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Role of a Novel Antidiarrheal Agent, BW942C, Alone or in Combination with Trimethoprim-Sulfamethoxazole in the Treatment of Traveler's Diarrhea

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The efficacy of BW942C, a novel enkephalinlike pentapeptide antidiarrheal agent, was compared with the efficacy of trimethoprim-sulfamethoxazole (TMP-SMX) and the combination of the two agents in a placebo-controlled trial of the 72-h treatment of acute diarrhea. Subjects with diarrhea but without bloody stools or fever greater than 102°F (38.9°C) were enrolled. Administered to 134 U.S. adults with diarrhea that developed shortly after their arrival in Guadalajara, Mexico, BW942C was more efficacious than TMP-SMX in relieving diarrhea and cramps in the first 12 h of therapy, especially among subjects with diarrhea caused by enterotoxigenic *E. coli*. In the BW942C treatment group, 25% of subjects eventually took additional therapy because their diarrhea did not respond to BW942C alone. Neurological side effects such as dizziness and light-headedness occurred more frequently among BW942C-treated subjects. Therapy for 3 days with TMP-SMX provided lasting relief comparable with previously reported 5-day therapy. Use of the combination of both agents provided the benefits of prompt relief afforded by BW942C and lasting relief afforded by TMP-SMX. BW942C might prove to be an agent suitable for the treatment of acute diarrhea, with TMP-SMX reserved for treatment of those who do not respond adequately. The empiric use of the combination of BW942C and TMP-SMX appears appropriate for the treatment of severe nondysenteric disease.

BW942C is a novel, enkephalinlike pentapeptide [Tyr-D-Met-(0)-Gly-pNO$_2$-Phe-Pro-NH$_2$ acetate] with demonstrated antidiarrheal properties in animal models and proven antisecretory activity against enterotoxins of *Escherichia coli* and *Vibrio cholerae* (10). In preliminary animal studies, BW942C appears to have a low abuse potential, limited effects on the central nervous system, a high therapeutic index, and a rapid onset of action. In volunteers with castor oil-induced diarrhea, treatment with BW942C compared with placebo led to a decrease in overall stool frequency, abdominal cramping, nausea, and vomiting. The only adverse effects noted were dizziness and dry mouth that occurred more frequently at high dosages (J. Ryan, J. Leighton, D. Kirksey, and G. McMahon, Clin. Pharmacol. Ther., in press).

This report examines the efficacy and safety of BW942C used alone as an antidiarrheal agent or in combination with an antibiotic, trimethoprim-sulfamethoxazole (TMP-SMX). The hypothesis was that use of BW942C might prove efficacious compared with placebo and that use of the agent in combination with TMP-SMX might afford earlier relief of diarrhea than is already possible with use of TMP-SMX alone. Although in a previous study TMP-SMX was given for 5 days (5), we administered it for only 3 days in this study in an effort to define a more cost-effective use of this antibiotic.

MATERIALS AND METHODS

A total of 134 male and female students, newly arrived in Guadalajara, Mexico, from the United States, were enrolled in a prospective, randomized, double-blind study during the summer of 1983. Subjects who presented to the clinic with acute diarrhea of no more than 48-h duration were eligible for inclusion. Acute diarrhea was defined as the passage of four or more unformed stools during the 24-h period before enrollment, or three unformed stools in 8 h; plus one additional symptom associated with enteric illness (abdominal pain or cramps, nausea, vomiting, or fever). Subjects with a temperature of 102°F (38.9°C) or greater, or with frank blood in the stool, were not enrolled. All subjects gave written informed consent before they were enrolled, and the study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston and by the sponsors of the summer educational programs: the University of San Diego and the University of Arizona.

Subjects were sequentially assigned to one of four treatment groups in a double placebo design: (i) a loading dose of two 10-mg capsules of BW942C and a placebo tablet identical in appearance to double-strength TMP-SMX (160 mg of TMP and 800 mg of SMX); (ii) two placebo capsules of BW942C, identical in appearance to the active drug, plus active TMP-SMX; (iii) both active formulations; or (iv) both placebo preparations. Subjects were randomized in blocks of 12. After the loading doses were taken, one 10-mg capsule of BW942C (or placebo) was taken orally five times per day, and one TMP-SMX tablet (or placebo) was taken orally in the morning and evening. Therapy was continued for 72 h. Subjects were not under dietary restrictions and were maintained as outpatients. All subjects were observed daily at the clinic site for signs of worsening of illness or adverse reactions, and to ensure compliance with the protocol. While the subjects were participating, the use of other antidiarrheal agents was prohibited. Time of medication dosages, consistency and time of passage of all stools, enteric symptoms, and possible adverse reactions to the medications were recorded by each subject in a daily diary for 3 days while medication was taken and for 2 days after medication was

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stopped. Blood and urine were collected from each subject at time of enrollment, and again on the day after cessation of therapy, to assess complete blood counts and differential counts, a battery of liver function tests, serum creatinine, and a urine analysis.

At the time of enrollment, each subject submitted a fresh unformed stool that was examined for the presence of mucus, frank and occult blood, fecal leukocytes, parasites, and enteric pathogens by standard laboratory methods at the field laboratory (7, 9). Five colonies of predominant *E. coli*-like organisms were saved and studied in Houston for the presence of enterotoxigenic *E. coli* by Y-1 adrenal cell assay for heat-labile enterotoxin, and by suckling mouse assay for heat-stable enterotoxin (9). Patients in whom parasites were identified in the initial stool sample were not excluded from further participation in the study. If the patient continued to have diarrhea on day 5, a second stool sample was examined and cultured to determine if the pretreatment pathogen had been eradicated.

For analysis, the subject was considered well when the last unformed stool had been passed. For those patients not already well, improvement was defined as passage of half or less than half the number of unformed stools in a given interval compared with the number passed in a corresponding pretreatment interval. Relapsing symptomatology was determined retrospectively and was defined as a reversal in improvement or a recurrence of symptoms at least 24 h after the patient had passed what appeared to be the last unformed stool. Treatment was considered to have failed when diarrhea worsened clinically within or after the 3-day treatment period or when diarrhea persisted beyond day 5 of the study. Patients declared as treatment failures were withdrawn from the study without breaking the code and were treated with open-label medications, usually TMP-SMX. Failure of treatment was not declared until at least 24 h after the initiation of therapy.

A symptom index was used to aid in analysis (8). Abdominal cramps (or pain), nausea, and vomiting were recorded by the subject as absent (none), mild (tolerable), moderate (distressing), and severe (incapacitating) and assigned an index value of 0, 1, 2, or 3, respectively. Temperature elevation was ranked as follows: 0, less than or equal to 100°F (37.7°C); 1, greater than 100°F and less than 102°F (38.9°C); 2, greater than or equal to 102°F and less than 104°F (40.0°C); and 3, greater than or equal to 104°F. Symptoms were analyzed in 12- and 24-h intervals during therapy and in 24-h intervals after therapy. Mean indices for each symptom for each treatment group were compared for the day of symptoms before enrollment and for each time period during the observation period.

Statistical analysis of data was done by using the Wilcoxon rank sum test with Z corrected for ties, chi-square test, or Fisher exact test, as appropriate. Significance is defined as a P value of ≤ 0.05.

RESULTS

Three subjects were excluded because of failing to return to clinic or to take medication. Five subjects discontinued therapy because of development of adverse reactions: one BW942C-treated subject complained of dizziness, headache, inability to concentrate, and tremulous hands; one TMP-SMX-treated subject developed a rash; and three combination-treated subjects developed hives and dizziness, had puffy eyes, or felt very tired. The four groups were equivalent by age, sex, severity and length of presenting illness, and fecal signs. While no significant differences existed in the etiologic agents identified in stools of the various treatment groups, only the subgroups with disease due to enterotoxigenic *E. coli* or unknown agent were large enough to analyze separately.

The mean times to passage of last unformed stool were 51, 24, 24, and 59 h for the BW942C (n = 31), TMP-SMX (n = 31), combination therapy (n = 31), and placebo (n = 33) groups, respectively. By this criterion, both TMP-SMX alone (P = 0.001) and combination therapy (P = 0.0001) were more efficacious than placebo, and combination therapy was more efficacious than BW942C treatment (P = 0.03). There was no significant difference ($P > 0.05$) between the mean times in the TMP-SMX and BW942C groups.

Because a number of subjects treated with BW942C alone developed relapsing symptoms which effectively increased the mean time to last unformed stool, analysis by this outcome variable does not demonstrate the early benefits of BW942C in reducing the rate of stooling and rendering a significant proportion of persons well and improved compared with placebo. The analysis in Fig. 1 reveals the early effects of the treatment regimens on the frequency of passage of unformed stools (Table 1). The significant differences support the conclusions that BW942C and combination therapy were more efficacious in the first 12 h than was placebo. Furthermore, BW942C was more efficacious than TMP-SMX during the first 12 h of therapy. During day 2 of treatment, TMP-SMX-containing regimens as well as the BW942C regimen were significantly more efficacious than placebo. During day 3 of treatment, combination therapy continued to be associated with significantly less stooling as compared with placebo, and evidence appeared that BW942C was not as efficacious as the other active treatment regimens. During the last day of treatment (day 3 of study) and during days 4 and 5 of study, unformed stools were passed significantly more frequently by patients treated with BW942C alone than by patients treated with TMP-SMX or combination therapy. On day 5 of study, BW942C-treated subjects passed more unformed stools than placebo-treated subjects, implying that a relapse or rebound of passage of unformed stools had occurred in the group treated with BW942C alone.

Because BW942C might improve patients without curing diarrhea the way an antibiotic might, the proportion of well and improved subjects after the first 12 h of therapy and after each day of therapy was examined (Fig. 2). Subjects declared improved during a given interval but who later had relapsing symptoms were removed from the improved category in the later interval analysis. No subject declared well experienced relapsing symptoms during therapy. In the first 12 h, combination therapy led to more well and well-plus-improved subjects than did placebo. Use of TMP-SMX led to more well subjects than did placebo, and use of combination therapy led to more well subjects than did BW942C alone. After 1 day of therapy, more patients were well in all active treatment groups compared with placebo, and combination therapy had led to more cures than had therapy with BW942C alone. The use of BW942C alone or in combination, but not of TMP-SMX alone, was associated with more well plus improved subjects than was use of placebo. By days 2 and 3 of study, TMP-SMX-containing regimens were more efficacious than BW942C alone.

After the first 12 h of therapy, the mean index for cramps was significantly ($P < 0.01$) less in the BW942C (0.48) than in the placebo group (0.88). Therapy with TMP-SMX led to relief of cramps compared to placebo in the 24- to 36-h

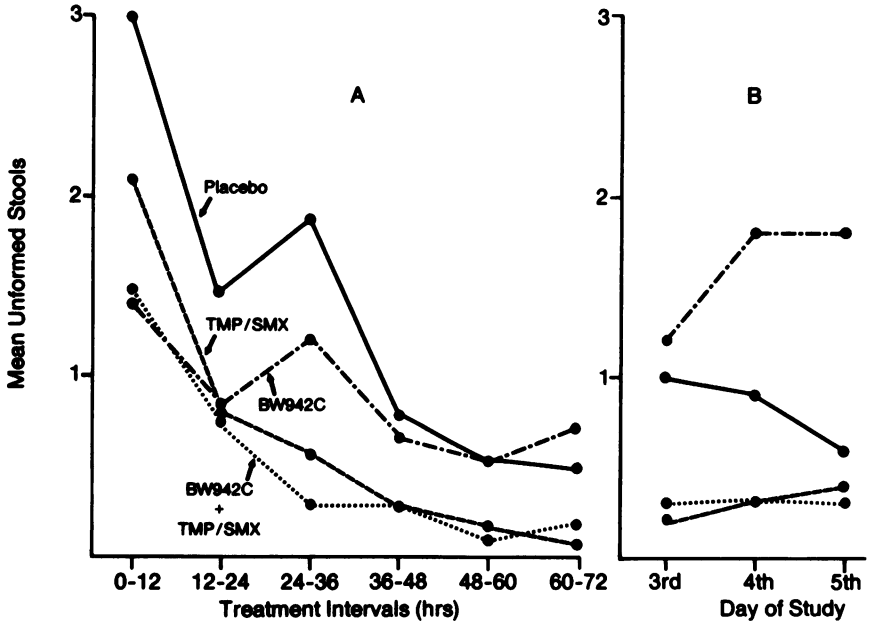

FIG. 1. Comparison of the mean number of unformed stools passed by all subjects by 12-h intervals during 72-h treatment with BW942C (n = 31), TMP-SMX (n = 31), combination therapy (n = 31), or placebo (n = 33) (A) and on the last day of treatment (day 3 of study) and the 2 days after treatment (B). Statistical differences are given in Table 1.

treatment interval (0.23 versus 0.67; P = 0.015) but not earlier. No active regimen significantly relieved nausea or vomiting compared with placebo, but the numbers are too small for significant conclusions.

The efficacy of BW942C-containing regimens in treatment of diarrhea due to enterotoxigenic *E. coli* is demonstrated in Fig. 3 (Table 2). Both BW942C-containing regimens were more efficacious than TMP-SMX in the first 12 h of therapy; however, use of BW942C alone was associated with a significant relapse of diarrhea toward the end of the 72-h period of therapy and during the 2 days after therapy. These data generally are corroborated by the data in Fig. 4, which shows the proportion of subjects well and well plus improved at various times after the beginning of therapy. All three active treatment regimens showed significant efficacy compared with placebo after 12 and 24 h of therapy. Only combination therapy was more efficacious than placebo after 48 and 72 h of therapy. After 72 h of therapy, the TMP-SMX-containing regimens were more efficacious than BW942C alone.

TABLE 1. Statistical differences in comparison of number of unformed stools passed by all subjects[a]

Time interval after beginning of treatment	Treatment[b]	P
0–12 h	BW942C vs placebo	0.0007
	BW942C vs TMP-SMX	0.02
	Combination vs placebo	0.035
24–36 h	BW942C vs placebo	0.01
	TMP-SMX vs placebo	0.003
	Combination vs placebo	0.0001
	Combination vs BW942C	0.02
48–60 h	Combination vs placebo	0.008
	Combination vs BW942C	0.03
60–72 h	TMP-SMX vs BW942C	0.006
	Combination vs BW942C	0.04
3 days	TMP-SMX vs BW942C	0.01
	Combination vs BW942C	0.005
	Combination vs placebo	0.03
4 days	TMP-SMX vs BW942C	0.007
	Combination vs BW942C	0.004
5 days	TMP-SMX vs BW942C	0.007
	Combination vs BW942C	0.001
	Placebo vs BW942C	0.01

[a] See Fig. 1.
[b] More efficacious treatment is listed first.

Among subjects with diarrhea caused by unknown pathogens, significant differences in the percentage of patients who were well or well plus improved at the end of 12 h were confined to more well subjects in the TMP-SMX (67% of 12 subjects) (P = 0.017) and combination therapy (60% of 10 subjects) (P = 0.047) groups than in the placebo group (20% of 15 subjects). At the end of 1 day, the percentage of well patients was still higher in the TMP-SMX (67%; P = 0.039) and the combination therapy (80%; P = 0.012) groups than in the placebo group (27%).

The numbers and etiologic agents of treatment failures and relapses occurring during and after therapy are examined in Table 3. Treatments with placebo and BW942C, respectively, were associated with more treatment failures during therapy compared with TMP-SMX ($P < 0.01$ and $P < 0.05$) or combination therapy ($P < 0.001$ and $P < 0.01$). Among relapses occurring during therapy, significant differences were confined to more relapses in the BW942C group than in the TMP-SMX ($P < 0.05$) or the combination therapy groups ($P < 0.05$). Treatment failures occurring after 72 h of therapy were significantly different ($P < 0.025$) only between the BW942C and TMP-SMX groups. Finally, relapses after therapy occurred more often in the BW942C group than in

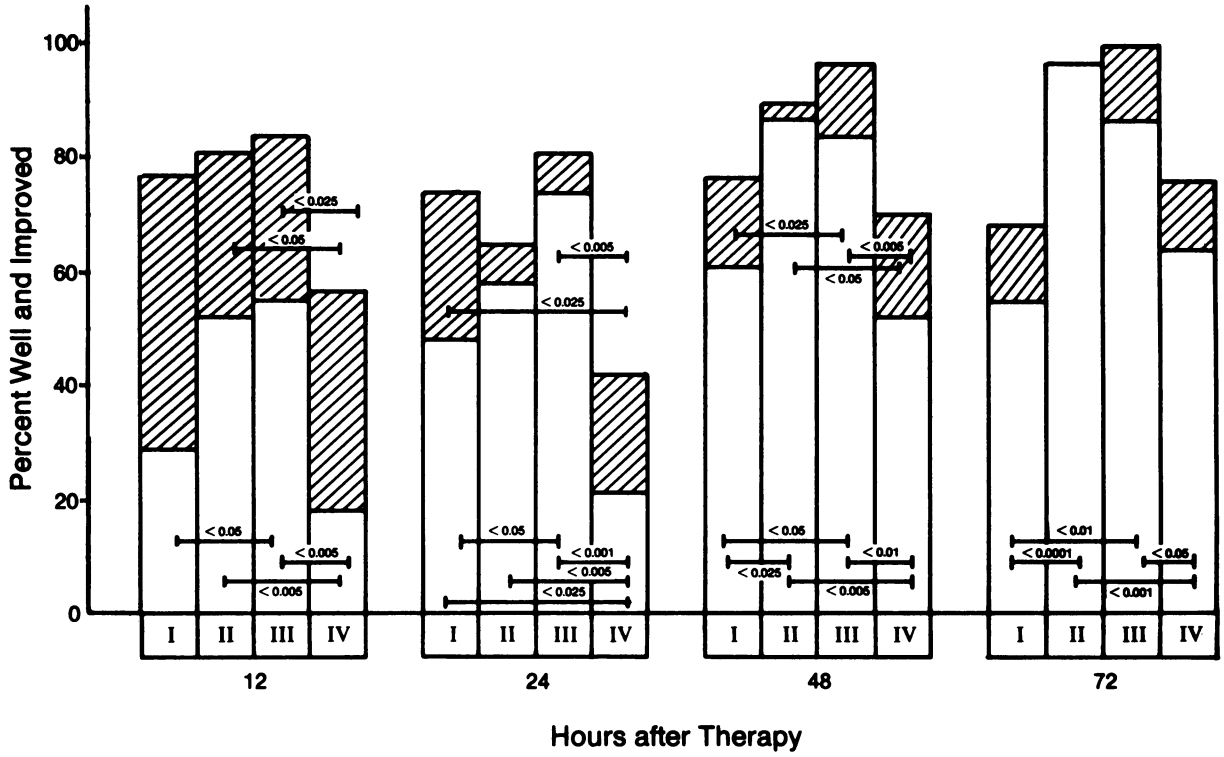

FIG. 2. Comparison of the percentage of all subjects who are well or improved in each treatment group by time after beginning therapy. Treatment group: I, BW942C; II, TMP-SMX; III, combination therapy; IV, placebo. Symbols: ▭, well subjects who have passed their last unformed stool; ▨, improved subjects who are not yet well, but who, during the period of analysis, pass one-half or less the number of unformed stools passed in the period of analysis before treatment. The bottom tier of statistics compares well subjects, and statistics in the top tier compares well plus improved subjects.

the TMP/SMX ($P < 0.005$) or the combination therapy group ($P < 0.001$), and more often in the placebo group than the combination therapy group ($P < 0.05$). The nature of relapsing symptoms following cessation of therapy included the passage of a mean number of six unformed stools per 24 h (range, 3 to 11), the presence of mild and moderate cramps in five subjects and one subject, respectively, and the presence of mild and moderate nausea in two subjects and one

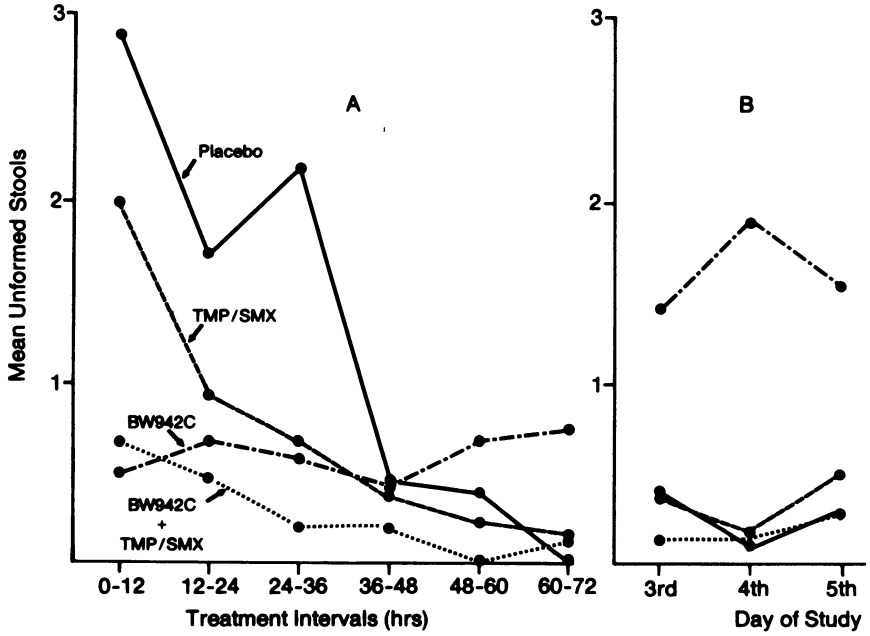

FIG. 3. Comparison of mean number of unformed stools passed by subjects with diarrhea caused by enterotoxigenic *E. coli* by 12-h intervals during 72-h treatment with BW942C ($n = 13$), TMP-SMX ($n = 14$), combination therapy ($n = 16$), or placebo ($n = 15$) (A), and on the last day of treatment (day 3 of study) and the 2 days following treatment (B). Statistical differences are given in Table 2.

subject, respectively. Subjects declined further therapy for these relapsing symptoms except for two subjects, one in the BW942C group with heat-stable-only *E. coli* disease and one in the placebo group with an unknown pathogen, who developed relapsing symptoms during therapy and were later declared treatment failures after therapy was stopped. All patients declared treatment failures were treated, usually with TMP-SMX.

The number of pathogens in each group in Table 3 was too small for significant comparisons. Notably, all persons in the BW942C treatment group with diarrhea due to *Shigella* (n = 4) or *Campylobacter* (n = 1) experienced a failure of treatment or had relapsing symptoms, and all except one subject with *S. flexneri* disease continued to excrete the pathogen on day 5. A number of subjects with enterotoxigenic *E. coli* disease also were declared treatment failures or had relapsing symptoms during and after therapy with BW942C.

A number of BW942C-treated subjects complained of possible side effects such as dizziness, light-headedness, restlessness, sleeplessness, difficulty concentrating, confusion, and euphoria. If each recorded symptom was compared across groups no significant differences occurred, but if these symptoms were lumped as a category, then among those who recorded possible side effects during the first 24 h, 9 of 32 (BW942C group), 2 of 31 (TMP-SMX group), 3 of 33 (combination therapy group), and 1 of 33 (placebo group) subjects had such side effects. The proportion with these side effects is significantly higher in the BW942C group than in the TMP-SMX ($P < 0.025$) and placebo ($P < 0.05$) groups. A total of 12 (18%) of 65 BW942C-treated subjects had these side effects, compared with 3 (5%) of 64 who did not receive BW942C ($P < 0.05$). These complaints resolved within 24 h after therapy was stopped, except for euphoria that persisted for 2 days in one patient. Other than rashes experienced by one person in each of the TMP-SMX-containing regimens, no other possible side effects occurred in excess in the active treatment groups compared with placebo. No significant changes in complete blood counts, differential counts, serum bilirubin, serum glutamic pyruvic transaminase, alkaline

TABLE 2. Statistical differences in comparison of number of unformed stools passed by subjects with diarrhea caused by enterotoxigenic *E. coli*[a]

Time interval after beginning of treatment	Treatment[b]	*P*
0–12 h	BW942C vs placebo	0.0007
	BW942C vs TMP-SMX	0.05
	Combination vs placebo	0.0006
	Combination vs TMP-SMX	0.05
12–24 h	Combination vs placebo	0.05
24–36 h	BW942C vs placebo	0.006
	TMP-SMX vs placebo	0.01
	Combination vs placebo	0.0003
48–60 h	Combination vs BW942C	0.02
	Combination vs TMP-SMX	0.05
	Combination vs placebo	0.03
60–72 h	Combination vs BW942C	0.04
	Placebo vs BW942C	0.02
3 days	Combination vs BW942C	0.005
4 days	TMP-SMX vs BW942C	0.03
	Combination vs BW942C	0.01
	Placebo vs BW942C	0.02
5 days	Combination vs BW942C	0.02
	Placebo vs BW942C	0.05

[a] See Fig. 3.
[b] More efficacious treatment is listed first.

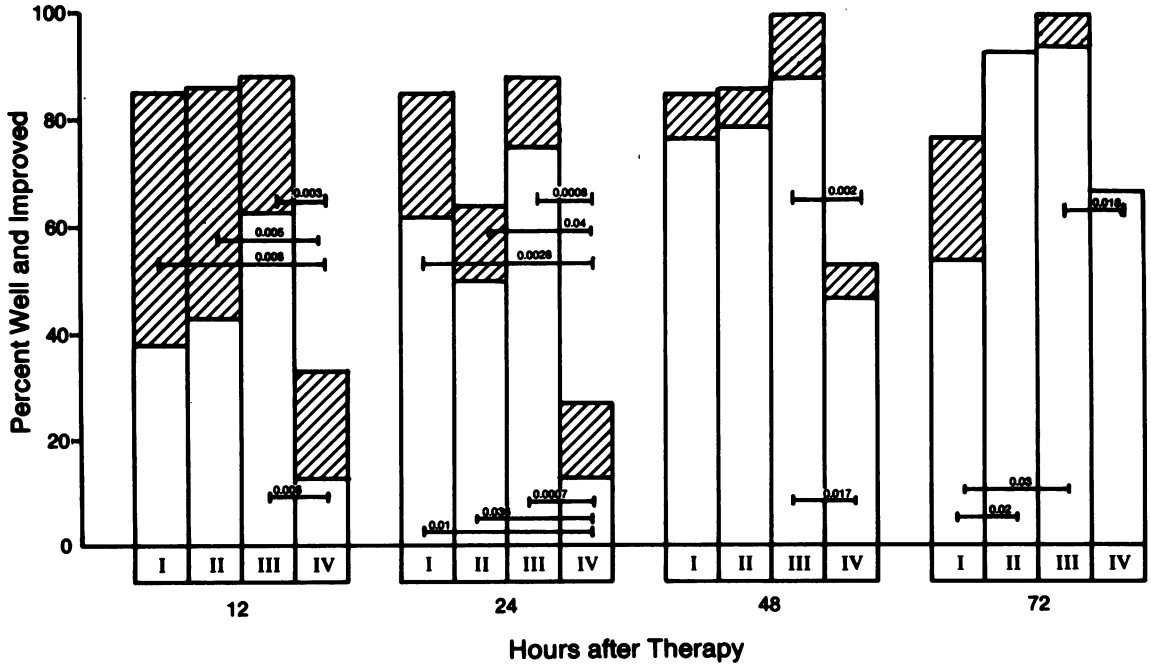

FIG. 4. Comparison of the percentage of subjects with diarrhea caused by enterotoxigenic *E. coli*, who are well or improved in each treatment group by time after beginning therapy. For explanation of Roman numerals, open and hatched bars, and statistics, see legend for Fig. 2.

TABLE 3. Subjects failing treatment or experiencing a relapse of diarrhea and the associated causal agents

Treatment group	No. of failures or relapses/total (%)			
	Treatment failures during therapy	Relapses during therapy	Treatment failures after therapy	Relapses after therapy
BW942C	6/31 (19) *Shigella flexneri*, 3 *Campylobacter* sp., 1 ST-only[a] *Escherichia coli*, 1 *Giardia lamblia*, 1	4/25 (16) ST-only *Escherichia coli*, 2[b] *Shigella flexneri*, 1 *Aeromonas* sp., 1	4/25 (16) ST-only *Escherichia coli*, 1 LT-only[c] *Escherichia coli*, 1 *Aeromonas* sp., 1 Unknown, 1	7/21 (33) Unknown, 4 ST-only *Escherichia coli*, 2 LT-only *Escherichia coli*, 1
TMP-SMX	1/31 (3) ST-only *Escherichia coli*, 1	0/30	0/30	1/30 (3) *Salmonella* sp. plus St-only *Escherichia coli*, 1
BW942C + TMP-SMX	0/31	0/31	1/31 (3) Unknown, 1	0/30
Placebo	7/33 (21) ST/LT *Escherichia coli*, 4 ST-only *Escherichia coli*, 1 *Pleisiomonas* sp., 1 Unknown, 1	1/26 (4) Unknown, 1[d]	3/26 (12) Unknown, 3	3/23 (13) Unknown, 2 ST-only *Escherichia coli*, 1

[a] ST, Heat stable.
[b] One subject was later declared a treatment failure after therapy.
[c] LT, Heat labile.
[d] This subject was declared a treatment failure after therapy.

phosphatase, and creatinine, or urine analysis, occurred in any treatment group.

DISCUSSION

The most appropriate approach to the treatment of traveler's diarrhea remains controversial (11). The present study demonstrates that the antisecretory agent BW942C is helpful in relieving the early symptoms of traveler's diarrhea compared with placebo. Compared with TMP-SMX, BW942C was more efficacious in the first 12 h of therapy in decreasing cramps and the rate of passage of loose stools. This early benefit of BW942C was especially apparent for subjects with diarrhea caused by enterotoxigenic *E. coli*.

Use of BW942C as a single agent might appear to be limited because of subjects who failed treatment or developed relapsing symptoms, both during and after therapy. These results do not preclude the stepwise use of BW942C followed by the use of TMP-SMX in that portion (25% treatment failures in this study) in whom adequate and clinically important relief of symptoms is not realized. The number of subjects with relapsing symptoms who were not declared treatment failures is of scientific interest and might have been significantly higher in the BW942C group than the placebo group in a larger study; none of these patients felt that his or her symptoms deserved additional therapy. However, relapsing symptoms were moderately severe in a few subjects; and out of the study setting, such patients might have desired additional therapy. The reason relapsing symptoms occurred, even during therapy, is not clear. The frequency of passage of loose stools was significantly higher in the BW942C group, compared with placebo, after therapy was stopped, suggesting a true rebound in symptoms caused by the use of a drug that treats symptoms but not the underlying infection. Another possibility is that BW942C is acting, in part, as an antiperistaltic agent, which class of antidiarrheal agents is suspected of prolonging diarrhea caused by invasive organisms (4, 6). However, in this study, relapsing symptoms were also seen in disease due to noninvasive organisms, so this consideration does not explain all of the relapsing symptoms. The finding of a rebound in symptoms in this study using BW942C suggests that the clinical course of treated diarrheal illness should be followed beyond the 48 or 72 h of therapy when the efficacy of symptomatic drugs is being evaluated.

BW942C produced the most rapid response of clinical symptoms; the antimicrobial agent excelled in producing symptomatic relief over time. Furthermore, combination therapy appeared to combine the advantages of both earlier and later relief of symptoms. The most practical role for the use of BW942C might be to institute therapy with both BW942C and TMP-SMX but to continue BW942C only for the first 24 h or so of illness. In any case, the use of two drugs will increase the likelihood of experiencing an adverse drug reaction. In this study, as in others, rash after use of TMP-SMX remains a consistent risk (1, 2, 5, 13). BW942C was reasonably well tolerated. Only one subject discontinued the drug due to dizziness. Symptoms like dizziness and light-headedness appeared to be more common among subjects receiving BW942C, but these symptoms did not require a change in therapy and disappeared quickly when BW942C was stopped. Combination therapy is probably best reserved for patients with severe diarrhea. This is still an important consideration, because 45% of subjects in a study of traveler's diarrhea in Mexico were judged to have severe diarrhea as defined as passage of 10 or more unformed stools in the first 48 h (3).

A benefit of the present study is the demonstration that 3 days of therapy with TMP-SMX was highly efficacious compared with placebo, and this result is comparable with published results employing 5 days of therapy (5). As suggested by the successful treatment of shigellosis with a single dose of tetracycline (12), single-dose antibiotic treatment of traveler's diarrhea might prove reasonable. This cost-effective approach, especially in combination with use of an agent like BW942C for early relief, should be studied.

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