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Comparison of Single-Dose Treatment with Norfloxacin and Standard 5-Day Treatment with Trimethoprim-Sulfamethoxazole for Acute Shigellosis in Adults

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Shigellae have been shown to be highly susceptible to new quinolone agents, with average MICs for 90% of isolates of <0.1 μg/ml. Because these agents also reach high concentrations in the stool after a single dose, the effectiveness of a single 800-mg dose of norfloxacin and of 5-day treatment with trimethoprim-sulfamethoxazole (TMP-SMX) were compared in a randomized trial. Patients with clinical dysentery received one of these treatment regimens, and clinical data and follow-up culture results were analyzed for patients whose stool culture on presentation grew shigellae. When 55 patients with shigellosis (26 treated with TMP-SMX, 29 treated with norfloxacin) whose bacterial isolates were susceptible to the antibiotic given were compared by treatment group, no significant differences were seen in days of illness (mean, 2.5 ± 0.65 days with TMP-SMX and 2.0 ± 0.47 days with norfloxacin; $P = 0.200$) or number of unformed stools after starting treatment (mean, 9.7 ± 2.37 stools with TMP-SMX and 7.6 ± 3.19 stools with norfloxacin; $P = 0.312$). Resistance in vitro to TMP-SMX was seen in 15% of *Shigella* isolates, whereas none was resistant to norfloxacin. Bacteriologic failure was found in 1 patient among 24 receiving TMP-SMX and in none of 25 patients receiving norfloxacin. One single dose of norfloxacin was as effective as 5 days of treatment with TMP-SMX in these adults with shigellosis.

Diarrheal diseases constitute a major cause of morbidity and mortality worldwide, especially in developing countries (2). Shigellosis is endemic in many of these countries, causing dysentery and occasionally outbreaks with high mortality (15). *Shigella* spp. are enteroinvasive organisms (7), resulting in a clinical picture of dysenteric stool with blood and pus, tenesmus, and fever. It is generally accepted that diarrheal disease due to *Shigella* spp. should be treated with antibiotics; this has been shown to shorten the course of fever and other symptoms as well as to shorten the duration of diarrhea and convalescent stool carriage (4, 10, 14, 22).

Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) have been the drugs of choice for shigellosis, and standard treatment courses for both have been 5 days (8, 14, 16). In recent years a significant increase in resistance to ampicillin has been detected in *Shigella* isolates (20), and in some parts of the world a progressive increase in resistance to TMP-SMX has been recognized as well (13, 18, 24).

Recently, the new quinolone antibiotics, such as norfloxacin, ciprofloxacin, enoxacin, and ofloxacin (3, 11, 12, 23, 29, 30), have been shown to have low MICs for 90% of enteropathogens, especially for shigellae. The clinical response in patients with acute dysentery treated with norfloxacin has been favorable in more than 95% of cases when treatment has continued for 5 days (9, 28). In 1984 we showed that norfloxacin given twice a day for 5 days was as effective as standard treatment with TMP-SMX for 5 days (A. Carcelen, E. Gotuzzo, A. Yi, C. Maguiña, and R. B. Sack, II Congr. Panam. Infect., abstr. no. 16, p. 45, 1984). In this study we observed that on day 3 of treatment 90% of the cases were asymptomatic, and all stool cultures on that day were negative. This finding led us to consider the possibility of further reducing the treatment course for diarrhea treated with quinolone antibiotics.

The objective of the present study was to evaluate the efficacy and safety of using a single 800-mg dose of norfloxacin in the treatment of acute shigellosis in adults in comparison with the standard treatment of TMP-SMX for 5 days.

MATERIALS AND METHODS

Adult patients with clinical dysentery in outpatient clinics and the emergency room at the Hospital General Base Cayetano Heredia, Lima, Peru, were interviewed by study personnel. Patients with three or more unformed stools with gross blood and/or mucus present in the prior 24 h and with no antibiotic therapy in the prior 48 h and who agreed to participate by informed consent were randomized by block randomization with a random number table to receive either trimethoprim-sulfamethoxazole (TMP-SMX) (160/800 mg) given twice a day for 5 days or norfloxacin (800 mg) given in the clinic as a single dose. Unformed stools were classified as soft when they conformed to the shape of the container and liquid if they were watery enough to be poured. The study protocol was reviewed and approved by the committee on human subjects of the Universidad Cayetano Heredia.

Baseline stool cultures were done in all cases before antibiotics were given. Fresh stools were inoculated into Cary-Blair transport medium (both with and without Skirrow antibiotics for isolation of *Campylobacter* spp.). Stool specimens were transported within 2 h to the reference laboratory, where they were plated onto MacConkey, salmonella-shigella, and sorbitol-enriched MacConkey agars, as well as GN broth and peptone water. Shigellae were identified by standard biochemical tests (19), and strains identified as shigellae biochemically were verified by agglutination with specific antisera. Susceptibility testing of *Shigella* strains

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TABLE 1. Admission characteristics of study patients[a]

Treatment	No. of patients			Mean age (yr) ± SD	Days with diarrhea ± SD	No. of stools during prior 24 h ± SD	No. of stools with the following characteristics					
							Consistency		Mucus		Gross blood	
	Total	Male	Female				Liquid	Soft	Present	Absent	Present	Absent
TMP-SMX	26	10	16	33.5 ± 13.9	2.3 ± 1.3	8.2 ± 5.2	22	4	20	6	18	8
Norfloxacin	29	10	19	31.3 ± 10.7	2.6 ± 1.5	5.5 ± 2.3[b]	25	4	25	4	21	8

[a] The numbers of each *Shigella* sp. isolated are as follows: in the TMP-SMX group, 20 *S. flexneri*, 3 *S. boydii*, and 3 *S. dysenteriae*; in the norfloxacin group, 16 *S. flexneri*, 5 *S. sonnei*, 5 *S. boydii*, and 3 *S. dysenteriae*.
[b] $P = 0.0138$.

was done by Kirby-Bauer disk diffusion method on Meuller-Hinton agar. Other pathogens sought by culture included *Campylobacter*, *Salmonella*, *Aeromonas*, *Plesiomonas*, and *Vibrio* spp.

All patients were given a card on which to record physical signs and symptoms (number of stools, consistency of stools, etc.) daily. Follow-up visits were conducted beginning 3 days after the start of the treatment regimen, and repeat stool cultures were attempted up to 2 weeks after completion of treatment. Only patients with pretreatment stool cultures positive for shigellae were included for analysis in this study. Outcome variables assessed included days from the onset of treatment until the last unformed stool, total number of stools after initiation of therapy, and frequency of stool culture positivity after antibiotic treatment. Statistical tests used were the Student *t* test with pooled variance and the chi-square test. Analyses of interactions and outcome variables by treatment group and severity were done by two-way analysis of covariance.

RESULTS

A total of 174 patients were enrolled, of whom 62 had stool cultures positive for shigellae. Other pathogens identified in these 174 patients included *Salmonella paratyphi* A in 1, *Vibrio fluvialis* in 1, *Campylobacter jejuni* in 2, and *Aeromonas* spp. in 20 (*A. hydrophila* in 5, *A. caviae* in 6, and *A. sobria* in 9). Two patients with shigellosis were excluded from the protocol because of poor compliance, and five patients were excluded from the TMP-SMX group because their bacterial isolate was resistant in vitro to TMP-SMX. The level of in vitro resistance of *Shigella* isolates to TMP-SMX in both treatment groups was similar (16% in the TMP-SMX group, 14% in the norfloxacin group). None of the shigellae isolated was resistant to norfloxacin. Of the 55 remaining patients with shigellosis, 26 received TMP-SMX and 29 received norfloxacin. Clinical characteristics of the patients studied and outcome variables in both groups are shown in Table 1. There were no statistical differences between the two study groups in regard to age and sex of the patients or in days of illness before presentation for medical consultation. Patients in the TMP-SMX group had more stools in the 24 h before presentation than did those in the norfloxacin group (mean, 8.2 stools with TMP-SMX and 5.5 stools with norfloxacin; $P = 0.0138$), but no differences were seen between the two populations in regard to days of illness before presentation, consistency of stools, or the presence of blood or mucus in the stools by history. *Shigella flexneri* was the most common species isolated in both groups.

Outcome parameters in the analyzed population are shown in Table 2. When means and 95% confidence intervals of outcome parameters were assessed, patients in the TMP-SMX group averaged 0.5 day longer duration of diarrhea (2.5 ± 0.65 days versus 2.0 ± 0.47 days; $P = 0.200$) and had more unformed stools after initiation of therapy than did patients in the norfloxacin group (9.7 ± 2.37 versus 7.6 ± 3.19 unformed stools; $P = 0.312$), although neither difference was statistically significant at the $P = 0.05$ level. The proportion of patients in both treatment groups with continued diarrhea at 24-h intervals after initiation of treatment were similar

TABLE 2. Outcome variables in patients receiving antimicrobial agents to which their *Shigella* isolate was susceptible

Patient group[a] and treatment	No. of patients	Days to last unformed stool	No. of unformed stools after start of treatment	No. of culture-positive follow-up stools/total
Total population				
TMP-SMX	26	2.5 (1.85–3.15)	9.7 (7.33–12.05)	1/24
Norfloxacin	29	2.0 (1.53–2.47)[b]	7.6 (4.41–10.79)[c]	0/25
Group A				
TMP-SMX	10	2.6 (1.26–3.94)	6.8 (4.57–9.03)	
Norfloxacin	17	1.4 (1.07–1.73)[d]	3.7 (2.58–4.74)[e]	
Group B				
TMP-SMX	16	2.5 (1.76–3.23)	11.5 (8.09–14.91)	
Norfloxacin	12	2.6 (1.66–3.54)[d]	11.8 (5.30–18.30)[e]	

[a] Group A patients reported fewer than six stools in the 24 h before treatment; group B patients reported six or more stools in the 24 h before treatment. *P* values were calculated by treatment group in the four groups defined by treatment group and number of stools in the 24 h before presentation by using two-way analysis of covariation. No difference by severity was detected for days to last unformed stool, although a significant different ($P = 0.002$) was detected by severity for the number of unformed stools after starting treatment that was independent of treatment group.
[b] $P = 0.200$.
[c] $P = 0.312$.
[d] $P = 0.250$.
[e] $P = 0.530$.

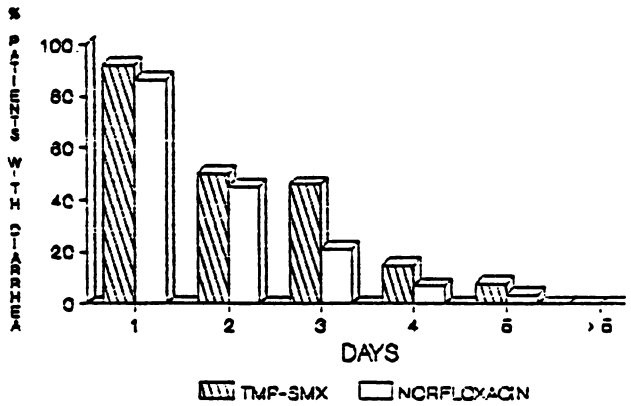

FIG. 1. Percentage of patients with continued diarrhea in each treatment group at specific intervals after initiation of treatment with TMP-SMX or norfloxacin. Days were measured as specific 24-h intervals after initiation of therapy.

(Fig. 1), with approximately 50% of patients without diarrhea 48 h after starting treatment and no patients with diarrhea at 5 days after starting treatment.

Follow-up stool cultures were done after the onset of therapy in 49 patients. In the TMP-SMX group the follow-up stool culture was done on day 3, 4, or 5 after the onset of treatment in 14 patients, whereas in 8 patients the follow-up stool culture was done during the first week after the end of treatment. In the norfloxacin group 22 patients were evaluated with a follow-up stool culture within the first week after receiving single dose treatment. Although follow-up stool culture before the end of the first posttreatment week would be optimal and was obtained in 22 (91.6%) of 24 cases in the TMP-SMX group and 22 (88%) of 25 cases in the norfloxacin group, a delay in return for follow-up resulted in a delay in the follow-up culture to the second posttreatment week in 5 cases (2 with TMP-SMX, 3 with norfloxacin). The repeat stool culture was positive for *Shigella* in 1 of 24 patients in the TMP-SMX group and 0 of 25 patients in the norfloxacin group. The initial *Shigella* isolate from the patient with positive follow-up culture was susceptible to TMP-SMX, but the shigella isolated on therapy was resistant to TMP-SMX (repeat culture 5 days after starting TMP-SMX, at the end of therapy).

Because patients in the TMP-SMX group had more unformed stools in the 24 h before treatment than did those in the norfloxacin group, the data were analyzed by severity based on this pretreatment variable by using two-way analysis of covariance (Table 2). In this repeat analysis each treatment group was divided into two groups, those with less than six stools in the 24 h before presentation and those with six or more stools in the 24 h before presentation. No difference in outcome variables by treatment group was found in this four-group analysis, although the smaller sample size resulting from the designation of subgroups reduced our ability to detect differences. A significant difference by severity based on the number of unformed stools in the 24 h before presentation was found when the total numbers of unformed stools after starting treatment were compared, but this difference was independent of treatment group and suggested that both treatment regimens were less effective in patients with more severe disease. Outcome variables in the norfloxacin group did not suggest more severe disease after treatment when compared with the TMP-SMX group in our analyses. No two-way interactions based on treatment group and number of stools in the 24 h before presentation were detected by analysis of variation.

No serious adverse reactions were found in either treatment group. The only drug-associated reaction noted was a pink evanescent macular rash that occurred in one patient on day 4 of treatment with TMP-SMX. The antibiotic was stopped, and the rash disappeared 2 days later. No central nervous system effects, rashes, or other side effects were noted in the norfloxacin group.

DISCUSSION

The new quinolones have shown great potential in the treatment of acute diarrheal diseases because of the high susceptibility of enteropathogens, including *Shigella* spp. Multiresistant *Shigella* isolates from Hong Kong have been shown to have MICs for 90% of isolates of less than 0.1 μg/ml for norfloxacin, ciprofloxacin, and ofloxacin, a finding which is very important considering the progressive increase in resistance of shigellae to ampicillin and TMP-SMX on a worldwide basis (17). In a 1985 review of enteropathogen resistance patterns from sites in the United States, Latin America, Asia, and Africa (21), in vitro resistance to ampicillin varied from 18 to 40% in most areas; resistance to TMP-SMX was especially high in studies from Latin America, with 23% resistance recorded in Brazil and 26% resistance recorded in Mexico.

Recent studies have shown the clinical efficacy of the new quinolones against enteropathogens when treatment has continued for a standard length of 5 days (9, 25, 27, 28; Carcelen et al., III Congr. Panam. Infect.). Several findings have suggested that a single dose of norfloxacin may be efficacious in the management of acute diarrheal disease, including a high drug concentration in stool 24 h after a 400-mg dose (200 to 2,700 μg/g of stool) that remains elevated for 3 days after the dose (5), the presence of enterohepatic recirculation of norfloxacin (6), and the low MIC for 90% of isolates of norfloxacin against enteropathogens (<0.1 μg/ml for *Shigella* spp.) (11, 23, 29). In adults, single-dose therapy with high doses of tetracycline (2.5 g) has been used with good efficacy in the treatment of acute diarrheal disease (26), but poor patient tolerance due to gastrointestinal pain at high doses limits the use of this regimen. Our results with single-dose treatment demonstrate no difference in outcome when compared with standard 5-day treatment with TMP-SMX in these patients with shigellosis. However, both TMP-SMX and norfloxacin treatment regimens were less effective in patients with more severe disease. Single-dose treatment offers a number of important advantages, including reduced cost of treatment and a reduction of side effects related to length of therapy. Furthermore, patient compliance can be assured by administering single-dose treatment in the primary care clinic setting, reducing treatment failures due to an incomplete treatment course. Although the current study has focused on the efficacy of single-dose treatment for shigellosis, the quinolone antibiotics are also effective in vitro against *Campylobacter* spp. (12), another important etiologic agent of dysentery common in developing countries that is generally resistant to TMP-SMX. If single-dose therapy with norfloxacin is also shown to be effective in the treatment of campylobacteriosis, it will provide a logical therapeutic approach to acute dysentery in situations where stool culture facilities are unavailable. Dual coverage of *Shigella* and *Campylobacter* spp. by an antibiotic is especially important in the treatment of dysenteric infections in children, from whom

Campylobacter spp. are isolated more frequently than from adults, but the association of cartilage deterioration in young experimental animals and clinical arthropathy with the use of quinolone antibiotics have restricted the use of these agents in children (1). Nevertheless, many clinical observations have suggested that in certain circumstances quinolone antibiotics may be used safely and effectively in children, and further research is necessary to determine whether single-dose norfloxacin is a viable and safe alternative to TMP-SMX in pediatric diarrheal diseases as well.

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LITERATURE CITED

1. **Alfaham, M., M. E. Holt, and M. C. Goodchild.** 1987. Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. Br. Med. J. **295**:699.
2. **Baum, S., and E. E. Arriaga.** 1980. Levels, trends, differentials, and causes of infant and early childhood mortality in Latin America. World Health Stat. Q. **33**:147–163.
3. **Carlson, J. R., S. A. Thornton, H. L. DuPont, A. H. West, and J. J. Matthewson.** 1983. Comparative in vitro activities of ten antimicrobial agents against enteropathogens. Antimicrob. Agents Chemother. **24**:509–513.
4. **Cheever, F. S.** 1952. The treatment of shigellosis with antibiotics. Ann. N.Y. Acad. Sci. **55**:1063–1069.
5. **Cofsky, R. D., L. DuBouchet, and S. H. Landesman.** 1984. Recovery of norfloxacin in feces after administration of a single oral dose to human volunteers. Antimicrob. Agents Chemother. **26**:110–111.
6. **Corcione, F., and B. Giordano.** 1985. Biliary pharmacokinetics of norfloxacin. Chemioterapia **4**(Suppl. 2):494–495.
7. **Donahue-Rolfe, A., G. T. Keusch, C. Edson, D. Thorley-Lawson, and M. Jacewicz.** 1984. Pathogenesis of *Shigella* diarrhea. IX. Simplified high-yield purification of *Shigella* toxin and characterization of subunit composition and function by the use of subunit-specific monoclonal and polyclonal antibodies. J. Exp. Med. **160**:1767–1781.
8. **DuPont, H. L.** 1985. *Shigella* species (Bacillary dysentery), p. 1269–1274. *In* G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett (ed.), Principles and practice of infectious diseases, 2nd ed. John Wiley & Sons, Inc., New York.
9. **DuPont, H. L., M. L. Corrado, and J. Sabbaj.** 1987. Use of norfloxacin in the treatment of acute diarrheal diseases. Am. J. Med. **82**(Suppl. 6B):79–83.
10. **Garfinkel, B. T., G. M. Martin, J. Watt, F. J. Payne, R. P. Mason, and A. V. Hardy.** 1953. Antibiotics in acute bacillary dysentery: observations in 1408 cases with positive culture. J. Am. Med. Assoc. **151**:1157–1159.
11. **Geddes, A. M.** 1986. Quinolones in enteric infections. Quinolones Bull. **2**:15–16.
12. **Goodman, L. J., R. M. Fliegelman, G. M. Trenholme, and R. L. Kaplan.** 1984. Comparative in vitro activity of ciprofloxacin against *Campylobacter* spp. and other bacterial enteric pathogens. Antimicrob. Agents Chemother. **25**:504–506.
13. **Gross, R. J., E. J. Threlfall, L. R. Ward, and B. Rowe.** 1984. Drug resistance in *Shigella dysenteriae*, *Shigella flexneri*, and *Shigella boydii* in England and Wales: increasing incidence of resistance to trimethoprim. Br. Med. J. **288**:784–786.
14. **Haltalin, K. C., J. D. Nelson, R. Ring III, M. Sladoje, and L. V. Hinton.** 1967. Double-blind treatment study of shigellosis comparing ampicillin, sulfadiazine, and placebo. J. Pediatr. **70**: 970–981.
15. **Keusch, G. T.** 1986. *Shigella*, p. 31–50. *In* S. L. Gorbach (ed.), Infectious diarrhea. Blackwell Scientific Publications, Boston.
16. **Levine, M. M.** 1986. Antimicrobial therapy of infectious diarrhea. Rev. Infect. Dis. **8**(Suppl. 2):S207–S216.
17. **Ling, J., K. M. Kam, A. W. Lam, and G. L. French.** 1988. Susceptibilities of Hong Kong isolates of multiply resistant *Shigella* spp. to 25 antimicrobial agents, including ampicillin plus sulbactam and new 4-quinolones. Antimicrob. Agents Chemother. **32**:20–23.
18. **Macaden, R. B., N. Gokul, P. Pereira, and P. Bhat.** 1980. Bacillary dysentery due to multi-drug resistant *Shigella dysenteriae*. Indian J. Med. Res. **71**:178–185.
19. **Martin, W. J., and J. A. Washington II.** 1980. *Enterobacteriaceae*, p. 195–219. *In* E. H. Lenette, A. Balows, W. J. Hausler, Jr., and J. P. Truant (ed.), Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.
20. **Meyer, P. W., and S. Lerman.** 1980. Rise and fall of shigella antibiotic resistance. Antimicrob. Agents Chemother. **17**:101–102.
21. **Murray, B. E.** 1986. Resistance of *Shigella*, *Salmonella*, and other selected enteric pathogens to antimicrobial agents. Rev. Infect. Dis. **8**(Suppl. 2):S172–S181.
22. **Nelson, J. D., H. Kusmiensz, L. H. Jackson, and E. Woodman.** 1976. Trimethoprim-sulfamethoxazole therapy for shigellosis. J. Am. Med. Assoc. **233**:1239–1243.
23. **O'Hare, M. D., D. Flemingham, G. L. Ridgeway, and R. N. Gruneberg.** 1985. The comparative *in vitro* activity of twelve 4-quinolone antimicrobial agents against enteric pathogens. Drug. Exp. Clin. Res. **11**:253–257.
24. **Paniker, C. K., K. N. Vimala, P. Bhat, and S. Stephen.** 1978. Drug resistant shigellosis in south India. Indian J. Med. Res. **68**:413–417.
25. **Pichler, H., G. Diridl, K. Stickler, and D. Wolf.** 1987. Clinical efficacy of ciprofloxacin compared with placebo in bacterial diarrhea. Am. J. Med. **82**(Suppl. 4A):329–332.
26. **Pickering, L. K., H. L. DuPont, and J. Olarte.** 1978. Single dose tetracycline for shigellosis in adults. J. Am. Med. Assoc. **239**:853–854.
27. **Ramirez-Ronda, C.** 1987. Quinolones in the treatment of gastrointestinal infections. Chemioterapia **6**:488–489.
28. **Ruiz-Palacios, G. M.** 1986. Norfloxacin in the treatment of bacterial enteric infections. Scand. J. Infect. Dis. **48**(Suppl.): 55–63.
29. **Shungu, D. L., E. Weinberg, and H. H. Gadebusch.** 1983. In vitro antibacterial activity of norfloxacin and other agents against gastrointestinal tract pathogens. Antimicrob. Agents Chemother. **23**:86–90.
30. **Van Hoof, R., J. M. Hubrechts, G. Roebben, H. J. Nyssen, E. Nulens, J. Leger, and N. De Schepper.** 1986. The comparative activity of pefloxacin, enoxacin, ciprofloxacin, and 13 other antimicrobial agents against enteropathogenic organisms. Infect **14**:294–297.