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Treatment of travellers' diarrhoea with fleroxacin: a case study

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A double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of fleroxacin for one or two days as treatment for patients with travellers' diarrhoea. A total of 195 patients who were suffering with acute diarrhoea of less than six days' duration were enrolled. One hundred and fifty-one patients, of whom 49 received placebo, 54 received fleroxacin 400 mg for one day and 48 received fleroxacin 400 mg for two days, were included in the analysis of efficacy. The results showed that fleroxacin was significantly superior to placebo, but that there was no significant difference in terms of efficacy between the one- and two-day regimens. Adverse events, particularly minor neuropsychiatric disturbances such as headache and insomnia, were significantly more common amongst patients receiving active treatment. In conclusion, a single dose of fleroxacin 400 mg could be recommended as self-treatment for visitors to high-risk countries who develop travellers' diarrhoea.

Introduction

Travellers' diarrhoea affects 30–50% of visitors from industrialized to developing countries (Steffen *et al.*, 1983). It is usually mild, self-limiting and of approximately four days' duration, although symptoms may be prolonged for more than seven days in about 10% of cases (Gorbach, 1982; Steffen *et al.*, 1983). Many of the aetiological agents of travellers' diarrhoea have been identified; the most frequently implicated pathogens are strains of enterotoxigenic *Escherichia coli* (ETEC), which have been isolated from 40–60% of those patients with travellers' diarrhoea who have positive stool cultures (Sack, 1990).

Both prophylactic and therapeutic approaches to travellers' diarrhoea have been investigated. Treatment strategies have included fluid replacement, bismuth subsalicylate for symptomatic relief, antimotility drugs such as loperamide, and antimicrobial agents. Considerable controversy surrounds the administration of antibiotics to patients with travellers' diarrhoea. The principal arguments against their use have been the risk of emergence of resistance to the agent prescribed (Farrar, 1985; Murray *et al.*, 1985) and side-effects, particularly allergic reactions. In both 1985 and 1992 it was recommended that antibiotic therapy should be reserved for severe, prolonged or dysenteric illnesses and that mild or moderate diarrhoea could be treated with drugs other than antibiotics, such as loperamide or bismuth subsalicylate (National Institute

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of Health Concensus Development Conference, 1985; Farthing *et al.*, 1992). On the other hand, antimicrobial therapy has been shown to reduce the duration of symptoms to between 24 and 36 h (Ericsson *et al.*, 1987) and, when combined with loperamide, to an even shorter period (Ericsson *et al.*, 1990).

Several antibiotics, including co-trimoxazole, doxycycline and mecillinam, have been considered for the treatment of patients with travellers' diarrhoea (Steffen *et al.*, 1988). However, bacterial resistance to each of these agents has been demonstrated in various parts of the world (Farrar, 1985) and alternatives are, therefore, necessary. In clinical trials where they have been evaluated as either treatment or prophylaxis, ciprofloxacin and norfloxacin have been shown to be effective (Johnson *et al.*, 1986; DuPont, Corrado & Sabbaj, 1987; Ericsson *et al.*, 1987; Lolekha *et al.*, 1988; Scott *et al.*, 1990). Fleroxacin is a new 6,8-difluoro-4-quinolone which also exhibits a broad spectrum of antibacterial activity (Hohl, von Graevenitz & Zollinger-Iten, 1988). It is rapidly absorbed after oral administration, reaches maximum serum concentrations within 1–2 h and has a long elimination half-life (8–12 h) which allows once-daily dosing. Fleroxacin also appears to be more active than norfloxacin in experimental infections (Hof & Fabrig, 1988). This study was undertaken to compare the efficacy and safety of fleroxacin 400 mg, administered orally once daily for either one or two days, with placebo as treatment for patients with travellers' diarrhoea.

Patients and methods

Hotel guests at a resort in The Gambia who were suffering with travellers' diarrhoea were enrolled in this double-blind, randomized, placebo-controlled study after giving written consent. The subjects were of either sex, between 18 and 80 years of age and suffering with an acute diarrhoeal illness of less than six days' duration; diarrhoea was defined as the passage of at least one watery or soft (unformed) stool, accompanied by abdominal cramps, vomiting or nausea. Exclusion criteria were: pregnancy; lactation; a female of child-bearing potential in whom pregnancy could not be excluded; a known or suspected allergy to nalidixic acid or its derivatives; hepatic disease; a history of convulsions; severe concomitant disease; previous participation in clinical trials involving fleroxacin or antimicrobial agents administered in the seven days preceding entry to the study. Other medications, with the exception of malaria prophylaxis, oral contraceptives, antihypertensive agents, hypnotics, oestrogens or vitamin supplements, were not permitted during the trial.

The clinical signs and symptoms of those patients fulfilling the entry criteria were recorded and a stool sample was submitted. Each subject was then randomly assigned to receive fleroxacin 400 mg od for two days (fleroxacin-2 group), fleroxacin 400 mg on day one and the placebo on day two (fleroxacin-1 group) or a placebo od for two days. The doses were administered by a physician who subsequently interviewed the patients at 24, 48 and 72 h. Throughout the 72 h of the study, patients recorded in a diary every 12 h the consistency of their stools and other symptoms.

Baseline stool samples underwent microbiological examination in Houston, Texas within 11 days according to the methods of Morgan *et al.* (1984). All bacterial pathogens were tested for susceptibility to fleroxacin by the Kirby-Bauer disc diffusion method; MICs were determined by a broth microdilution method (National Committee for Clinical Laboratory Standards, 1984).

The primary efficacy parameter was stool consistency 48 h after starting treatment.

Secondary parameters (for exploratory analysis were time to total resolution of diarrhoea and all other symptoms. The investigator, who was blinded throughout the evaluation, assessed the overall clinical outcome at 72 h, defining cure as the absence of symptoms, improvement as reduced frequency and a change of stool consistency from liquid to soft and failure as persistently liquid stools and/or no reduction in frequency. Safety was assessed by recording the adverse events experienced by patients in the three groups.

Statistical analysis was performed by Chi-square or Kruskal-Wallis tests. Where necessary, the Fisher exact test was applied to confirm the results of the Chi-square test. A P value $<0{\cdot}05$ was considered significant. In order to avoid controlling the Type I error for multiple comparisons of the same parameter, orthogonal partitions of the overall test statistics were performed as follows: (i) placebo *vs* fleroxacin-1 or fleroxacin-2; (ii) fleroxacin-1 *vs* fleroxacin-2.

Results

A total of 195 patients, of whom 66 received placebo, 64 received fleroxacin 400 mg for one day and 65 received fleroxacin 400 mg for two days, were entered into the study. Forty-four patients were excluded from evaluation for the following reasons: concomitant treatment (22 patients); protocol violations (nine); incorrect duration of therapy (five); re-entry into the study resulting in exclusion of the second treatment episode from analysis (three); premature withdrawal because of adverse events (three); failure to return for the follow-up interview (two). One hundred and fifty-one patients were therefore included in the analysis of efficacy; of these 151, there were 49 in the placebo group, 54 in the fleroxacin-1 and 48 in the fleroxacin-2 groups respectively. The three groups were similar in terms of male:female ratio (54–59% males) and age (means 36–39 $\pm$ 11–12 years).

The pre-treatment clinical signs and symptoms of travellers' diarrhoea were also similar in the three groups (Table I); mucus diarrhoea was observed most frequently

Table I. Pre-treatment clinical signs and symptoms of patients with travellers' diarrhoea

Sign/symptom		No. (%) of patients placebo group ($n = 49$)	fleroxacin-1 group ($n = 54$)	fleroxacin-2 group ($n = 48$)
Abdominal cramp:	absent	7 (14)	6 (11)	7 (15)
	mild	14 (29)	10 (19)	11 (23)
	moderate	20 (41)	29 (54)	19 (40)
	severe	8 (16)	9 (17)	11 (23)
Nausea:	absent	25 (51)	19 (35)	16 (33)
	mild	13 (27)	14 (26)	14 (29)
	moderate	10 (20)	15 (28)	11 (23)
	severe	1 (2)	6 (11)	7 (15)
Vomiting:	absent	38 (78)	41 (76)	41 (85)
	mild	6 (12)	2 (4)	3 (6)
	moderate	—	3 (6)	2 (4)
	severe	5 (10)	8 (15)	2 (4)

Table II. Enteric pathogens isolated before treatment

Pathogen	No. (%) of pathogens placebo group	fleroxacin-1 group	fleroxacin-2 group
Bacteria total	21	23	25
ETEC	14 (29)	12 (22)	18 (38)
Salmonella spp.	2 (4)	5 (9)	5 (10)
P. shigelloides	1 (2)	2 (4)	1 (2)
Aeromonas spp.	1 (2)	1 (2)	—
Protozoa total	6	11	1
Entamoeba histolytica (cyst)	3 (6)	5 (9)	—
E. coli	2 (4)	4 (7)	—
E. histolytica (trophozoite)	2 (4)	2 (4)	—
Entamoeba hartmannii	—	2 (4)	—
Entamoeba nana	—	1 (4)	—
Giardia lamblia	—	1 (2)	1 (2)
Iodamoeba butschlii	—	1 (2)	—
No pathogen(s)	25 (51)	24 (44)	23 (48)
No specimen received	—	2 (4)	—

amongst patients in the placebo group (27%), compared with seven and 13% in the active treatment groups. Only two patients had blood mixed with the stools.

The distributions of pathogens isolated from the stool samples collected at entry were similar in all three treatment groups (Table II). In approximately half of the samples no pathogen was identified. The most common bacterial pathogens in all three groups were ETEC strains. MICs of fleroxacin for the 61 ETEC isolates varied between 0·06 and 1·0 mg/L, for *Salmonella* spp. ($n = 15$) between 0·13 and 0·5 mg/L and for the *Plesiomonas shigelloides* isolates ($n = 13$) between 0·06 and 0·5 mg/L; the MICs for the three *Aeromonas* spp. were the same (0·25 mg/L). No *Campylobacter* or *Shigella* spp. were isolated.

The effect of treatment on stool consistency is shown in Table III. At 48 h the stools were of normal consistency in 36 of 54 (67%) patients treated with fleroxacin for one day, in 34 of 48 (71%) patients treated with fleroxacin for two days and in 18 of 49 (37%)

Table III. Stool consistency at 12-hourly intervals for patients included in the analysis of efficacy

Interval (h) after starting treatment	Number of patients placebo group ($n = 49$)			fleroxacin-1 group ($n = 54$)			fleroxacin-2 group ($n = 48$)		
	normal	soft	watery	normal	soft	watery	normal	soft	watery
Pre-treatment	—	14	35	—	21	33	—	15	33
0–12	10	9	30	16	8	30	12	6	30
12–24	14	15	20	32	11	11	23	14	11
24–36	21	14	14	35	12	7	31	12	5[a]
36–48	18	17	14	36	16	2[b]	34	13	1[b]

NB· If a patient did not pass any stools in a 12 h period, the stool consistency was taken to be normal (formed).

[a] $P < 0·05$, [b] $P < 0·01$, compared with the placebo group.

Table IV. Assessment of resolution of all symptoms at 12-hourly intervals for patients included in the analysis of efficacy

Interval (h) after starting treatment	No. (%) of patients placebo group ($n = 49$)	fleroxacin-1 group ($n = 54$)	fleroxacin-2 group ($n = 48$)
0–12	6 (12)	4 (7)	2 (4)
12–24	11 (22)	22 (41)	7 (15)
24–36	14 (29)	21 (39)	21 (44)
36–48	14 (29)	28[a] (52)	24[a] (50)

Resolution of all symptoms is defined as: absence of abdominal cramps, nausea, vomiting, diarrhoea with blood and diarrhoea with mucus; normal stool consistency; temperature <37·5°C (if recorded).
[a] $P < 0{\cdot}05$ compared with placebo group.

patients who received the placebo; the differences in response rates between the fleroxacin-treated groups and the placebo group were statistically significant ($P < 0{\cdot}01$), but the difference between the two fleroxacin groups was not. Moreover, unformed stools produced by most of the fleroxacin-treated patients had become soft, whereas those produced by patients in the placebo group were watery or soft in equal numbers. The effects of fleroxacin on stool consistency were similar when the patients were grouped into those from whom a bacterial pathogen was isolated at entry and those from whom a pathogen was not isolated.

The time to complete resolution of diarrhoea was shorter in the two fleroxacin-treated groups; by 36 h, symptoms had resolved in 14% of patients in the placebo group and in 50% of patients in both groups given fleroxacin. By 48 h, these figures had increased to 37%, 67% and 71% for the placebo, fleroxacin-1 and fleroxacin-2 groups respectively. The mean time to production of the last unformed stool was 27·0 and 27·3 h in the two fleroxacin groups and 45·1 h in the placebo group.

An assessment of the resolution of all symptoms at 12-hourly intervals is shown in Table IV. At 48 h, 14 of 49 (29%) of placebo-treated patients experienced resolution of all symptoms compared with 28 of 54 (52%) and 24 of 48 (50%) of patients treated with fleroxacin for one and two days respectively. The differences between the fleroxacin and placebo groups were statistically significant ($P < 0{\cdot}05$), but the difference between the two fleroxacin groups was not.

The investigators' evaluation of clinical response at 72 h is given in Table V; there

Table V. Investigator's evaluation of clinical response at 72 h

Response	No. (%) of patients placebo group ($n = 49$)	fleroxacin-1 group ($n = 54$)	fleroxacin-2 group ($n = 48$)
Cure	23 (47)	43 (80)	39 (81)
Improvement	15 (31)	6 (11)	7 (15)
Failure	10 (20)	4 (7)	2 (4)
Not assessable	1 (2)	1 (2)	—

Table VI. Adverse events and their relationships to the trial drugs

Adverse events	No. of events reported and relationship to trial drugs								
	placebo group			fleroxacin-1 group			fleroxacin-2 group		
	remote	possible	probable	remote	possible	probable	remote	possible	probable
Gastrointestinal (nausea, vomiting etc.)	2	7	1	4	14	8	7	15	7
Nervous system (insomnia, headache etc.)	1	2	—	3	4	3	4	7	8
Musculo-skeletal (arthralgia, myalgia)	1	3	—	4	4	—	6	6	—
Skin (rash, pruritus etc.)	—	—	1	1	—	—	1	4	1
General (fatigue, pain etc.)	5	11	2	1	10	3	5	14	—
Miscellaneous	—	—	—	2	6	—	—	—	—
Total	9	23	4	15	38	14	23	46	16

was a statistically significant difference in cure rates between the fleroxacin-treated groups and the placebo group ($P < 0{\cdot}01$). Over 80% of patients treated with fleroxacin were considered cured, compared with 47% of patients given the placebo. There was no significant difference in the proportions of patients who were cured, improved or not improved according to whether a bacterial pathogen had or had not been identified. Of the two patients who failed to respond, and from whom a pathogen was isolated, one was infected with a strain of ETEC and the other with both an ETEC and a *Salmonella* spp.

Safety was evaluated in 190 patients, of whom 64 received placebo, 61 were in the fleroxacin-1 group and 65 were in the fleroxacin-2 group. Adverse events judged by the investigator to be remotely, possibly or probably related to the trial drugs (Table VI) were reported by 25 of 64 (39%) patients in the placebo group (36 incidents), 36 of 61 (59%) in the fleroxacin-1 group (67 incidents) and 42 of 65 (65%) in the fleroxacin-2 group (85 incidents); the differences between the placebo and fleroxacin groups were statistically significant ($P < 0{\cdot}01$). The most frequently reported adverse event was fatigue, which might have been accounted for by the gastrointestinal infection itself; this was observed in 27%, 23% and 28% of patients in the placebo, fleroxacin-1 and fleroxacin-2 groups respectively. Other adverse events, which included nausea, constipation, insomnia, headache and dizziness, were more common in the two fleroxacin groups. Insomnia, skin reactions (rash, pruritus, sunburn) and arthralgia were reported more frequently by patients who received fleroxacin for two days. Four patients withdrew prematurely from the study because of adverse events. Two patients (one with erythema, one with abdominal pain and constipation) were in the placebo group and two (one with sunburn and one with insomnia, myalgia and prickly skin) were in the fleroxacin-2 group. None of the adverse events was considered serious.

Discussion

The 400 mg dosage of fleroxacin was chosen for this study because the serum concentrations achieved after a single oral dose (C_{max} $4{\cdot}24 \pm 1{\cdot}08$ mg/L) (Weidekamm *et al.*, 1988) are higher than the MIC_{90}s (0·5 mg/L) for those pathogens usually associated with gastrointestinal tract infection (Manek, Andrews & Wise, 1986). Ten to 15% of fleroxacin is excreted unchanged in the faeces, and only 0·5% is in the form of the *N*-demethyl derivative; this corresponds to a daily excretion of approximately 30 mg (7·5%) of a 400 mg dose. Assuming faeces are produced at the rate of 200 g/day, fleroxacin concentrations would normally be 100–200 μg/g. Additionally, 2·7% of a dose is recoverable from bile obtained via a T-tube drain during a period of 24 h. The mean maximum biliary concentrations are $\geqslant 10$ mg/L following a single oral dose of 400 mg. Thus, the concentrations of active drug achieved in the gastrointestinal tract substantially exceed the MICs of important bacterial enteropathogens.

Treatment was limited to one or two days because previous studies had shown excellent results after equally short periods (Ericsson *et al.*, 1990; Petrucelli *et al.*, 1992) and because self-treatment should be limited to 48 h (Farthing *et al.*, 1992). A control group was considered justifiable on the grounds that travellers' diarrhoea is self-limiting; its inclusion also enabled a more reliable assessment of the safety profile of fleroxacin.

Approximately 80% of fleroxacin-treated patients were cured after 72 h, compared

with 47% of patients who received the placebo. These results were similar to those of a previous study in which 74% of norfloxacin-treated patients were cured by 72 h compared with 38% in the placebo group (Wiström *et al.*, 1989). Time until production of the last unformed stool was shorter than that reported in a study of a different patient population in which ciprofloxacin was used (Petrucelli *et al.*, 1992).

In the present study, pathogens were not isolated from 47·7% of patients; this was higher than previously reported rates where the faeces of 20–40% of patients with travellers' diarrhoea failed to yield an enteric pathogen (Sack, 1990). Our low isolation rate may be accounted for by the long interval between collection and microbiological examination of the specimens, which may have reduced the likelihood of detecting *Campylobacter* spp. in particular. Additionally, it has been suggested that previously unrecognized, antibiotic-susceptible bacteria may play an aetiological role, the magnitude of the effect of antibiotics being greater than would otherwise be expected from their activities against the known bacterial pathogens (Sack, 1990). No attempt was made to exclude viral causes of travellers' diarrhoea in this study.

Antimicrobial susceptibility *in vitro* does not invariably predict a favourable clinical response (Keusch, 1988) and persistence of the pathogen does not correlate with prolonged diarrhoeal symptoms (Ericsson *et al.*, 1988). For this reason, test-of-cure stool cultures were not obtained. This was justified by the observation that the effects of fleroxacin on stool consistency were similar, irrespective of whether or not pathogens were isolated from pre-treatment faecal samples.

Short-term self-treatment with antibiotics for travellers' diarrhoea has distinct advantages over chemoprophylaxis as both antibiotic usage and treatment time are markedly reduced. Furthermore, it may be unacceptable to some travellers to take antibiotics for prolonged periods.

The fluoroquinolones are highly active *in vitro* against a broad range of enteric pathogens, including ETEC, *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Campylobacter jejuni* and *Vibrio* spp. They are also well tolerated and have a reduced capacity for promoting the development of resistance (Ericsson *et al.*, 1987; Scott *et al.*, 1990). Norfloxacin, in a dosage of 400 mg daily, has been shown to be effective as short-term prophylaxis for acute diarrhoea (Scott *et al.*, 1990). Similarly, ciprofloxacin (500 mg daily) conferred 94% protection against the onset of travellers' diarrhoea (Reves *et al.*, 1988). However, in another study, ciprofloxacin and co-trimoxazole were equally effective as treatment for travellers' diarrhoea in American students visiting an area of Mexico where trimethoprim resistance amongst bacterial enteropathogens was low (Ericsson *et al.*, 1987). The average durations of diarrhoea were 29, 20 and 81 h for patients given ciprofloxacin, co-trimoxazole and placebo respectively.

Fleroxacin is a new fluoroquinolone with both a broad antibacterial spectrum which includes the organisms commonly causing diarrhoea (Hohl *et al.*, 1988) and superior pharmacokinetics (Weidekamm *et al.*, 1988). In the present study, 400 mg of fleroxacin was administered once daily for one or two days. Approximately 50% of patients treated with this agent were relieved of all symptoms by 48 h, compared with only 29% of those who received a placebo. Adverse events were reported by 39%, 59% and 65% of patients in the placebo, fleroxacin-1 and fleroxacin-2 groups respectively. None of these was considered serious and only two patients in the fleroxacin-2 group withdraw from the study prematurely as a result of adverse reactions. Fatigue was the most frequently recorded adverse event, but was reported by similar numbers of patients in each of the three groups. Other adverse events, including insomnia, skin rash, erythema, sunburn

and arthralgia, were reported more often by patients in the fleroxacin-2 group than by those in the fleroxacin-1 group.

Fleroxacin was well tolerated when given as a single 400 mg dose, and since the one- and two-day regimens were comparable with respect to efficacy, a single dose of fleroxacin would therefore be the treatment of choice for patients with travellers' diarrhoea, expecially in those areas of the world where resistance to other antibiotics is high. Further studies involving larger numbers of patients will be required to confirm our findings and to evaluate the benefits of combining fleroxacin with loperamide.

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