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Optimal Dosing of Trimethoprim-Sulfamethoxazole When Used with Loperamide To Treat Traveler's Diarrhea

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To explore the optimal dosing regimen for trimethoprim-sulfamethoxazole (TMP-SMX) when used in combination with loperamide to treat traveler's diarrhea, 190 U.S. adults with acute diarrhea were enrolled in a double-blind, randomized trial in Guadalajara, Mexico. All patients received loperamide (4-mg loading dose; 2 mg after each loose stool, not to exceed 16 mg/day for 3 days) and were randomized to receive a 3-day course of TMP-SMX (160:800 mg twice daily for six doses) (group A), a single large dose of TMP-SMX (320:1,600 mg) (group B), or a large loading dose (320:1,600 mg) followed by standard doses for 3 days (160:800 mg twice daily for five doses) (group C). Patients in group C responded best ($P < 0.01$), with 75% of subjects recovered from diarrhea in 12 h compared with 34 h (group A) and 33 h (group B). Similar differences in favor of group C were noted in the subset of patients who presented with moderate to severe diarrhea. On average, patients in group C took significantly ($P < 0.05$) less loperamide (1.2 mg) after the 4-mg loading dose compared with patients in group A (2.4 mg) or group B (2.0 mg). We conclude that the most efficacious treatment of traveler's diarrhea in the interior of Mexico is to take loperamide in usual doses to control symptoms in combination with a single large dose of TMP-SMX, which should then be continued for 3 days in standard doses.

Travel to developing countries is associated with an increased risk of diarrheal illness, generally caused by ingestion of enteric pathogens. Approaches to the control of traveler's diarrhea have included patient education, chemoprophylaxis, and various forms of treatment. Travelers appear to have trouble controlling dietary risks despite education (10). Chemoprophylaxis with antimicrobial agents is controversial (2, 9). Prophylaxis with bismuth subsalicylate tablets confers at best 65% protection (3, 13). Treatments for traveler's diarrhea include fluid replacement; symptomatic relief with agents such as bismuth subsalicylate, adsorbents, and antimotility agents; and the use of antimicrobial agents as single doses or for as long as 5 days (4–7).

Specifically, the combination of trimethoprim-sulfamethoxazole (TMP-SMX) and loperamide was highly effective in the treatment of traveler's diarrhea in Guadalajara, Mexico, where the predominant organism is enterotoxigenic *Escherichia coli* (ETEC) (7). The average duration of diarrhea in the combination-treated group was 1 h, and about half of the subjects passed no more unformed stools after enrollment. We designed the present study to explore the most effective dosing regimen for TMP-SMX when also used in combination with loperamide. A 3-day regimen of TMP-SMX was compared with a single large dose given solely or followed by standard therapy.

MATERIALS AND METHODS

During the summers of 1988 and 1989, 190 U.S. adults, who had recently arrived in Guadalajara, Mexico, to attend summer school classes conducted by the Universities of San Diego and Arizona or to attend medical school at the University Autonoma de Guadalajara, were enrolled in a prospective, randomized, double-blind study of the treatment of acute diarrhea. The study was approved by school directors and by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston. The definition of diarrhea was passage of three or more unformed (soft or watery) stools in 24 h plus an additional symptom of enteric disease, such as abdominal cramps, nausea, vomiting, or fever. During these summers other treatment studies of mild to moderate diarrhea received enrollment priority. Subjects who passed frankly bloody stools or who had temperature elevations above 39°C were excluded from enrollment. Subjects with lesser degrees of blood in stool or fever were enrolled. No subject was enrolled when the duration of diarrhea was longer than 14 days. All subjects signed an informed consent and submitted an unformed stool sample for analysis prior to beginning therapy.

All stool samples were inspected for blood and analyzed in the field laboratory in Mexico for the presence of fecal leukocytes and parasites and for the growth of *Shigella*, *Salmonella*, *Campylobacter*, *Plesiomonas*, and *Aeromonas* organisms, and as previously described, five colonies of *E. coli*-like organisms from each stool sample's growth were picked and transported to Houston on nutrient stabs for subsequent testing for the production of heat-labile or heat-stable enterotoxins (11).

All subjects received open-label loperamide as a 4-mg oral loading dose followed by 2 mg after each loose stool (not to exceed 16 mg/day). By random assignment, subjects also received one of the following oral TMP-SMX treatment regimens: group A, TMP-SMX (160:800 mg) every 12 h for six doses; group B, TMP-SMX (320:1,600 mg) immediately; or group C, TMP-SMX (320:1,600 mg) immediately and then 160:800 mg every 12 h for five doses. Placebo capsules were used to maintain double blinding of the TMP-SMX dosing regimens.

All subjects were informed about fluid replacement and dietary adjustments, which they practiced ad libitum. Sub-

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jects were treated as outpatients in Mexico and were observed daily at the clinic site for the worsening of illness and appearance of adverse experiences and to ensure compliance with the protocol. While the subjects were participating, the additional use of other antimicrobial or antidiarrheal agents was prohibited.

All subjects kept daily diaries of times of passage of stools, symptoms, and possible side effects of medication. Diaries were kept until the subject was well and passing formed stools and were kept for at least 5 days. For subjects whose illness failed to respond to therapy or worsened, treatment could be declared a failure as long as the subjects had passed, in a 24-h period, more than half the number of unformed stools that had qualified them for enrollment and that number exceeded three. Treatments were also arbitrarily declared failures if subjects continued to pass any number of unformed stools at the end of 120 h. Subjects whose treatments were declared failures were asked to resubmit a stool sample for analysis, and they were treated with a 3-day course of norfloxacin at a dose of 400 mg orally twice a day.

For purposes of analysis, moderate to severe diarrhea at enrollment was defined as passage of six or more unformed stools within the previous 24 h. The duration of diarrhea was defined as the number of hours from enrollment to passage of the last unformed stool, followed by at least 24 h free of all symptoms.

Subjects noncompliant with the dosing schedule (missing one dose of TMP-SMX or more than one dose of loperamide) were initially excluded from an efficacy analysis and then included in an intent-to-treat analysis. Since the conclusions of both analyses were substantially the same, results of the latter analysis are presented. Persons whose treatments were declared failures were presumed in the survival analysis to be still ill at 120 h. Comparability testing of treatment groups was done by analysis of variance, and efficacy comparisons were done by generalized Wilcoxon (Breslow) survival analysis. Significance was defined as $P < 0.05$.

RESULTS

Eleven, nine, and nine subjects in groups A, B, and C, respectively, refused further participation in the study after enrollment because of perceived inconvenience and were dropped from analysis. None had failed to respond favorably to therapy as judged by informal questioning. Treatment groups were comparable by age, sex, and severity and duration of diarrhea prior to treatment. No significant differences were found in the frequency of nausea, vomiting, cramps, fever, and number of stools passed in the 24-h period before enrollment among the three treatment groups (Table 1).

Results of therapy are shown in Fig. 1. Loperamide plus standard 3-day or single-large-dose TMP-SMX therapy appeared to be equivalently effective. Treatment with loperamide and a large loading dose of TMP-SMX followed by standard doses every 12 h for 3 days was most efficacious compared with treatment of the other two groups ($P < 0.01$). For comparison purposes the time elapsed between initiation of therapy and cure for 50 and 75% of all patients is displayed in Table 2; these data are a direct reflection of the data shown in the curves in Fig. 1. Subset analysis shows that patients in group C responded best to therapy compared with patients in groups A and B whether they presented with mild to moderate ($P = 0.053$) or moderate to severe ($P < 0.09$) illness. Similar comparative responsiveness favoring regimen C was noted in the treatment of illness due to *Shigella* strains and ETEC; however, the numbers were too small to reach significance. Once well, no subject redeveloped diarrhea, nausea, vomiting, cramps, or fever during the 5-day observation period. Eight patients in group A, four in group B, and six in group C had not yet passed formed stools at 120 h and were the only subjects with treatment failures. The differences in the number of treatment failures were not significant. Except for *Campylobacter* and *Cryptosporidium* spp., all organisms (Table 2) isolated from subjects with declared treatment failures were sensitive to TMP-SMX.

The mean dosages of loperamide taken in the first 24 h

TABLE 1. Enrollment characteristics of the three treatment groups

Characteristic	Treatment group[a]		
	A	B	C
No.:			
Enrolled	62	64	64
Excluded from analysis	11	9	9
Of women analyzed	30	29	37
Of men analyzed	21	26	18
Mean age of subjects (yr)	30	29	29
No. (24 h prior to enrollment):			
Of mean unformed stools	6.6	6.5	7.0
Presenting with[b]:			
Nausea	16/12/5	23/8/2	18/11/2
Vomiting	4/4/1	2/3/2	5/3/1
Cramps	16/24/6	7/26/3	20/19/7
Temp elevation[c]	4	3	2
No. with causal agent(s):			
Shigella sp. alone	16	14	19
ETEC alone	8	9	12
Shigella sp. + ETEC	5	3	2
Others	2	6	5
Unknown	20	23	17

[a] See text for definition of treatment groups.
[b] Mild (tolerable)/moderate (distressing)/severe (incapacitating).
[c] <39°C.

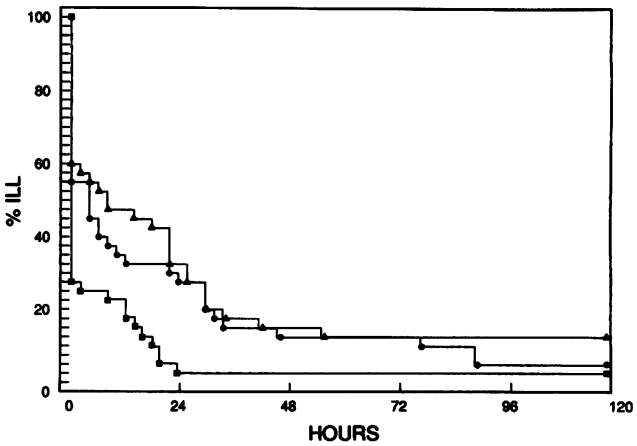

FIG. 1. Comparative outcomes of the treatment of traveler's diarrhea. All subjects received loperamide. Triangles indicate group A ($n = 51$), treated with 3-day therapy with TMP-SMX. Circles indicate group B ($n = 55$), treated with a single large dose of TMP-SMX. Squares indicate group C ($n = 55$), treated with a large loading dose of TMP-SMX followed by standard 3-day therapy with TMP-SMX. For details of dosages, see text.

TABLE 2. Comparative outcomes for the therapy of acute diarrhea in the three treatment groups

Outcome	Treatment group[a]		
	A	B	C
h of diarrhea after treatment of:			
All illness[b]			
50% well	11	4	0
75% well	34	33	12
Mild to moderate illness[c]			
50% well	3	1	0
75% well	29	30	1
Moderate to severe illness[d]			
50% well	21	12	0
75% well	34	35	12
No. of treatment failures			
Total	8	4	6
With causal agent(s):			
Shigella sp.	1	1	5
ETEC	2		
Shigella sp. + ETEC		1	
Shigella sp. + ETEC + *Aeromonas* sp.	1		
Shigella sp. + *Campylobacter* sp.	1		
Plesiomonas sp.		1	
Plesiomonas sp. + *Cryptosporidium* sp.	1		
No pathogen isolated	2	1	1
Avg mg of loperamide taken after loading dose in first 24 h	2.4	2.0	1.2

[a] See text for definition of treatment groups.
[b] n = 51, 55, and 55 in groups A, B, and C, respectively; $P < 0.09$ favoring group C.
[c] n = 27, 27, and 28 in groups A, B, and C, respectively; $P < 0.09$ favoring group C. Mild to moderate illness is defined as fewer than six unformed stools in the 24 h prior to enrollment.
[d] n = 24, 28, and 27 in groups A, B, and C, respectively; $P < 0.09$ favoring group C. Moderate to severe illness is defined as six or more unformed stools in the 24 h prior to enrollment.

after the initial 4-mg loading dose were analyzed to be certain that subjects in group C had not responded best to therapy simply because they took more loperamide. To the contrary, subjects in group C (Table 2) took significantly less loperamide than subjects in groups A and B. Finally, no serious adverse events were reported by patients in any of the drug regimens.

DISCUSSION

Our previous work showed that loperamide plus TMP-SMX for 3 days was effective therapy for traveler's diarrhea (7). In that study we also demonstrated benefit from a single large dose of TMP-SMX without loperamide. We had assumed in the design of the present study that loperamide plus a single large dose of TMP-SMX would prove as effective as the other regimens studied and would be the regimen of choice due to cost effectiveness. The results showed that loperamide plus a loading dose of TMP-SMX followed by a standard 3-day course was clearly superior to the other regimens. We feel that the differences are clinically relevant in the first 24 h of therapy. The benefits appear to accrue to patients with both more severe and less severe disease, although the subset analyses did not quite reach statistical significance because of small numbers. We feel that a cost-effective recommendation can be made from these data: start combination therapy with loperamide and a large loading dose of antibiotic, continue loperamide for the first day or two as necessary, and continue the antibiotic every 12 h for 3 days only when the initial illness is relatively severe or substantial illness persists 12 h after beginning therapy. To avoid confusion, however, most patients should probably be instructed simply to take loperamide and the loading dose of antibiotic followed by standard therapy for 3 days regardless of disease severity or course.

Caution must be exercised when comparing data from the present study with previously reported results of combination therapy. In the present study the median time to cure was 11 h in group A (Table 2), and this compares with 1 h for the same drug regimen in a previous study (7). However, in the present study the most prevalent organism was a *Shigella* sp., compared with ETEC in the previous study. This difference likely reflects the different enrollment priorities of the studies, and since shigellosis is generally a more severe disease than ETEC disease in our studies (8), the difference in causal agents likely explains the differences in responsiveness between studies.

Caution must also be exercised before extrapolating these data to the use of loperamide plus a quinolone. TMP-SMX remains a useful antimicrobial agent for the interior of Mexico (1), and this finding is supported by the susceptibility to TMP-SMX of enteric isolates associated with treatment failure in the present study. However, in many parts of the world quinolones are preferred because of the relative incidence of *Campylobacter* disease and disease caused by other isolates that are resistant to TMP-SMX. One study of loperamide plus ciprofloxacin for 3 days showed a trend toward benefit when ETEC caused disease (14). Another did not find that the addition of loperamide to a single dose of ciprofloxacin was beneficial when *Campylobacter jejuni* was prevalent (12). The efficacy of loperamide plus a large loading dose of a quinolone should be studied further in traveler's diarrhea that occurs in many parts of the world where ETEC is the prevalent organism.

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REFERENCES

1. **Bandres, J. C., J. J. Mathewson, C. D. Ericsson, and H. L. DuPont.** 1992. Trimethoprim-sulfamethoxazole remains active against enterotoxigenic *Escherichia coli* and *Shigella* spp. in Guadalajara, Mexico. Am. J. Med. Sci. **303**:289–291.
2. **DuPont, H. L., and C. D. Ericsson.** Therapy and chemoprophylaxis in travelers' diarrhea. N. Engl. J. Med., in press.
3. **DuPont, H. L., C. D. Ericsson, P. C. Johnson, J. M. Bitsura, M. W. DuPont, and F. J. de la Cabada.** 1987. Prevention of travelers' diarrhea by the tablet formulation of bismuth subsalicylate. JAMA **257**:1347–1350.
4. **DuPont, H. L., C. D. Ericsson, J. J. Mathewson, and M. W. DuPont.** 1992. Five versus three days of ofloxacin therapy for traveler's diarrhea: a placebo-controlled study. Antimicrob. Agents Chemother. **36**:87–91.
5. **DuPont, H. L., C. D. Ericsson, R. R. Reves, and E. Galindo.** 1986. Antimicrobial therapy for travelers' diarrhea. Rev. Infect. Dis. **8**(Suppl.):S217–S222.
6. **Ericsson, C. D., H. L. DuPont, and P. C. Johnson.** 1986. Non-antibiotic therapy for travelers' diarrhea. Rev. Infect. Dis. **8**(Suppl.):S202–S206.
7. **Ericsson, C. D., H. L. DuPont, J. J. Mathewson, M. S. West, P. C. Johnson, and J. M. Bitsura.** 1990. Treatment of travelers' diarrhea with sulfamethoxazole and trimethoprim and loperamide. JAMA **263**:257–261.
8. **Ericsson, C. D., T. F. Patterson, and H. L. DuPont.** 1987. Clinical presentation as a guide to therapy for travelers' diarrhea. Am. J. Med. Sci. **30**:91–96.
9. **Gorbach, S. L., and R. Edelman (ed.).** 1985. National Institutes of Health Consensus Development Conference. Travelers' di-

arrhea. JAMA **263**:257–261.
10. **Kozicki, M., R. Steffen, and M. Schär.** 1985. Boil it, cook it, peel it, or forget it? Does this rule prevent travellers' diarrhoea? Int. J. Epidemiol. **14**:169–172.
11. **Mathewson, J. J., P. C. Johnson, H. L. DuPont, D. R. Morgan, S. A. Thornton, L. V. Wood, and C. D. Ericsson.** 1985. A newly recognized cause of travelers' diarrhea, enteroadherent *Escherichia coli*. J. Infect. Dis. **151**:471–475.
12. **Petruccelli, B. P., G. S. Murphy, J. L. Sanchez, S. Walz, R. DeFraites, J. Gilnett, R. L. Haberberger, P. Echeverria, and D. Taylor.** 1992. Treatment of travelers' diarrhea with ciprofloxacin and loperamide. J. Infect. Dis. **165**:557–560.
13. **Steffen, R., R. Heusser, and H. L. DuPont.** 1986. Prevention of travelers' diarrhea by nonantibiotic drugs. Rev. Infect. Dis. **8**(Suppl. 2):S151–S159.
14. **Taylor, D. N., J. L. Sanchez, W. Candler, S. Thornton, C. McQueen, and P. Echeverria.** 1991. Treatment of travelers' diarrhea. Ciprofloxacin plus loperamide compared with ciprofloxacin alone. Ann. Intern. Med. **114**:731–734.