

A Double Blind, Randomized, Placebo-Controlled Study of SP-303 (Provir) in the Symptomatic Treatment of Acute Diarrhea Among Travelers to Jamaica and Mexico

Daniel DiCesare, M.D., Herbert L. DuPont, M.D., John J. Mathewson, Ph.D., David Ashley, Ph.D., Francisco Martinez-Sandoval, M.D., James E. Pennington, M.D., and Steven B. Porter, M.D., Ph.D.

The University of Texas–Houston School of Public Health and Medical School, Houston, Texas; St. Luke’s Episcopal Hospital and Baylor College of Medicine, Houston, Texas; Western Health Area Administration, Ministry of Health, Montego Bay, Jamaica; Universidad Autonoma de Guadalajara, Guadalajara, Mexico; and Shaman Pharmaceutical Company, South San Francisco, California

OBJECTIVE: The study was designed to evaluate the effectiveness of SP-303 (Provir), a plant-derived product with novel antisecretory properties, in the treatment of travelers’ diarrhea.

METHODS: A total of 184 persons from the United States who acquired diarrhea in Jamaica or Mexico were enrolled in a double-blind, placebo-controlled study examining the effectiveness of three doses of SP-303 in reducing illness. Subjects were treated with 125 mg, 250 mg, or 500 mg SP-303 or a matching placebo four times a day for 2 days. Subjects kept daily diaries of symptoms and were seen each day for 3 days. Of the subjects, 169 (92%) were included in the efficacy analysis.

RESULTS: The most common etiological agent identified was enterotoxigenic *Escherichia coli*, found in 19% of subjects. The mean time interval from taking the first dose of medication until passage of the last unformed stool during 48 h therapy (TLUS₄₈) was 38.7 h for the placebo group. TLUS₄₈ was shortened by SP-303: 30.6 h for the 125-mg dose group ($p = 0.005$); 30.3 h for the 250-mg group; and 32.6 h for the 500-mg group ($p = 0.01$). Treatment failures were seen in 29.3% in the placebo group compared with 7.3% ($p = 0.01$), 4.3 ($p = 0.002$), and 9.8 ($p = 0.026$) in the three treatment groups. SP-303 was well tolerated at all doses.

CONCLUSIONS: SP-303 was effective in shortening the duration of travelers’ diarrhea by 21%. This antisecretory approach works directly against the pathophysiology of travelers’ diarrhea and is not likely to potentiate invasive forms of diarrhea or to produce posttreatment constipation. (Am J Gastroenterol 2002;97:2585–2588. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Despite widespread knowledge of the causes of and sources of travelers’ diarrhea, the illness remains a major public health problem. Because of its importance and the often remote setting where illness occurs, travelers are characteristically armed with one or more medications of self-treatment of the disease (1). Bacterial agents are the most common cause of diarrhea in travelers (2). Mucosal loss of fluid and electrolytes represent the most important intestinal mechanism of diarrhea in travelers with diarrhea and in other nontravelers with acute diarrhea regardless of cause (3–5). Considering the important mechanism of diarrhea in this setting, antisecretory drugs represent a new approach to therapy for acute diarrhea. An antisecretory agent working through inhibition of intestinal calmodulin was shown to be effective in reducing the number of stools passed in diarrhea and the duration of illness of international travelers (6).

SP-303 is a novel investigational agent for the treatment of secretory diarrhea. It has been isolated and purified from the plant *Croton lechleri*, which is widely distributed throughout Central and South America. Traditional healers use the plant’s red viscous latex in these areas to treat a number of illnesses including acute diarrhea. SP-303 is a large heterogeneous natural polymer that degrades in the presence of gastric acid. *In vitro* studies using intestinal epithelial cells suggest that the mechanism of action of SP-303 is through inhibition of chloride ion secretion (7). A phase II trial to evaluate the safety and efficacy of three doses of SP-303 in the symptomatic treatment of acute diarrhea among travelers was carried out at sites in Jamaica, Mexico, and along the United States–Mexico border.

MATERIALS AND METHODS

The study was conducted at the following sites: Ocho Rios, Jamaica; Guadalajara, Mexico; Morelia, Mexico; and US

border towns targeting travelers returning from Mexico. Eligible subjects were otherwise healthy adults (>17 yr) who were travelers to Mexico or Jamaica and who presented with a clinical history of abrupt onset of nonbloody diarrhea of 48 h or less duration. Diarrhea consisted of passage of three or more unformed stools during the 24 h before enrollment in association with one or more symptoms of enteric infection (nausea, vomiting, abdominal pain or cramps, excess gas/flatulence, urgency, tenesmus, or fecal incontinence). Subjects were excluded if they met the following criteria: 1) were pregnant or nursing women, 2) had taken more than two doses of any antidiarrheal medication in the 24 h before enrollment, 3) had severe malnutrition, 4) had fever greater than 39°C and/or frank bloody and/or mucus stools, 5) required antibiotics or other prescription therapy for diarrheal disease, 6) had signs or symptoms of intestinal obstruction, 7) were scheduled to depart the study locale before completion of the study, or 8) had received any investigational drug within 30 days or vaccines for prevention of cholera or enterotoxigenic *Escherichia coli* (*E. coli*) within 5 yr before enrollment. Subjects were required to furnish a stool sample, which was verified as being unformed. They were then randomized to receive SP-303 (Provir, Shaman Pharmaceuticals, Inc., South San Francisco, CA) at a dose of 125 mg, 250 mg, or 500 mg, or a matching placebo four times a day for 2 days. They were observed for an additional 24 h.

At the time of enrollment, study procedures included measurement of vital signs, a brief physical examination, and a pretreatment stool sample, which was processed for etiological agents by published methods (2). In brief, all samples were inspected for blood (occult or gross) and mucus, and were then analyzed in our field laboratories in Jamaica or Mexico for presence of fecal leukocytes, parasites, and growth of *Shigella*, *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *Plesiomonas*, and *Aeromonas*. Three to five colonies of *Escherichia*-like organisms from each stool sample were picked, inoculated into peptone stabs, and transported to Houston for testing for production of heat labile and heat stable enterotoxins. *E. coli* strains producing heat labile or heat stable enterotoxins were considered to be enterotoxigenic *E. coli*.

During the 3-day course of the study (2 days of treatment and 1 day of observation), subjects kept a diary in which they recorded time, frequency, and consistency of each bowel movement as well as medications taken. Stools were considered to be formed if they retained their shape, soft if they assumed the shape of a container (like pudding), and watery if they could be poured. Stools of mixed form were classified as the least formed element (8). Every 12 h, subjects rated the severity of each of seven enteric symptoms (nausea, vomiting, abdominal pain or cramps, excess gas/flatulence, urgency, tenesmus, and fecal incontinence). Subjects were followed daily on an outpatient basis and any adverse events were recorded. Severity of diarrheal illness was graded as mild (no change in itinerary required), mod-

erate (change in itinerary required), or severe (patient was disabled by their illness, generally confined to bed). Evaluable subjects were those who were compliant with the protocol and completed the full 48 h of treatment and 24 h of posttreatment observation, or who were dropped prematurely as treatment failures. Three major parameters were used to evaluate treatment efficacy (8). The first parameter was time to last unformed stool in 48 h (TLUS₄₈), defined as the time from taking the first dose of study medication to the time of passage of the last unformed stool during the 48 h of treatment. The second was improvement in diarrheal illness, defined as the number of study subjects who claimed either partial or complete improvement during day 1 or day 2 of therapy. The third parameter was treatment failures, defined as the number of study subjects who were terminated from the study because of continuing severe diarrhea despite taking the study medication.

An exploratory analysis on improvement in GI symptoms was performed by calculating a nonvalidated GI index score (GIS). To compute the GIS, scores of 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) were assigned to each of the seven enteric symptoms. The GIS was then defined as the total score of all seven enteric symptoms during each of the four consecutive 12-h periods over the course of treatment (ranging from 0 to a maximal score of 21 for each period).

Statistical Considerations

In establishing the sample size it was assumed that the maximal response rate in the placebo group would be $\leq 40\%$ compared with a response rate of $\geq 70\%$ in patients receiving SP-303. Based on these assumptions, a sample size of 44 subjects per treatment group would detect this degree of efficacy with a two-tailed type 1 error of 0.05 and a power of 80%. In the analysis of TLUS₄₈, the log rank statistic was used. In the analyses of improvement and treatment failures, the χ^2 test was used. Comparisons of GIS scores were performed by the Wilcoxon test. Regarding safety evaluation, all subjects who received any amount of study medication were included in the safety analysis. Adverse events were tabulated and compared between treatment groups by χ^2 . All tests were two tailed and were performed at the 0.05 significance level. All analyses were performed on an intent-to-treat basis, without excluding assigned cases.

RESULTS

Demographic variables, including age, sex, nationality, ethnicity, body height, body weight, severity of disease pre-enrollment, and number of unformed stools passed in the 24 h before enrollment were comparable for all groups. In Table 1, general characteristics of study subjects are given. A total of 184 patients were enrolled in the study. Of these, 169 (91.8%) were evaluable for efficacy. Fifteen patients were not evaluable because of noncompliance (two patients), concomitant medication needed for another indication (four patients), patient decision (six patients), loss to

Table 1. Patient Demographics in Placebo-Controlled Clinical Trial Evaluating the Effectiveness of SP 303 in Treatment of Travelers' Diarrhea Acquired in Jamaica, Mexico, and US Border Areas

Subjects enrolled	184
Subjects evaluable	169
Jamaica	109
Mexico	47
US border areas	13
Age (yr)	30.0
Sex (% male)	57.6
Ethnicity (% white)	88.6
Unformed stools in prior 24 h (mean)	6.6
Disease severity (% moderate)	46.7

follow-up (one patient), family emergency (one patient), and onset of fever and other symptoms (one patient).

The mean number of unformed stools passed in the 24 h before enrollment was 6.6; the number was slightly higher in the Provir treatment groups compared with the placebo group, but the differences were not statistically significant. In all, 46.7% of the subjects reported the severity of their symptoms as moderate. The results of stool examinations for etiological agents were comparable across all groups. Of all subjects, 28% had at least one pathogenic organism identified in their stool. The most common etiological agent identified was enterotoxigenic *E. coli*, which was found in 19% of subjects.

In Table 2, mean and median TLUS₄₈ values are given for the four treatment groups. The mean number of hours from initiation of treatment until passage of the last unformed stool in 48 h was 38.7 for the placebo group. This value was shortened by Provir: 8.1 h by the 125-mg dose group ($p = 0.005$); 8.4 h in the 250-mg group ($p = 0.0004$); and, 6.1 h in the 500-mg group ($p = 0.01$). Comparable differences were seen in the corresponding medians with reductions from placebo in the three Provir groups by 9 h, 10 h, and 7 h in the three groups, respectively. Similar results were observed when the TLUS was analyzed over the entire 72-h treatment period (data not shown). Partial or complete improvement on day 1 according to the patients' assessments occurred in 65.9% in the placebo versus 85.4% ($p = 0.04$), 91.3% ($p = 0.003$), and 68.3% ($p = ns$) in the three Provir groups. Treatment failures were seen in 29.3% in the pla-

Table 3. Comparison of Exploratory Gastrointestinal Index Scores (GIS) Among Treatment Groups (169 Evaluable Travelers' Diarrhea Treated With SP 303 or Placebo)

Parameter	Treatment Group			
	Placebo	SP 303 125 mg	SP 303 250 mg	SP 303 500 mg
Baseline	5.6	6.2	5.9	5.7
First 12 h	4.2	3.8	3.5*	3.7
Second 12 h	3.2	2.7	2.0†	2.8

* $p = 0.055$.

† $p = 0.008$.

cebo group compared with a rate of failure to respond to treatment in 7.3% ($p = 0.01$), 4.3% ($p = 0.002$), and 9.8% ($p = 0.026$) in the three respective Provir groups. GIS scores were lower in all Provir treatment groups during the first and second 12 h of therapy when compared with the placebo group, despite being equal to or higher than placebo at baseline; only the differences in the 250-mg group were statistically significant (Table 3). With respect to individual symptoms, abdominal pain and urgency were most markedly affected by treatment with Provir (data not shown). We did not collect information to determine a relationship between duration of pretreatment diarrhea and response to therapy.

Provir was well tolerated at all doses administered. The occurrence of adverse events was balanced among the treatment arms, and no adverse event was considered by the investigator to be definitely related to the study drug.

DISCUSSION

In this study, Provir, a drug that blocks intestinal chloride channels as studied *in vitro* in the Ussing chamber (7), was safely administered to adult travelers from the United States who acquired diarrhea while in Jamaica or Mexico. The drug shortened the duration of diarrhea by 21% (8 h) during 48 h of therapy. The response to therapy is even more impressive when considering the rate of partial or complete improvement and failure to respond to treatment in the various groups. Provir, at a dose of 125 mg and 250 mg, produced an 85–91% partial or complete improvement according to the drug-treated subjects, compared with a clin-

Table 2. Comparison of Efficacy Parameters in Evaluation of Treatment Groups (169 Evaluable Travelers' Diarrhea Treated With SP 303 or Placebo)

Parameter	Treatment Group			
	Placebo	SP 303 125 mg	SP 303 250 mg	SP 303 500 mg
Mean TLUS ₄₈	38.7	30.6	30.3	32.6
Median TLUS ₄₈	44	35	34	37
p Value		0.005	0.0004	0.01
Partial or complete improvement (day 1), %	65.9	85.4	91.3	68.3
p Value		0.04	0.003	ns
Treatment failure, %	29.3	7.3	4.3	9.8
p Value		0.01	0.002	0.026

ical response rate of only 66% for the placebo-treated subjects ($p < 0.01$), and treatment failures occurred only rarely in the patients with diarrhea treated with the two optimal doses of active drug, 4–7% versus 29% ($p < 0.01$). Non-diarrhea enteric symptoms were improved by Provir therapy compared with placebo using a GI index score developed for this study. Future study is indicated to determine the validity and usefulness of the GIS used. No clear dose response of Provir was shown to be effective in the present study. The optimal dose seems to be 125–250 mg four times a day for 2 days. A comparison was not made between treatment with Provir and conventional antidiarrheal drugs such as loperamide and bismuth subsalicylate. It is our impression that the effect of the drug was approximately equivalent to what might be achieved with these drugs (9, 10), although a loading dose of these agents may be required for maximal effect of the drug (11).

Antisecretory drugs ameliorate acute diarrhea through a physiological approach. The mechanism of most forms of acute diarrhea seems to be through mucosal secretion (3–5). A number of antisecretory agents are being developed for management of acute diarrhea. They include zaldaride, a selective intestinal inhibitor of calmodulin (6, 11); racecadotril, an enkephalinase inhibitor (12); and Provir. Zaldaride is an intestinal calmodulin-inhibiting drug that has antidiarrheal effects comparable to those of Provir. However, zaldaride is absorbed, and there is concern about cardiovascular effects at high doses. Provir is minimally absorbed explaining its low frequency of side effects. Racecadotril was used to successfully treat children in Peru with viral and nonviral gastroenteritis (12). The very different mechanisms of the drugs that have been evaluated in patients with acute diarrheal disease reflect the various secretory pathways through which acute diarrhea is produced. Antisecretory drugs seem not to have antimotility effects. This antisecretory approach works directly against the enterotoxic pathophysiology of travelers' diarrhea and is likely not to potentiate invasive forms of diarrhea, a rare complication of antimotility drugs (13), or to induce posttreatment constipation, a common complication of therapy with motility-inhibiting drugs. There is reason to think that antisecretory therapy will become the routine therapeutic approach in the future for enterotoxin-mediated diarrhea and other forms of secretory diarrhea, in view of their physiological approach in these conditions.

Reprint requests and correspondence: Herbert L. DuPont, M.D., St. Luke's Episcopal Hospital, 6720 Bertner Avenue, MC 1-164, Houston, TX 77030.

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