

## Comparison of Norfloxacin and Nalidixic Acid for Treatment of Dysentery Caused by *Shigella dysenteriae* Type 1 in Adults

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**A severe epidemic of dysentery began late in 1979 in northeast Zaire and spread to Rwanda, Burundi, and Tanzania. The epidemic strain is a multiply resistant *Shigella dysenteriae* type 1, which acquired resistance against trimethoprim and more recently against nalidixic acid in the course of the epidemic. A comparative open trial in Rwandan adults with Shiga dysentery involved 18 patients treated with norfloxacin at 400 mg twice daily and 12 patients treated with nalidixic acid at 1 g three times daily for 5 days. All isolates showed in vitro susceptibility to both drugs. Though norfloxacin eliminated *Shigella* organisms from stools more rapidly than nalidixic acid, its clinical superiority did not reach the level of significance. Norfloxacin is a promising drug and is more effective than nalidixic acid in the treatment of multiresistant shigellosis.**

It is widely accepted that antibacterial agents are indicated for the treatment of severe shigellosis. Ampicillin and cotrimoxazole are currently regarded as the drugs of choice, although their effectiveness has been seriously curtailed by the worldwide emergence of multiply resistant strains.

An epidemic caused by the Shiga bacillus originated late in 1979 in northeast Zaire (7) and subsequently spread to Rwanda (3), Burundi (26), and Tanzania (19), causing high morbidity and mortality.

The epidemic strain (9) was initially resistant to ampicillin, tetracycline, chloramphenicol, sulfonamide, and streptomycin. This led to the widespread use of co-trimoxazole as the agent of choice. Since September 1981 a majority of strains from Zaire, Rwanda, and Burundi have also acquired resistance to trimethoprim (8). Late in 1981, nalidixic acid was introduced as first-line therapy for shigellosis, and this was soon followed by a drop in the fatality rate. In April 1982 the first nalidixic acid-resistant strain was isolated in Kivu, Zaire (10, 16). Several such strains have now emerged, and as of July 1985 the majority of *Shigella dysenteriae* isolates in that area were nalidixic acid resistant. Their isolation from pre-treatment stool specimens indicates that these strains are already spreading in the community in that part of Zaire.

Since the nalidixic acid-resistant strains retained full in vitro susceptibility to norfloxacin, we decided to compare both drugs in a field trial in Rwanda, where nalidixic acid resistance had not emerged at that time.

### MATERIALS AND METHODS

The field drug trial was performed at the 172-bed hospital of Gisenyi, the administrative and medical capital of a prefecture with 615,000 inhabitants. Gisenyi is situated at an altitude of 1,500 m on the Rwandan shore of the volcanic lake Kivu. It enjoys a temperate climate with heavy rainfall. The surrounding area is very densely populated. Cattle raising and agriculture are the main activities apart from local trade with nearby Zaire. Due to the volcanic nature of the soil, wells and toilets are scarce and sanitation is poor.

The Shiga epidemic reached the Gisenyi area in the first week of February 1985, attained its peak in March, and

returned to an endemic level in May. During the peak 7-week period, 442 patients with dysentery were admitted to the Gisenyi hospital; *S. dysenteriae* type 1 was isolated from the stools of 412 of them. Although people of all ages were affected, the highest incidence was in the age category of 20 to 24 years, with a slight preponderance of males (55%). The case-fatality rate was 2%.

Patients admitted to the trial were all over 15 years old and presented with bloody mucoid stools. The average duration of illness before admission was 3 to 4 days. Patients with a history of dysentery for more than 5 days were removed from the protocol.

Patients were hospitalized for a minimum of 5 days or until clinically cured. Stool cultures were performed on the day of admission and on days 3 and 5 of the hospital stay. Primary plating was done on MacConkey and salmonella-shigella agars, and standard methods were used for the isolation and identification of *Shigella* organisms. All isolates were submitted to the Department of Microbiology at the University Hospital of Louvain, Louvain, Belgium, for confirmation and serotyping. Susceptibility tests were performed with the standardized disk diffusion test, and MICs were determined by agar dilution in Mueller-Hinton agar (BBL Microbiology Systems) with inocula of  $10^5$  to  $10^6$  CFU per spot delivered by a multipoint inoculator. The antibiotics were tested in twofold serial dilutions at concentrations ranging from 0.004 to 32  $\mu\text{g/ml}$ . The plates were incubated overnight at 36°C, and the MIC was read as the lowest concentration of antibiotic which inhibited visible growth. A wet fecal smear was examined microscopically for parasites. No other laboratory investigations could be performed.

Patients were assigned to norfloxacin or nalidixic acid treatment by the day of admission. Patients admitted on 4 and 18 February received a 400-mg tablet of norfloxacin twice daily for 5 days. Patients entering on 26 March received a 1-g tablet of nalidixic acid three times a day for 5 days.

Clinical response was monitored by keeping daily records of the temperature, the nature and number of stools, and the possible adverse effects that could be attributed to the drug. No other antibiotics or antidiarrheal drugs were administered. Some patients received mebendazole or antiamoebic

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TABLE 1. Comparability of treatment groups

Treatment group (n)	Infectious agent		Mean age (range) (yr) <sup>a</sup>	Sex <sup>b</sup>		Mean no. of stools on admission (range) <sup>c</sup>	No. of patients with associated parasites	No. of associated parasites
	<i>S. dysenteriae</i> type 1	Other shigellae		M	F			
Norfloracin (18)	17	2 <sup>d</sup>	25.7 (16-50)	10	8	24.8 (9-60)	6	15 <sup>e</sup>
Nalidixic acid (12)	11	1	29.7 (16-52)	8	4	30.2 (6-90)	4	5 <sup>f</sup>

<sup>a</sup> Difference between the groups was not significant by the Student *t* test.

<sup>b</sup> Difference between the treatment groups was not significant by the Fisher exact probability test.

<sup>c</sup> Difference between the groups was not significant by the Mann-Whitney U test.

<sup>d</sup> One patient had a double infection (see the text).

<sup>e</sup> The parasites found in patients treated with norfloracin were: *Ascaris* sp., four patients; *Trichuris* sp., six patients; *Strongyloides* sp., one patient; *Entamoeba histolytica*, two patients; *Taenia* sp., one patient; and *Pentatrichomonas* sp., one patient.

<sup>f</sup> The parasites found in patients treated with nalidixic acid were (one isolate each): *Balantidium* sp., *Ascaris* sp., *Trichuris* sp., *Strongyloides* sp., and *Pentatrichomonas* sp.

drugs whenever required. Oral rehydration fluid was given in case of dehydration.

Patients were considered to be clinically cured when they passed three or fewer formed stools per day. Cured patients were discharged on day 5 or on the day that they met the criterion for cure.

### RESULTS

Of the 30 patients who met the criteria for admission to the trial, 18 were assigned to receive norfloracin and 12 were assigned to receive nalidixic acid. The age, sex distribution, and severity of illness as reflected by the number of stools on the day of admission, were comparable in the two treatment groups (Table 1). There was a slightly higher proportion of females, a slightly lower mean age, and a somewhat lower number of stools on the admission day in the norfloracin group. The differences, however, were small and not statistically significant.

All 30 patients had a pretreatment stool culture positive for *Shigella*; 28 were positive for a strain of *S. dysenteriae* type 1 resistant to ampicillin, chloramphenicol, tetracycline, streptomycin, sulfonamide, and trimethoprim. One patient in the norfloracin group was infected with a strain of *S. dysenteriae* type 2 which was only resistant to tetracycline, while another had a double infection with *S. dysenteriae* type 1 and *Shigella flexneri* type 2a (resistant to tetracycline and chloramphenicol). One patient in the nalidixic acid group yielded a strain of *S. flexneri* type 6 (biovar boyd 88) resistant to tetracycline, streptomycin, and sulfonamide.

The results of follow-up cultures and clinical response on days 3 and 5 are shown in Table 2. Only 10 patients (5 in each group) were not cured clinically by treatment day 5. They remained in the hospital until clinical cure was attained. The last patient from both groups was discharged on day 9, and there were no deaths. Stool cultures were invariably negative on day 3 with norfloracin treatment, against only 3 of the 12 stools with nalidixic acid treatment.

The antibiotic susceptibility of strains reisolated from follow-up specimens did not differ from that of the original isolates. All strains were fully susceptible to norfloracin and nalidixic acid. MIC for norfloracin ranged from 0.015 to 0.06 µg/ml, with a MIC for 90% of the strains of 0.03 µg/ml. All isolates were inhibited by 1 µg of nalidixic acid per ml (MIC for 90% of the strains, 1 µg/ml), with the exception of the two isolates of *S. flexneri*, which required 2 µg/ml for complete inhibition of growth.

### DISCUSSION

A severe epidemic of dysentery began late in 1979 in Central Africa. The first cases were documented in northeast

Zaire (7), and the epidemic subsequently spread to the eastern part of the country and to Rwanda, Burundi, and Tanzania. The epidemic strain was identified as *S. dysenteriae* type 1, and plasmid profiles of isolates from Zaire and Rwanda showed great similarity with strains isolated in Somalia in 1976 (9).

The outbreak was of unusual severity, and a case-fatality rate of nearly 50% was reported from the rural areas where the epidemic originated (7). After co-trimoxazole became the standard treatment, mortality in hospitalized patients decreased to 5.6% (7) to 2.4% (17). Co-trimoxazole was replaced as drug of choice by nalidixic acid in 1981. Since September 1981 more than 10,000 patients in Kivu, Zaire, were treated with nalidixic acid (16), and it took 4 years for resistance to this drug to become a problem in that area.

Nalidixic acid has been used with apparent success as an alternate drug for the treatment of endemic shigellosis since 1965. A cure rate of 88.5% was obtained in the treatment of *Shigella sonnei* dysentery in Liverpool, with a dosage of 1 g every 6 h for 5 days (20). This was soon followed by a report

TABLE 2. Bacteriological and clinical treatment results

Treatment group (n)	No. of culture-positive patients on day		No. of patients with diarrhea on day <sup>a</sup>		% Diminution of no. of abnormal stools after day		No. of patients with adverse effects <sup>b</sup>
	3 <sup>c</sup>	5 <sup>d</sup>	3	5	3 <sup>e</sup>	5 <sup>f</sup>	
	Norfloracin (18)	0	0	16	5	63	
Nalidixic acid (12)	9	2	11	5	34	75	2 <sup>h</sup>

<sup>a</sup> Diarrhea was defined as three or more liquid or mucosanguinolent stools per day. The difference between the two groups was not significant by the Fisher exact probability test.

<sup>b</sup> The difference in the number of patients between the two groups was not significant (Fisher exact probability test, *P* = 0.42). Also not significant was the difference in total cases of adverse effects (Fisher exact probability test, *P* = 0.14).

<sup>c</sup> The difference between the two groups was significant (Fisher exact probability test, *P* < 0.0001).

<sup>d</sup> The difference between the groups was not significant (Fisher exact probability test, *P* = 0.15).

<sup>e</sup> The difference between the groups was not significant (Mann-Whitney U test, *P* = 0.15).

<sup>f</sup> The difference between the groups was not significant by the Mann-Whitney U test.

<sup>g</sup> Adverse effects experienced by patients on norfloracin were nausea (one case), vomiting (four cases), palpitations (three cases), headache (one case), and fatigue (one case).

<sup>h</sup> Adverse effects experienced by patients on nalidixic acid were vomiting (two cases) and hiccuping (one case).

on the appearance during treatment of drug-resistant variants (15).

There are few controlled studies on the efficacy of nalidixic acid in the treatment of shigellosis. In one trial the activity of the drug was found to be intermediate between those of ampicillin and a placebo (13). In a recent placebo-controlled, double-blind study in Swedish travelers (14), the cure rate with nalidixic acid (dosage, 1 g four times a day for 7 days) was 72% versus 21% with the placebo.

With the recent increase of trimethoprim resistance in *Shigella* organisms isolated in several continents (12), nalidixic acid became the first-line therapy for shigellosis in some temperate and tropical countries (2, 4, 18, 21, 23), with unanimous claims for success.

Our recent experience in Zaire and a report from India (22) on the massive emergence of nalidixic acid-resistant *S. dysenteriae* type 1 prompted us to switch to one of the newer quinolones and to compare its activity with that of nalidixic acid in an area where the epidemic strain was still susceptible to this drug.

The new fluorinated piperazinyl quinolones have markedly enhanced in vitro activity against enterobacteria and against all other enteric pathogens with the exception of *Clostridium difficile* (5, 6, 11, 25). Some of the newer analogs are 100-fold more active than nalidixic acid, and resistant clones are less likely to appear with these drugs, which remain active against nalidixic acid-resistant variants. The new quinolones are well absorbed after oral administration and reach therapeutic concentrations in the serum and in the stool. Those features, combined with a long elimination half-life, make them particularly attractive for treating bacterial gastroenteritis.

Up to now there has been only limited clinical experience with the new quinolones in the treatment of shigellosis. In Brazil, a comparative study with co-trimoxazole showed norfloxacin in a dose of 400 mg twice or three times daily to be efficacious and safe in the treatment of acute enteritis caused by different species of *Shigella* (C. V. F. de Godoy, H. Boruchowsky, and L. S. Hinaishi, Abstr. 270 Intern. Congr. Infect. Dis. Cairo, p. 75, 1985). A multicenter open trial comparing norfloxacin co-trimoxazole for the treatment of bacterial enteritis was recently reported from Mexico (24). The investigators concluded that norfloxacin was at least as effective as co-trimoxazole for the treatment of shigellosis.

Our own results in the treatment of severe dysentery caused by a multidrug-resistant Shiga bacillus confirm the experience reported in Latin America. Norfloxacin in a dose of 400 mg given twice daily for 5 days eradicated *Shigella* organisms from the stools of all patients by treatment day 3, a result which was statistically better than that obtained with a 5-day course of nalidixic acid at 1 g three times per day. The clinical superiority of norfloxacin however, was less impressive and did not reach statistical significance in view of the limited number of patients treated with nalidixic acid. With both drugs adverse effects were mild and comparable in frequency. Moreover, their nature let us suppose that they were less likely related to the drug than to the disease itself.

The less satisfactory results obtained with nalidixic acid possibly be related to the dosage of 3 g daily, which is inferior to the 4 g recommended by other authors. We used the lower dosage to avoid gastric intolerance in severely ill patients, whose average body weight was lower than that of well-nourished European subjects.

Our choice of norfloxacin from among a half dozen new quinolones was dictated by the fact that it was the first analog of this class to be licensed and commercially available

in a number of countries. Other analogs, such as ciprofloxacin, have a higher intrinsic in vitro activity against *Shigella* (1).

Our results confirm the enthusiasm generated by the previous reports on the efficacy and safety of norfloxacin in the therapy of infectious diarrhea. More clinical trials will be needed to define its optimal use, particularly its minimum effective dose and length of treatment. The place of other analogs in the treatment of shigellosis will also have to be defined. The long-term place of quinolones in the treatment of bacterial gastroenteritis will clearly depend on the possible emergence of acquired resistance.

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