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Single-Dose and Three-Day Regimens of Ofloxacin versus Trimethoprim-Sulfamethoxazole for Acute Cystitis in Women

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We compared the safety and efficacy of a single 400-mg dose of ofloxacin, ofloxacin (200 mg) once daily for 3 days, and trimethoprim-sulfamethoxazole (160:800 mg) twice daily for 7 days for the treatment of acute uncomplicated cystitis (urinary tract infection [UTI]) in women. At 5 weeks posttreatment, 35 (81%) of 43 patients treated with single-dose ofloxacin, 40 (89%) of 45 treated with 3 days of ofloxacin, and 41 (98%) of 42 treated with trimethoprim-sulfamethoxazole were cured ($P = 0.03$, single-dose ofloxacin group versus trimethoprim-sulfamethoxazole group). Retreatment for symptomatic recurrent UTI was given to 7 (16%) of 43 patients initially treated with single-dose ofloxacin, 3 (7%) of 45 patients treated with 3 days of ofloxacin, and 0 of 42 patients treated with trimethoprim-sulfamethoxazole ($P = 0.01$, single-dose ofloxacin group versus trimethoprim-sulfamethoxazole group). There was a trend in each of the three treatment groups toward an association between persistent or recurrent episodes of significant bacteriuria and a history of UTI in the past year and with diaphragm use. Ofloxacin was more effective than trimethoprim-sulfamethoxazole in eradicating *Escherichia coli* from rectal cultures during or soon after therapy, but there were no differences at later follow-up visits. Adverse effects were equally common among the three treatment groups. We conclude that single-dose ofloxacin was less effective than 7 days of trimethoprim-sulfamethoxazole for treatment of uncomplicated cystitis in women, while the 3-day ofloxacin regimen and the trimethoprim-sulfamethoxazole regimen were not significantly different in efficacy.

The majority of cases of acute cystitis in young healthy women are effectively treated with conventional oral antimicrobial agents such as trimethoprim-sulfamethoxazole or nitrofurantoin. Ampicillin and sulfonamides have become less reliable in such cases because of the high prevalence of resistance to these agents among common uropathogens (10). The new fluoroquinolone antimicrobial agents, of which ofloxacin is one, have also been demonstrated to be effective for treatment of cystitis (24). While these agents are not considered the treatment of choice for uncomplicated cystitis, they are often used in patients who are intolerant of conventional agents, who have resistant pathogens, or in whom the presence of a complicating factor is more likely.

Single-dose or 3-day regimens of antimicrobial agents are becoming increasingly popular for the treatment of uncomplicated cystitis because, compared with conventional regimens, they tend to be as effective and are associated with fewer adverse effects, better compliance, and lower cost (10). However, there are no published data on the use of the new fluoroquinolones in single-dose regimens for the treatment of uncomplicated cystitis in the United States. We therefore compared the safety and efficacy of ofloxacin in a single-dose regimen with a regimen of once-daily doses of ofloxacin for 3 days and with a conventional 7-day regimen of trimethoprim-sulfamethoxazole for the treatment of acute uncomplicated cystitis in women. We also studied the effects of these regimens on rectal and perineal colonization with coliforms.

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MATERIALS AND METHODS

Study population. Women presenting to the University of Washington Student Health Center or the Seattle-King County Sexually Transmitted Disease Clinic were eligible for enrollment if they were at least 18 years old and had symptoms of acute cystitis, including dysuria, frequency, urgency and/or suprapubic pain. Patients were ineligible if they were pregnant, nursing, or not using a reliable contraceptive method; if they had evidence of upper urinary tract infection, such as a temperature greater than 37.5°C or flank pain or tenderness; a history or evidence of a functionally or anatomically abnormal urinary tract; a history of four or more urinary tract infections (UTIs) in the past year; symptoms of UTI for longer than 7 days prior to presentation; a history of allergy to carboxyquinolones, sulfonamides or trimethoprim; serum creatinine of >2.0 mg/dl; or use of a systemic antibacterial agent within 14 days of presentation. The study was approved by the University of Washington Human Subjects Review Committee, and all patients gave written informed consent.

Study design. At the initial visit, eligible patients underwent a complete history and physical examination, collection of a midstream urine sample for evaluation of bacteriuria and pyuria, pelvic examination for evidence of sexually transmitted diseases, and cervical swab cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Patients were then placed into random groups, by using randomization lists provided by Ortho Pharmaceutical Corporation, for one of three treatment regimens: ofloxacin (400 mg) as a single dose, ofloxacin (200 mg) once daily for 3 days, and trimethoprim-sulfamethoxazole (160:800 mg) twice daily for 7 days. The patients were asked to return 2 to 3 days after enrollment (early follow-up visit), 5 to 9 days after treatment (1-week posttreatment visit), and 4 to 6 weeks after treat-

ment (5-week posttreatment visit). At each follow-up visit, a genitourinary history was taken, patients were asked about adverse effects by using a checklist, and a midstream urine sample was collected for culture. At the enrollment and follow-up visits, rectal, urethral, and vaginal swabs for aerobic bacterial cultures were collected from patients by using previously described methods (4). All specimens were transported to the appropriate laboratory within 4 h of collection.

Microbiologic methods. Standard microbiologic procedures were used in isolating and identifying organisms from the cervical, urinary, rectal, urethral, and vaginal cultures (12). Urinary leukocyte counts were determined on unspun urine specimens by using a hemacytometer. Antimicrobial susceptibility tests were done on uropathogens isolated at enrollment and follow-up visits by using the disk diffusion method (2).

Evaluability criteria and definitions. Data on all patients who took their assigned antibiotic regimens and who returned for follow-up were included in analyses of rectal, vaginal, and urethral flora and adverse effects. For analyses of treatment outcome, patients were considered evaluable if they had $\geq 10^2$ CFU of a uropathogen per ml of midstream urine and pyuria (≥ 10 polymorphonuclear leukocytes per mm^3) at enrollment and if they returned for at least one posttreatment visit. Bacteriuria was defined as being significant at a follow-up visit if there were $\geq 10^2$ uropathogens per ml with symptoms and pyuria (UTI) or if there were $\geq 10^5$ uropathogens per ml without symptoms (asymptomatic bacteriuria). Cure at a given visit was defined as the absence of significant bacteriuria at the visit in patients who had not been retreated for recurrent UTI prior to the visit. For those patients for whom we had sufficient data, we also evaluated the frequency of recurrence patterns. Cure with early recurrence was defined as eradication of the initially infecting species and recurrence of significant bacteriuria with a different species at or before the 1-week posttreatment visit or a negative culture at the early follow-up visit followed by significant bacteriuria with the initially infecting species at the 1-week posttreatment visit. Cure with late recurrence was defined as having initially negative follow-up cultures followed by significant bacteriuria at the 5-week posttreatment visit. Failure was defined as having significant bacteriuria with the initially infecting species at the early follow-up visit.

Statistical methods. The chi-square statistic and Fisher's exact test were used to test for differences between the treatment groups, and 95% confidence intervals were constructed to evaluate the effects of treatment regimens on UTI and on rectal and vaginal floras.

RESULTS

Characteristics of study population. Of the 150 enrolled women, 144 (96%) were evaluable for treatment outcome: 48 were treated with single-dose ofloxacin, 49 were treated with 3 days of ofloxacin, and 47 were treated with trimethoprim-sulfamethoxazole. Six patients were not evaluable because of the absence of significant bacteriuria at enrollment (five patients) or no follow-up (one patient). *Escherichia coli* was the only pathogen or copathogen in 120 infections (83%); other members of the family *Enterobacteriaciae* were the primary pathogens in 8 infections (6%); *Pseudomonas aeruginosa* was the primary pathogen in 1 infection (1%); *Staphylococcus saprophyticus* was the primary pathogen in 11 infections (8%); other gram-positive cocci were the primary pathogens in 4 infections (3%).

TABLE 1. Characteristics of evaluable patients at enrollment by treatment regimen

Characteristic	Treatment regimen		
	Ofloxacin, single-dose	Ofloxacin, 3-day	TMP-SMX[a]
No. of evaluable women	48	49	47
Mean age (yr)	25	25	24
Caucasian (%)	81	76	85
Never married (%)	83	73	89
Median duration of symptoms before treatment (days)	2.0	2.0	2.0
With history of UTI (%)	71	69	72
With UTI in past yr (%)	48	31	40
Using diaphragm (%)	27	27	15
With $<10^5$ uropathogens at enrollment (%)	38	27	19

[a] TMP-SMX, trimethoprim-sulfamethoxazole.

At enrollment, all patients treated with ofloxacin were infected with organisms susceptible to this drug, whereas three treated with trimethoprim-sulfamethoxazole were infected with organisms resistant to this drug. Patients treated with ofloxacin were more likely to be using a diaphragm for contraception and to have low-quantity bacteriuria at enrollment than patients treated with trimethoprim-sulfamethoxazole, and the single-dose ofloxacin group had a higher prevalence of UTI in the past year than the other groups—none of these differences were statistically significant (Table 1). Two patients (one in each ofloxacin group) had *Chlamydia* infections at enrollment, and none had gonorrhea. The patients with *Chlamydia* infections were treated at the first follow-up visit at which this information was known and were considered nonevaluable for UTI outcome at all subsequent visits.

Treatment outcome. All treatment regimens were highly successful in eradicating the initially infecting strain, with only 1 of 48 treated with single-dose ofloxacin, 0 of 49 treated with 3 days of ofloxacin, and 1 of 47 treated with trimethoprim-sulfamethoxazole having persistent significant bacteriuria with the initially infecting strain at the early follow-up visit. However, there were more early and late recurrences in patients treated with ofloxacin compared with trimethoprim-sulfamethoxazole, and many of these recurrences, especially in those patients treated with single-dose ofloxacin, were symptomatic and required retreatment with antibiotics. Forty-one (98%) of 42 patients treated with trimethoprim-sulfamethoxazole who returned for the 5-week posttreatment visit were cured at this visit, including one who had transient asymptomatic bacteriuria with the same species as the initially infecting strain 1 week after treatment (Table 2). One patient had significant bacteriuria with the initially infecting strain at all three posttreatment visits, and her treatment was therefore considered a microbiologic failure; she was not retreated, since her symptoms and pyuria resolved. On the other hand, 35 (81%) of 43 patients treated with single-dose ofloxacin who returned for the 5-week posttreatment visit were cured at this visit ($P = 0.03$ compared with the trimethoprim-sulfamethoxazole group), including one patient, whose treatment was considered a failure, who had transient asymptomatic bacteriuria with the initially infecting strain at the early follow-up visit (Table 2). Seven patients treated with this regimen had a recurrent

TABLE 2. Treatment outcome in women with cystitis by treatment regimen

Cure by visit after treatment at:	No. cured/no. returning for visit (%) with treatment regimen of[a]:		
	Ofloxacin, single-dose	Ofloxacin, 3-day	TMP-SMX[c]
Wk 1	42/45 (93) (86–100)	44/48 (92) (84–99)	42/44 (95) (89–100)
Wk 5	35/43 (81) (70–93)	40/45 (89) (80–98)	41/42 (98)[b] (93–100)

[a] Ranges in parentheses give 95% confidence intervals for proportions.
[b] $P = 0.03$ for the difference between ofloxacin (single-dose) and trimethoprim-sulfamethoxazole.
[c] TMP-SMX, trimethoprim-sulfamethoxazole.

symptomatic UTI which required retreatment ($P = 0.01$ compared with the trimethoprim-sulfamethoxazole group) and one had asymptomatic bacteriuria at or within 3 days of the last follow-up visit. All cases except the late asymptomatic recurrence were with the same species as the initially infecting strain. Overall, 9 (21%) of 43 patients treated with this regimen had persistent or recurrent significant bacteriuria, compared with 2 (5%) of 42 treated with trimethoprim-sulfamethoxazole ($P = 0.05$). Two of five patients treated with single-dose ofloxacin who had infections caused by *S. saprophyticus* had early symptomatic recurrences with this pathogen.

Forty (89%) of 45 patients treated with 3 days of ofloxacin who returned for the 5-week posttreatment visit were cured at this visit ($P = 0.2$ compared with the trimethoprim-sulfamethoxazole group) (Table 2). Two cured patients had same-species early recurrences, and three had different-species early recurrences. One of the latter patients had a symptomatic recurrence at the early follow-up visit which cleared spontaneously before the 1-week posttreatment visit. Bacteriuria in all five patients cleared spontaneously before the last follow-up visit. At the last visit, three patients had a recurrent symptomatic UTI (each caused by the same species as the initially infecting strains) which required retreatment, and two had asymptomatic bacteriuria, one with the initially infecting species. Overall, 9 (20%) of 45 patients treated with 3 days of ofloxacin had persistent or recurrent significant bacteriuria (one patient had both an early and a late recurrence with different uropathogens) ($P = 0.03$ compared with the trimethoprim-sulfamethoxazole group).

Two patients whose initially infecting strains were resistant to trimethoprim-sulfamethoxazole were cured with this agent, and the other had a reduction in symptoms, resolution of pyuria, and 10^2 CFU of *E. coli* per ml at the early follow-up visit but was retreated. None of the 16 available isolates from recurrent infections in ofloxacin-treated patients were resistant to ofloxacin.

Recurrence of significant bacteriuria was associated with a history of UTI in the year prior to enrollment, especially in those treated with single-dose ofloxacin (Table 3). Likewise, patients who reported diaphragm use as their contraceptive method at enrollment were much more likely to have persistent or recurrent significant bacteriuria after treatment: 9 (30%) of 30 diaphragm users compared with 11 (11%) of 98 nonusers (Table 3). There was also a weak association between low-quantity bacteriuria at enrollment and persistence or recurrence of bacteriuria in all treatment groups (Table 3). The rate of persistent or recurrent significant bacteriuria was higher in both ofloxacin groups than in the trimethoprim-sulfamethoxazole group after controlling for prior history of UTI, diaphragm use, and quantity of uropathogens at enrollment alone (Table 3) and jointly.

Effects on rectal and perineal flora. Among patients who had rectal colonization with *E. coli* at enrollment, ofloxacin was more effective than trimethoprim-sulfamethoxazole in reducing rectal colonization with *E. coli* at the early follow-up visit: rectal *E. coli* was present in 27 (59%) of 46 patients treated with single-dose ofloxacin, 26 (55%) of 47 patients treated with 3 days of ofloxacin, and 37 (77%) of 48 patients treated with trimethoprim-sulfamethoxazole ($P = 0.02$ for comparison of both ofloxacin groups combined with the trimethoprim-sulfamethoxazole group) (Table 4). There were no significant differences among the groups at later follow-up visits. Among patients who had *E. coli* colonization of the vagina before treatment, ofloxacin and trimethoprim-sulfamethoxazole appeared to have a similar effect in reducing vaginal colonization during and after therapy (Table 5). The effect of all three regimens on urethral colonization with *E. coli* was similar to the effect on vaginal flora (data not shown).

Adverse effects. Adverse effects thought to be probably or definitely related to the treatment regimen were reported in 30% of those treated with single-dose ofloxacin, 32% of those treated with 3 days of ofloxacin, and 40% of those treated with trimethoprim-sulfamethoxazole. Gastrointestinal complaints were reported by 12, 14, and 18%; central nervous system side effects were reported by 14, 10, and 10%; and vaginitis was reported by 4, 4, and 10% of patients in the three treatment groups, respectively. All side effects were mild and, except for one patient on trimethoprim-sulfamethoxazole who developed a rash, did not result in premature cessation of treatment.

DISCUSSION

Alternative therapeutic agents for the treatment of cystitis are desirable because of the high prevalence of resistance to

TABLE 3. Factors at enrollment associated with persistence or recurrence of significant bacteriuria in women treated for acute cystitis by treatment regimen

Factor at enrollment	No. with bacteriuria/no. evaluable (%) with treatment regimen of:		
	Ofloxacin, single-dose	Ofloxacin, 3-day	TMP-SMX[a]
History of UTI in past yr			
Yes	7/22 (32)	3/13 (23)	1/17 (6)
No	2/21 (10)	6/33 (18)	1/24 (4)
Diaphragm user			
Yes	4/11 (36)	4/13 (31)	1/6 (17)
No	5/31 (16)	5/33 (15)	1/34 (3)
With $\geq 10^5$ uropathogens			
Yes	5/27 (19)	6/35 (19)	1/33 (3)
No	4/16 (25)	3/11 (27)	1/7 (14)

[a] TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 4. Isolation of rectal *E. coli* in women with cystitis by treatment regimen and visit

Treatment regimen	% with rectal *E. coli* (no. tested)[a]			
	Before treatment	At early follow-up[b]	1 wk after treatment[b]	5 wk after treatment[b]
Ofloxacin, single-dose	96 (48)	59 (46) (44–73)	56 (43) (41–71)	93 (40) (84–100)
Ofloxacin, 3-day	94 (50)	55 (47) (41–70)	43 (48) (30–58)	84 (45) (74–95)
TMP-SMX[c]	100 (47)	77 (48) (65–89)	45 (44) (31–61)	88 (43) (79–98)

[a] Ranges in parentheses give 95% confidence intervals for proportions.
[b] Among women in whom rectal *E. coli* was present before treatment.
[c] TMP-SMX, trimethoprim-sulfamethoxazole.

ampicillin and sulfonamides (25 to 35% of *E. coli* strains) (10) and the increasing prevalence of resistance to trimethoprim in some parts of the world (14, 17). Moreover, short-course regimens, such as single-dose or 3-day regimens, have gained widespread popularity because of the potential advantages of better compliance, fewer side effects, lower costs, and less risk of developing antimicrobial resistance (10, 15). Although the new fluoroquinolones, norfloxacin (20, 22, 24), ciprofloxacin (1, 8, 24), and ofloxacin (9, 23, 24), have all been demonstrated to be effective in the treatment of uncomplicated and complicated UTIs when given for 7 to 10 days, there are few studies of short-course regimens with these agents for treatment of uncomplicated cystitis.

Recent studies and reviews suggest that single-dose therapy with trimethoprim-sulfamethoxazole and especially β-lactams may be less effective than 7 days of therapy with these drugs (10, 15). Three-day regimens of β-lactams also appear to be less effective than 7-day regimens, while trimethoprim-sulfamethoxazole is as effective in 3-day regimens as in longer regimens (15). Recent uncontrolled studies in women with uncomplicated cystitis have shown cure rates 4 weeks after treatment with ciprofloxacin 100- and 250-mg single-dose regimens of 74 to 79% (7) and with 250- and 750-mg single-dose regimens of 64 to 70% (19). Similar to our experience, only two of four infections caused by *S. saprophyticus* were cured in one study (7). Ofloxacin in a 100-mg single-dose regimen resulted in an 80% cure rate 4 weeks after treatment in one uncontrolled study (18) and an 86% cure rate in another study with an unstated follow-up interval (13). In another study with an unstated follow-up interval, the cure rate in women treated with a 100-mg single-dose regimen of ofloxacin was significantly lower (73%) than that in the comparison group treated with a longer regimen of trimethoprim-sulfamethoxazole (93%) (16). While these observed cure rates are similar to those in our single-dose ofloxacin group, they are inferior to cure rates we have observed with short or conventional regimens of trimethoprim-sulfamethoxazole for uncomplicated cystitis (5, 9). Our data show that a single 400-mg dose of ofloxacin was highly effective in the initial eradication of bacteriuria but was more likely to be followed by a recurrent symptomatic UTI requiring retreatment, compared with a conventional regimen of trimethoprim-sulfamethoxazole. Norfloxacin (6) and ofloxacin (3, 9) have previously been shown to be effective in 3-day regimens with twice-daily dosing for treatment of uncomplicated cystitis. Women treated with a once-daily 200-mg dose of ofloxacin for 3 days in this study had significantly more posttreatment recurrences of significant bacteriuria than those treated with trimethoprim-sulfamethoxazole, but most of the recurrences were asymptomatic and resolved spontaneously. A direct comparison is necessary to determine whether a 3-day once-daily regimen of ofloxacin is less effective than a 3-day twice-daily regimen.

Persistence of coliforms in the vagina after treatment has been found to be associated with frequent early recurrences of cystitis (5). We found in the current study, as we found in our previous study (9), that ofloxacin was initially more effective than trimethoprim-sulfamethoxazole in eradicating *E. coli* from the rectum, but colonization was high in all treatment groups several weeks after treatment. Other investigators have demonstrated a dramatic but transient effect of ofloxacin against rectal coliforms (11, 21). Neither of the ofloxacin regimens demonstrated substantial differences compared with the trimethoprim-sulfamethoxazole regimen in the eradication of *E. coli* from the vagina and urethra of women with UTI. Thus, differential effects of the treatment regimens on the rectal, vaginal, or urethral flora do not appear to explain the higher frequency of recurrences in those patients treated with ofloxacin.

Previous studies of short-course treatment for uncomplicated cystitis in women have demonstrated an association between posttreatment recurrence of UTI and a previous history of UTI (5, 18), high-quantity bacteriuria (5), and diaphragm use (5). Likewise, in our study, a history of UTI in the previous year and diaphragm use were associated with persistent or recurrent significant bacteriuria in each study group. However, high-quantity bacteriuria was associated with a trend toward a lower rate of persistent or recurrent

TABLE 5. Isolation of vaginal *E. coli* in women with cystitis by treatment regimen and visit

Treatment regimen	% with vaginal *E. coli* (no. tested)[a]			
	Before treatment	At early follow-up[b]	1 wk after treatment[b]	5 wk after treatment[b]
Ofloxacin, single-dose	71 (48)	21 (34) (7–34)	36 (36) (20–52)	35 (31) (19–52)
Ofloxacin, 3-day	64 (50)	15 (33) (3–27)	24 (34) (9–38)	49 (35) (32–65)
TMP-SMX[c]	77 (47)	26 (38) (12–40)	22 (36) (9–36)	33 (36) (18–49)

[a] Ranges in parentheses give 95% confidence intervals for proportions.
[b] Among women in whom vaginal *E. coli* was present before treatment.
[c] TMP-SMX, trimethoprim-sulfamethoxazole.

bacteriuria in all our study groups. Our conclusion that trimethoprim-sulfamethoxazole treatment was associated with a lower rate of persistent or recurrent significant bacteriuria remained after controlling for all these potentially confounding factors. Larger studies with adequate power are necessary to determine whether any or all of these factors are independently associated with an increased risk of recurrent infection.

The role of the new fluoroquinolone antimicrobial agents such as ofloxacin in the treatment of UTI is evolving. Safe, effective, and cheap regimens presently exist for the majority of uncomplicated UTIs and generally should be used for initial therapy. Quinolones are effective alternative therapeutic agents in women who are known or suspected of having antimicrobial-agent-resistant organisms or who are allergic to or otherwise do not tolerate more conventional regimens. We have demonstrated that ofloxacin in a single dose of 400 mg resulted in a lower cure rate than a longer regimen of trimethoprim-sulfamethoxazole, while ofloxacin (200 mg) given once daily for 3 days produced an intermediate cure rate. Both of the ofloxacin regimens resulted in significantly more recurrences than the trimethoprim-sulfamethoxazole regimen, but these were largely asymptomatic and resolved spontaneously in the 3-day ofloxacin group. Taken together with the results from our previous study (9), these results suggest that a 3-day twice-daily ofloxacin regimen is possibly more effective than a 3-day once-daily regimen and that both are probably superior to single-dose ofloxacin therapy. We have also demonstrated greater activity of ofloxacin than of trimethoprim-sulfamethoxazole on rectal *E. coli* soon after initiating therapy (but not later) and excellent activity of ofloxacin against vaginal and urethral *E. coli*. Further studies should examine whether short-course quinolone regimens are associated with a higher recurrence rate of UTI than conventional regimens and, if confirmed, the possible mechanisms, since this association does not appear to be due to a lack of activity against the rectal and perineal reservoir of coliforms. Investigators in UTI treatment studies should consider the possible confounding effects of a prior history of UTI, diaphragm use, and colony count of the infecting pathogen on the risk of developing recurrent UTI following treatment.

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