Double blind trial of loperamide for treating acute watery diarrhoea in expatriates in Bangladesh

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SUMMARY To determine if loperamide is effective and safe in treating watery diarrhoea, we randomly assigned 50 adult expatriates in Bangladesh with more than three unformed stools in the previous 24 hours and illness of less than 72 hours to receive loperamide or a placebo. On entry into the five day study patients took two capsules (one loperamide capsule=2 mg) and one after each unformed stool up to a maximum of eight per day. The groups did not significantly differ in pretreatment features or pathogens identified. Mean number of stools on study day 1 was 2.6 in the loperamide group and 4.0 in the placebo group ($p=0.035$); on day 2 it was 1.3 versus 3.4 ($p<0.001$). Differences in stool frequencies during the final three study days, or proportion of patients with cramps, nausea, or vomiting on any study day, were not significant. No serious side effects occurred in either group. We conclude that loperamide, by decreasing stool frequency during the early part of illness, may have a role in the symptomatic treatment of this self-limiting disease.

Every year about 16 million people travel from industrialised to developing countries, and one third will develop diarrhoea.¹ In one study 20% of affected travellers were bedridden, and 40% had to alter their schedules.²

This considerable morbidity has prompted efforts to identify symptomatic therapies, which are of four general types. Oral rehydration solutions replace fluid loss but do not influence duration of illness or stool frequency. Some antimicrobial agents decrease the duration of illness and alleviate symptoms.^{3,4} Adsorbants such as bismuth salts, although effective, are impractical because of the large volumes required.^{5,6} Lastly the synthetic opiate like antimotility (and possibly antisecretory) agents diphenoxylate and loperamide hydrochloride⁷ are widely used despite few controlled trials⁸ and concern about their use in patients with shigellosis.⁹

In this study we examined the effectiveness of loperamide compared with placebo in treating watery diarrhoea among expatriates in Bangladesh.¹⁰

Methods

PATIENTS

Patients selection and study design

The International Centre for Diarrhoeal Disease Research, Bangladesh, (ICDDR, B) operates a Travellers' Clinic for expatriates. Patients attending the clinic were eligible for the study if they were 18 years or older, had more than three unformed stools in the previous 24 hours, and had been ill less than 72 hours. Patients were excluded if they had received prior treatment, had visible blood or mucus in their stool, or had a body temperature $\geq 39.0^{\circ}\text{C}$.

After written informed consent, patients submitted a fresh faecal specimen for microscopic examination and microbiologic culture. Patients were assigned a sequential study number and corresponding bottles containing the study drug. Treatment had been previously randomised using a random number table. Both loperamide and placebo were prepared as identically appearing capsules, and staff and patients were blinded as to the treatment being given.

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Patients were given two capsules (each loperamide capsule contained 2 mg) at the start of the study and instructed to take one capsule after each unformed bowel movement, to a maximum of eight capsules per day. They were also provided with sachets of oral rehydration solution. Patients were enrolled in the study between 10 am and 12 noon; the first study day consisted of the 14 to 12 hours until midnight; subsequent study days of the 24 hours from midnight to midnight.

During the five study days patients were requested to keep a diary with the following information: number and character of bowel movements, number of capsules taken, presence of nausea, vomiting, or abdominal cramps, and possible adverse effects of therapy. Patients were also requested to submit additional stool samples for microscopic examination and microbiologic culture on the third and fifth study days.

Patients who had *Shigella* isolated from their stool were withdrawn from the study. No antimicrobial therapy, or other adjunctive therapy, were provided to patients with other enteropathogens.

LABORATORY METHODS

A wet mount of faeces was examined microscopically for ova, cysts, and trophozoites of parasites, and the number of red and white blood cells. If cysts or trophozoites were initially absent, the sediment was examined after formol-ether concentration.¹¹

Stool was cultured for *Salmonella* spp, *Shigella* spp, *Vibrio cholerae*, *Campylobacter*, and *Escherichia coli* using standard methods.¹² Colonies of *E. coli* were tested for the production of heat labile toxin (LT) by the Chinese hamster ovary cell assay¹³ and for heat stable toxin (ST) by the infant mouse assay.¹⁴ Rotavirus was diagnosed using an enzyme-linked immunosorbent assay without blocking.¹⁵

STATISTICAL ANALYSIS

The significance in the difference in means was tested using Student's *t* test. Differences in mean number of stools was tested using a one-tailed test, on the assumption that loperamide might decrease, but could not increase, stool frequency. All other means were tested using a two-tailed test. Differences in proportions were compared using the χ^2 test. All testing was done using Stat-Pac software (Walton Associates, Minneapolis, Minn, USA).

The study was approved by the Ethical and Research Review Committees of the ICDDR, B.

Results

Fifty patients from 11 North American and West European countries were enrolled; 27 received

Table 1 Patients' characteristics on admission

Patients (n)	Loperamide (n=27)	Placebo (n=23)
Men (% of patients)	63	65
Age (yr)*	34.4 (30; 24-65)	37.9 (34; 23-62)
Weight (kg)*	68.4 (69; 52-91)	68.0 (70; 47-91)
Cramps (%)	77	70
Nausea (%)	63	57
Vomiting (%)	4	13
Length of stay in Bangladesh (days)*	145 (60; 3-160)	312 (100; 1-2100)
Duration of diarrhoea before study (hours)*	38.5 (36; 3-72)	36.3 (28; 3-72)
Stools in preceding 24 hours* (n)	7.1 (6; 3-24)	6.9 (6; 3-20)
Stool WBC/HPF*†	8.8 (6; 1-40)	11.2 (8; 0-100)
Stool RBC/HPF*‡	0.7 (0; 0-6)	1.2 (0; 0-6)

*Results given as mean (median; range). †WBC/HPF = white blood cells per high power microscopy; ‡RBC/HPF = red blood cells per high power microscopy. There were no significant differences between treatment groups in any of the characteristics.

loperamide and 23 placebo. Three loperamide treated patients withdrew before the study's completion (two after day 2, the third after day 4); similarly four placebo treated patients withdrew (three after day 2 and the fourth after day 4). For both groups the results before withdrawal were included. Reasons for withdrawal in the loperamide group were lack of improvement in diarrhoea in one patient, severe cramping in a second patient, and infection with *Shigella flexneri* in a third. Three placebo treated patients withdrew because of a lack of improvement in diarrhoea, and the fourth was infected with *Shigella flexneri*. One *Shigella dysenteriae* type 1 infected patient in the loperamide group continued in the study for all five days.

There were no significant differences in characteristics of the groups on admission (Table 1). None of the patients had clinical signs of dehydration. Of the 27 patients in the loperamide group nine submitted three stool samples, 12 two samples, and six one sample; among the 23 placebo patients 15 submitted three samples, six two samples, and two one sample. Enteric pathogens identified from any of these samples are shown in Table 2.

The Figure shows that loperamide patients had significantly fewer stools on study day 1 and 2 than did placebo treated patients. In loperamide treated patients during the five consecutive study days cramps were present in 70%, 65%, 36%, and 16% of the patients; in placebo treated patients the corresponding figures were 78%, 63%, 44%, 40%, and

Table 2 Pathogens identified in any stool collected

Organism	Loperamide (n=27)	Placebo (n=23)
<i>Campylobacter jejuni</i>	2	4
<i>E coli</i> ST	6	2
<i>E coli</i> ST and ST	0	1
<i>E coli</i> LT	1	1
<i>Shigella</i> spp	1	1
<i>Vibrio</i> spp	1	0
Rotavirus	1	0
<i>Giardia lamblia</i>	0	0
<i>Campylobacter jejuni</i> and rotavirus	0	1
<i>Campylobacter jejuni</i> and <i>Shigella</i> spp	1	0
<i>E coli</i> LT and ST and <i>Giardia lamblia</i>	1	0
No pathogen identified	13	13

30%. These differences were not significant. Nausea and vomiting occurred less frequently than cramping and did not significantly differ between the groups. Three loperamide treated patients complained of dizziness. Constipation was a complaint of four patients taking loperamide and of three patients taking placebo.

Discussion

In experimental studies loperamide, a piperidine derivative, slows gut motility by its effects on the intestinal musculature resulting in an increased gut capacity and a delay in intestinal content passage.⁷ Animal studies have suggested that loperamide may also have antisecretory effects.⁷ The clinical importance of these effects, however, remain unclear. Controlled trials differ as to whether loperamide is useful in the treatment of acute infectious diarrhoea.^{6, 8, 16-20} One study in travellers' diarrhoea

demonstrated reduction in stool frequency during the first 48 hours of loperamide treatment and in occurrence of cramping.⁶ Another controlled study of loperamide was conducted among Swedish adults with watery diarrhoea half of whom had recently travelled abroad.⁸ During the five day study period the mean number of stools in loperamide treated patients was five, significantly less than in placebo treated patients but not considered of clinical importance. There was no difference in the number of stools during the first day of the study. Compared with patients in our study, however, patients in that study were less severely ill as determined by stool frequency and had a less acute illness. This perhaps explains the difference in findings between the two studies.

A concern about the use of antimotility agents for infectious diarrhoea is that they may aggravate disease caused by invasive enteropathogens.⁸ Although we excluded patients with clinical symptoms of dysentery, one patient with *S dysenteriae* type 1 infection, and one patient with simultaneously *Shigella flexneri* and *C jejuni* infection, received loperamide. Neither of them developed complications, a finding that is consistent with other studies showing that in adults with infectious watery diarrhoea loperamide does not prolong pathogen excretion or increase severity of illness.^{6, 7} In children with watery diarrhoea, however, complications of loperamide treatment, including shock and enterocolitis, have been reported and we consider it prudent not to provide loperamide treatment to children with acute watery diarrhoea.^{21, 22}

In conclusion, although watery diarrhoea in adult travellers and expatriates in Bangladesh is usually a self-limiting disease, the reduction in stool frequency that loperamide provides may be beneficial to many of these patients.

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Figure Number of stools per day (mean and standard error of the mean) in patients treated with loperamide or placebo during the 24 hours before the start of the study (day 0) and during the five day study period. *p=0.035; **p<0.001.

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