications provided low (<28%) but significant ($P <$ .02) levels of protection. In 1983, Turner [12] said that all British Airways employees and their families were given the option of taking prophylactic streptotriad during short-term travel. It was noted anecdotally that British teams participating in the Olympic games in Rome (in 1960) and Mexico (in 1998), many of whom were taking streptotriad prophylaxis, had fewer episodes of traveler's diarrhea than did their Australian competitors, who were not taking such prophylaxis [12].

Furazolidone was studied as prophylaxis against traveler's diarrhea by Nelson et al. [19], in a poorly controlled trial involving Royal Air Force pilots. They were able to show a rate of protection of up to 30% with the use of 2 different doses of the drug.

STUDIES FOLLOWING THE RECOGNITION OF ETEC AS A MAJOR ETIOLOGIC ORGANISM

With the observation that ETEC was the primary cause of traveler's diarrhea, the possibility that antimicrobials could have a major effect on the prevention of traveler's diarrhea became a reality. The recognition of ETEC as a cause of watery diarrheal disease was first made in 1968 [20], on the basis of early work by De et al. [21], who used a rabbit ileal loop technique. The organisms were found in adults and children with severe watery diarrhea that was clinically indistinguishable from cholera. Over the next several years, ETEC was found to be the most common bacterial cause of diarrhea in children in the developing world [22] and a significant cause of diarrhea among the White Mountain Apaches in the United States [23].

The recognition that these organisms were the most common cause of traveler's diarrhea in travelers to Mexico was noted in 1975, by Gorbach et al. [24], and in 1976, by Merson et al. [25]. The latter study involved a group of gastroenterologists. A third sentinel study, done in 1975 by Sack et al. [26], involved Peace Corps volunteers (PCVs) traveling to Kenya; that study demonstrated that ETEC was the most frequent cause (62% of cases due to ETEC) of traveler's diarrhea in Kenya. Not only was the ETEC common, but it was also highly susceptible to almost all antimicrobials.

DOXYCYCLINE

Doxycycline was initially chosen for study on the basis of the following factors: (a) the susceptibility of ETEC to the drug; (b) the long-acting nature of the drug, which allows for a single daily dose; (c) the secretion of the drug into the small intestine, which is the site of ETEC colonization; (d) its known efficacy in treating cholera; and (e) the safety of the drug and the rarity of adverse events associated with its use. During a 3-year period, 5 studies (funded by the US Army Medical Research and Development Command) were done using doxycycline prophylaxis for PCVs [27–31].

The first study involved a similar group of 39 PCVs traveling to Kenya in 1976 [27]. This prospective, randomized, double-blind study showed that doxycycline (100 mg/day given daily for 3 weeks) provided 86% protection against traveler's diarrhea. An identical study involving 50 PCVs traveling to Morocco in 1977 yielded similar results (83% protection) [28].

Three additional studies of doxycycline treatment for PCVs were done in Honduras and Thailand. In the first study, which was done in Honduras in 1978 [29], 46 PCVs were studied; a dose of 100 mg of doxycyline, administered twice weekly, was used. The rate of protection was only 27% (not significant); this low level of protection was thought to be due either to the interval of the drug given or to the increasing resistance of ETEC to doxycycline. A second study of 44 PCVs traveling to Honduras, which was done in 1980 [30], used a dose of 100 mg of doxycycline once daily, and showed a level of protection lower than that seen in the Kenyan and Moroccan studies; however, the rate of protection was still significant (68%). In the last study, which involved 63 PCVs traveling to Thailand in 1980 [31], the protection rate was 59%, but was not statistically significant ($P = .12$). In that study, the attack rate in the placebo group was low (24%), and there were only a few ETEC organisms isolated. In 1983, a study of short-term visits (duration, 0.5–2.5 days) by military personnel to Mexico [32] showed a protection rate of 81%.

TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMZ)

Studies of the effectiveness of TMP-SMZ were done in 1979 and 1980 by DuPont et al. [33, 34] and involved groups of students from the United States traveling to Mexico for short summer training programs. The first study [33] showed that using TMP-SMZ for 3 weeks provided 73% protection; the second study, in which the drugs were taken for 2 weeks, showed 95% protection [34]. In the latter study, TMP alone was also studied in a third group of students, and it yielded a lower rate of protection (59%).

A nonabsorbable antimicrobial, bicozamycin, was also studied in students visiting Mexico and was found to be 100% protective in a small number of students [35]. Two other antibiotics have been studied: erythromycin [36] and mecillinam [37]. Both were found to yield significant protection against traveler's diarrhea. Table 1 summarizes the results of the many studies of the prevention of traveler's diarrhea.

DISCUSSION

The discovery that ETEC was the primary cause of traveler's diarrhea provided a basis for rational attempts to prevent and treat the disease. Both doxycyline and TMP-SMZ provided sig-

Table 1. History of early antimicrobial prophylaxis for travelers' diarrhea, before (in the 1960s) and after (in the 1970s and later) the recognition of enterotoxigenic *Escherichia coli* as an etiologic agent.

Years, drug, location	Rate of protection, %	Reference
1960s		
Enteriovioform	0	[15]
Neomycin	0–50	[17]
Phthalylsulfathiozole	25–50	[17]
Streptotriad	⩽28	[18]
Furazolidone	0–30	[19]
1976–1980, doxycyline[a]		
Kenya and Morocco	80–85	[27, 28]
Honduras and Thailand	50–60	[29–31]
1979–1980		
Trimethoprim-sulfamethoxazole, Mexico	71–95	[33]
Trimethoprim, Mexico	59	[34]
1981, erythromycin	100	[36]
1983, mecillinam	75	[37]
1985, bicozamycin[b]	100	[35]

[a] In studies conducted in the 1970s and later, medication was administered for 2–3-week periods.
[b] The study had very few subjects.

nificant protection for travelers (doxycyline for PCVs around the world and TMP-SMZ for students visiting Mexico).

Although these antimicrobials were used to specifically prevent ETEC infection, the high degree of efficacy indicated that infection with other causative bacteria (non-ETEC) was being prevented as well. Only later were some of these bacteria, including enteroaggregative *E. coli*, identified [38]. In spite of the best microbiological methods, there are still many cases of traveler's diarrhea (~25%) for which no pathogen can be identified.

In spite of the efficacy of these antimicrobials in the prevention of traveler's diarrhea, there was considerable concern regarding their widespread use. In January 1985, a Consensus Conference held at the National Institutes of Health came to the conclusion that these drugs should not be used for prophylaxis: "Antimicrobial agents are not recommended for prevention of traveler's diarrhea. Such widespread usage in millions of travelers would cause many adverse effects, including some severe ones, while preventing a disease for which mortality has not been reported. Instead of universal antimicrobial prophylaxis, a more sensible approach is rapid institution of effective treatment that can shorten the disease to 30 hours or less in most people" [39, page S232].

The primary concern was the possibility of serious adverse effects—primarily, allergic reactions—resulting from the use of drugs to prevent a relatively mild illness. Of secondary concern was the possibility that these drugs, if used widely, could facilitate the development of antibiotic resistance. This phenomenon could occur in the persons taking the drugs or in the populations being visited by tourists. Because antimicrobials are sold without prescriptions in nearly all the developing world, the latter concern is probably not important. Many physicians who practice travel medicine would, however, consider using antimicrobial prophylaxis for short periods of time for certain patients who may be at higher risk of developing the more severe consequences of traveler's diarrhea.

Over the past years, ETEC has become increasingly resistant to tetracyclines and TMP-SMZ, and neither drug would now be as effective as it was 25–30 years ago. There are now, however, new antimicrobials (primarily, the fluoroquinolones) that have also been shown to be ~90% effective in preventing traveler's diarrhea [40]. In addition, a new nonabsorbable antimicrobial agent, rifaximin, is now available [41] and may prove to be useful in prophylaxis. These drugs are discussed elsewhere in this symposium. Therefore, the Consensus Statement may have to be revisited, to determine whether these recommendations are still valid.

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