Antimicrobial Versus Ampicillin in the Treatment of Traveler’s Diarrhea

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Ninety-four U.S. students who acquired diarrhea in Mexico were treated with furazolidone (47 subjects) or ampicillin (47 subjects) on a double-blind random basis. Of 47 students, 26 (55%) who received furazolidone (100 mg four times daily for 5 days) recovered from illness within 48 h after initiation of therapy, in contrast to 15 of 47 (32%) who received ampicillin (500 mg four times daily for 5 days) (P < 0.05). Altogether, 74% of students treated with furazolidone and 49% of those receiving ampicillin were well within 72 h (P < 0.05).

When furazolidone was compared with ampicillin, clinical illness was shortened on the average from 65 to 61 h for enterotoxigenic Escherichia coli diarrhea, from 83 to 58 h for shigellosis, from 82 to 51 h for diarrhea unassociated with a detectable agent, and from 72 to 57 h for all cases irrespective of etiology. Although not dramatically effective in the current trial, the broad spectrum of activity of furazolidone is of interest. Because of its in vitro activity against Campylobacter strains and known effectiveness in treating giardiasis, furazolidone should be considered in therapy for diarrhea of unknown etiology in certain settings when laboratory processing of stools for etiological agent is not feasible.

Previous studies have shown that a majority of the cases of diarrhea which occur when persons travel from industrialized countries to developing regions are caused by bacterial pathogens (7, 17). The most important agents in this setting are enterotoxigenic Escherichia coli, Shigella, Salmonella, and Campylobacter strains. Trimethoprim-sulfamethoxazole (TMP-SMX) is an effective form of therapy for traveler’s diarrhea (7). It is not active against Campylobacter strains, which is a limiting factor in the empiric therapy of acute diarrhea in general. Recently, we carried out an in vitro study wherein 243 bacterial enteropathogens obtained from various parts of the world were tested for their susceptibility to antimicrobial agents (2). We were impressed with the high degree of activity of furazolidone against all strains of enteropathogens tested, with the exception of a few strains of Yersinia enterocolitica. Since furazolidone was found to be active against the important agents of traveler’s diarrhea, the present study was designed. Ampicillin was selected as a control, recognizing that it is not considered to be the current treatment of choice for traveler’s diarrhea. However, ampicillin is widely used in Mexico for diarrhea, and a majority of the bacterial enteropathogens we have obtained in the last 2 years from Mexico have been shown to be susceptible to the drug. Furthermore, information was already available as to the clinical response of the illness in the population under study when other active compounds (TMP-SMX and bicozamycin) were employed in previous studies (7, 8).

MATERIALS AND METHODS

The study population comprised 100 male and female students from the United States enrolled in summer programs sponsored by the Universities of San Diego and Arizona in Guadalajara, Mexico. The criterion for admission to the study was diarrhea of ≤60-h duration. Diarrhea was defined as the passage of four or more unformed stools in 24 h or three unformed stools in an 8-h period. Each subject also had to have at least one sign or symptom of gastrointestinal infection: nausea, vomiting, abdominal pain or cramps, or fever. After informed consent was obtained, a freshly passed unformed stool was collected and submitted to the field-site laboratory for enteropathogen detection by previously published methods (17a). Stools were examined for Shigella, Salmonella, Campylobacter, and Aeromonas isolates and protozoal parasites in our Guadalajara laboratory. Five E. coli colonies from each diarrheal stool were studied for enterotoxigenicity (both heat-stable [ST] and heat-labile [LT] enterotoxins) in Houston (6).

For bacterial enteropathogen strains that remained viable, antimicrobial susceptibility testing was later performed in Houston by Kirby-Bauer disk diffusion methods.

Identical encapsulation of the furazolidone and ampicillin allowed a double-blind study to be performed, with the students randomly assigned to receive one of the two trial medications. The dosing regimens were one 100-mg capsule four times daily (furazolidone) or one 500-mg capsule four times daily (ampicillin). Both antibiotics were prescribed for 5 days. During the 5-day treatment period, patients were required to keep a daily diary of the number and consistency of stools, associated signs and symptoms of enteric illness, and the medication dosing schedule. In addition, they were required to report daily to the clinic for evaluation.

As found in previous clinical trials in this population, the best parameter of drug efficacy is time from initiation of therapy until the passage of the last unformed stool (7, 8). In this trial, the students were considered to have recovered when the last unformed stool was passed and other signs and symptoms of enteric infection were no longer present.

Statistical analysis of data was done with the Wilcoxon rank-sum test, with Z corrected for ties, chi-square, or Fisher’s exact test, as appropriate. Significance was defined as a P value less than or equal to 0.05.
RESULTS

Five students failed to complete the study or were dropped from the trial for a variety of reasons, including having a parasite in diarrheal stools, early return to the United States, or taking a second antibiotic concomitantly. A sixth student who received furazolidone developed a rash during therapy and was removed from the study because of the adverse reaction. The rash was limited to both wrists, a knee, the sole of a foot, and both hands. The study population comprised 94 subjects. Patients in both treatment groups reported a similar duration of illness and severity of symptoms before enrollment in the trial.

Table 1 lists students by major etiological agents isolated during the trial and by the number of patients within each etiology category who recovered from diarrhea within 48 to 72 h of receiving therapy. Four categories of etiological agents had sufficient numbers of subjects to be compared: all patients, those with enterotoxigenic E. coli diarrhea, those with shigellosis, and those in which an etiological agent could not be found. The enterotoxigenic E. coli isolated in the furazolidone group consisted of 8 ST only, 1 LT only, and 6 ST and LT, whereas for ampicillin-treated subjects 12 ST only, 5 LT only, and 4 ST and LT were identified. Campylobacter sp. was isolated once in each group; 11 Salmonella isolates were obtained (8 in the furazolidone group and 3 in the ampicillin group). One individual with diarrhea in the furazolidone group had an Aeromonas hydrophila strain isolated from the illness stool. The numbers of Campylobacter, Salmonella, and Aeromonas isolates were too small to allow a statistical comparison to be made. Four of eight patients (50%) with salmonellosis who received furazolidone recovered within 48 h, and six of eight (75%) were well within 72 h. Only three subjects assigned to the ampicillin group had a Salmonella strain isolated in stool (one recovered within 48 h, and two recovered by 72 h). Altogether, 26 of 47 subjects (55%) who received furazolidone recovered within 48 h of initiation of therapy, in contrast to 15 of 47 (32%) in the ampicillin group (P < 0.05); 35 of 47 patients (74%) in the furazolidone group and 23 of 47 ampicillin-treated subjects (49%) were well within 72 h (P < 0.05). Although differences in recovery rate were not significant when the groups were stratified by etiology, differences similar to those for the unstratified groups were seen and favored those treated with furazolidone.

Table 2 shows the response to treatment in mean number of hours from initiation of therapy until passage of the last unformed stool. The differences were not significant by Wilcoxon rank-sum test. However, in all strata except Salmonella sp., the mean duration of diarrhea was shorter in the furazolidone group.

Two subjects given furazolidone, one with enterotoxigenic E. coli infection and one with an unknown agent, and two persons treated with ampicillin (both unknown causes) worsened on therapy and were declared treatment failures. They were removed from the study and given TMP-SMX. In addition, 8 furazolidone-treated students (2 with enterotoxigenic E. coli, 2 with Shigella sonnei, 1 with enterotoxigenic E. coli plus S. sonnei, 1 with Salmonella B, 1 with enterotoxigenic E. coli plus Aeromonas sp., and 1 with an unknown agent) and 10 ampicillin-treated individuals (4 with enterotoxigenic E. coli, 2 with S. sonnei, 2 with enterotoxigenic E. coli plus S. sonnei, and 2 with unknown agents) still had not passed a formed stool within the 5 days of therapy. We considered these subjects to also be treatment failures, making the frequency of treatment failures 21% for furazolidone and 26% for ampicillin.

We examined the susceptibility of a majority of enterotoxigenic E. coli, Shigella, and Salmonella strains isolated from students treated with either drug. In the furazolidone-treated group, all strains tested were susceptible to furazolidone, including 13 enterotoxigenic E. coli, 11 Shigella, and 4 Salmonella. In the ampicillin-treated group, 12 of 16 enterotoxigenic E. coli strains tested were susceptible to ampicillin, as were 6 of 7 Shigella strains and 3 of 3 Salmonella strains. The greater frequency of occurrence of ampicillin-resistant strains when compared with furazolidone-resistant organisms might at least partially explain the difference in clinical response between the two drugs. Although there appeared to be a trend toward greater clinical improvement in the ampicillin-treated cases in whom a susceptible isolate was obtained (compared with those excreting a resistant organism), the numbers were too small to allow a useful analysis.

During the course of the study, several students complained to the field staff that they had developed facial flushing after consuming alcohol. In a number of instances, a

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Drug group</th>
<th>No. of students (%)</th>
<th>No. (%) recovered within:</th>
<th>Mean duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Furazolidone</td>
<td>Ampicillin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterotoxigenic E. coli</td>
<td>15 (32)</td>
<td>9 (60)</td>
<td>11 (73)</td>
<td>48 h</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>21 (45)</td>
<td>9 (43)</td>
<td>11 (52)</td>
<td>72 h</td>
</tr>
<tr>
<td>Shigella sp.</td>
<td>Furazolidone</td>
<td>13 (28)</td>
<td>7 (54)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>10 (21)</td>
<td>2 (20)</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>Salmonella sp.</td>
<td>Furazolidone</td>
<td>8 (17)</td>
<td>4 (50)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>3 (6)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>Furazolidone</td>
<td>11 (23)</td>
<td>6 (55)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>12 (26)</td>
<td>2 (17)</td>
<td>5 (42)</td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td>Furazolidone</td>
<td>47 (100)</td>
<td>26 (55)</td>
<td>35 (74)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>47 (100)</td>
<td>15 (32)</td>
<td>23 (49)</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05; other differences are not significant.
* Includes one patient with Campylobacter infection, who recovered within 48 h.
typical and rather impressive flushing reaction was documented by our field investigators. A questionnaire was administered to as many subjects as could be located, asking whether they had consumed alcohol during the study and whether they had experienced facial flushing or skin rash; 40 of 47 subjects in each group responded. A total of 17 of 40 furazolidone-treated students had consumed alcohol, and 9 recalled experiencing a flushing-type reaction (53% of those taking alcohol). For the ampicillin-treated subjects, 20 subjects had consumed an alcoholic beverage during their therapy for diarrhea, and 2 (10%) had experienced flushing. The difference between the two groups was significant ($P = 0.0054$). Both drugs were otherwise well tolerated, although 12 students in the furazolidone group commented that their urine had turned dark yellow.

**DISCUSSION**

Results of the present study indicate that furazolidone is more effective than ampicillin in therapy for acute traveler's diarrhea. Furazolidone appeared to be more active than ampicillin in therapy for enterotoxigenic *E. coli* diarrhea, shigellosis, and illness in which an etiological agent could not be detected, although differences between the two treatment groups were not significant for these three etiology categories. We have recently provided data that a proportion of this undiagnosable illness is due to enteroadherent *E. coli* strains which do not produce conventional *E. coli* enterotoxins (16).

An important question is, how effective is furazolidone compared with other newer agents that have been shown to have a high degree of activity against bacterial agents seen in this setting. Although a side-by-side comparison is not available, we do have similar information collected in an identical fashion from earlier studies that employed students in the same summer program in Guadalajara and thus can provide a historical comparison. In these earlier trials, TMP-SMX, TMP alone, and bicozamycin were compared with a placebo (5, 7, 8). Speed of recovery within 48 to 72 h, mean number of hours of diarrhea, and frequency of treatment failure were compared. Furazolidone was superior to the two placebos employed in the earlier trials. However, TMP-SMX, TMP alone, and bicozamycin, which showed approximately equal effectiveness, each appeared to be more effective than furazolidone by all test parameters. The slower clinical response of furazolidone compared with other agents despite in vitro susceptibility of infecting strains could partially relate to an effect of the drug on intestinal function or flora resulting in the passage of small numbers of undigested stools.

However, furazolidone has some advantages in therapy for acute diarrhea that are not apparent in this trial. Furazolidone has previously been shown to be active against a variety of agents not commonly encountered by the U.S. student population in Mexico. In cholera, furazolidone has been shown to be as effective as tetracycline in reducing the duration of diarrhea, *Vibrio* excretion, and intravenous fluid requirements among adults and children (3, 13). Also, this drug is currently the recommended agent in therapy for giardiasis in infants and young children, since there exists a pediatric suspension formulation and cure rates are higher due to better acceptability (4). Although the published data offer various results as to the relative effectiveness of furazolidone, quinacrine, and metronidazole in therapy for giardiasis, all three are effective in more than 80% of cases (1, 4, 14, 18, 19). Furazolidone may be active against certain forms of bacteremic salmonellosis (10, 12), and it is currently used as a form of therapy for *Campylobacter* enteritis in areas of China. We have offered further support that *Campylobacter* isolates may respond favorably to furazolidone, in view of the in vitro activity of the drug against *Campylobacter jejuni* isolates from diverse world regions (2), although no clinical data on effectiveness of the drug against *Campylobacter* diarrhea is currently available. Conflicting data exist on the value of furazolidone therapy for pediatric shigellosis (9, 11, 15).

Currently, we think that furazolidone has a place in therapy for acute diarrhea. Although TMP-SMX should be considered the treatment of choice for shigellosis and perhaps for severe diarrhea due to enterotoxigenic *E. coli*, the broad spectrum of activity of furazolidone may counterbalance the less dramatic effect of the drug against *Shigella* and enterotoxigenic *E. coli* infections. Furazolidone should be considered in the therapy of patients with diarrhea of unknown etiology in areas or settings in which *Campylobacter* and *Shigella* isolates are both likely agents and when laboratory processing of stools for enteropathogens is not feasible. We currently recommend that backpackers and hikers traveling to mountainous areas where giardiasis is endemic take a supply of furazolidone with them to use in the empiric therapy of acute diarrhea while in the remote areas. No currently available drug found to be useful against the common bacterial agents also shows a high degree of activity against *Giardia* infection. However, when furazolidone is given to treat possible *Giardia* infection it must be given for a full 7 to 10 days (18). Also, giardiasis may have an incubation period of 1 week or longer, so that the illness may develop after travelers leave the area of high risk. From the study reported here, we urge physicians to warn their patients that alcohol consumption can lead to a disulfiram-type flushing reaction while taking furazolidone. This will be a limiting factor for certain persons who wish to take a supply of effective drugs with them as they travel to areas of high diarrhea risk.

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**LITERATURE CITED**

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