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Treatment of Community-Acquired Acute Uncomplicated Urinary Tract Infection with Sparfloxacin versus Ofloxacin

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The efficacy and safety of a 3-day regimen of sparfloxacin were compared with those of a 3-day regimen of ofloxacin for the treatment of community-acquired acute uncomplicated urinary tract infections. Four hundred nineteen women were enrolled in a randomized, open-label, observer-blinded, multicenter study; 204 received sparfloxacin as a 400-mg loading dose on the first day and 200 mg once daily thereafter, and 215 received ofloxacin as 200 mg twice daily. A total of 383 patients met the criteria for clinical evaluability, and 174 were also bacteriologically evaluable; all treated patients were included in the safety analysis. *Escherichia coli* (86%) and *Staphylococcus saprophyticus* (4.6%) were the organisms most commonly isolated. Positive clinical responses were obtained 5 to 9 days after therapy in more than 92% of the patients in each group; sustained clinical cure rates 4 to 6 weeks after therapy were 78.3 and 76.9% in the sparfloxacin and ofloxacin groups, respectively. A positive bacteriologic response was observed in 98% of the bacteriologically evaluable patients in each treatment group at 5 to 9 days posttherapy and in 88.2 and 92.6% of the patients in the sparfloxacin and ofloxacin groups, respectively, 4 to 6 weeks after therapy. Almost 90% of all adverse events were of mild or moderate severity; the most frequent events at least possibly related to drug treatment were those common to the fluoroquinolones, namely, nausea, diarrhea, headache, insomnia, and photosensitivity. Photosensitivity was more frequent in the sparfloxacin group (6.9% versus 0.5% in the ofloxacin group); insomnia was more frequent in the ofloxacin group (3.7% versus 1.0% in the sparfloxacin group). These data suggest that a once-daily, 3-day regimen of sparfloxacin is effective and generally well tolerated in the treatment of acute uncomplicated urinary tract infections.

Standard therapy for acute uncomplicated urinary tract infections (UTIs) consists of a 3-day regimen with trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim, or fluoroquinolones. Although TMP-SMZ is often the drug of choice, fluoroquinolones are recommended for patients with recurrent infection, treatment failures, and allergies to other antimicrobial agents (27, 31). With the development of resistance, fluoroquinolones may be preferred since UTI pathogens demonstrate lower levels of resistance to fluoroquinolones compared to other therapies such as TMP-SMZ, amoxicillin, and sulfonamides (5, 27).

Single-dose regimens have also been tested but have been less effective, with lower cure rates and more frequent recurrences than those achieved with the more optimal 3- to 5-day therapy (5, 21, 27). Short-course treatment offers distinct advantages in terms of patient compliance and convenience, as well as providing cost benefits, fewer side effects, and reduced levels of bacterial exposure to drugs.

Sparfloxacin is extremely effective against a broad spectrum of gram-negative and gram-positive organisms (16, 22), including those implicated in UTIs. It is excreted unchanged in the urine at concentrations well above the MICs for uropathogens (14, 15), has a long-lasting postantibiotic effect (1, 23), and induces relatively little bacterial resistance (3). Thus, sparfloxacin was considered to have significant potential to further improve the effectiveness of treatment, patient convenience, and patient compliance with short-course therapy for uncomplicated UTI.

The purpose of this randomized, open-label, observer-blinded, multicenter study was to compare the safety and effectiveness of a 3-day regimen of sparfloxacin for the treatment of women with community-acquired uncomplicated acute UTI with those of ofloxacin, a drug currently indicated for this condition (13).

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MATERIALS AND METHODS

Patient population. The study population consisted of women (age, 18 to 64 years) who presented with at least two of the following symptoms of acute uncomplicated UTI: dysuria, frequency, urgency, and suprapubic pain. The diagnosis of uncomplicated UTI required a positive dipstick urine leukocyte esterase test and a pretreatment midstream urine culture which grew $\geq 10^5$ CFU of a single known uropathogenic bacterial species per ml. Patients were not eligible for study participation if they were known to be pregnant, lactating, or premenopausal and not using a reliable method of contraception. Patients were excluded from the study if they had nosocomial UTI; had a diagnosis of acute pyelonephritis; had evidence of complicated UTI (including symptoms of more than 7 days' duration, a temperature of >38°C, costovertebral angle tenderness, or flank pain); had had symptoms of UTI within the previous 4 weeks; had received systemic antibacterial therapy within 3 days prior to their initial visit or had a concomitant infection requiring such therapy; had genitourinary tract disease or abnormalities that might preclude evaluation of the therapeutic response; had gastrointestinal symptoms or conditions that might preclude adequate drug adsorption or were taking antacids; had congenital prolonged electrocardiographic

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TABLE 1. Definitions of clinical and by-patient bacteriologic outcomes

Clinical outcome and result	Definition of response
Clinical outcome	
Cure	Resolution of all signs and symptoms of UTI
Improvement	Resolution or reduction of the majority of the original signs and symptoms of UTI, with no new or worsened symptoms
Failure	No resolution and no reduction of a majority of original signs and symptoms, worsening of one or more of the above, new signs or symptoms, or the need for intervention with other antimicrobial agents
Indeterminate	Lack of necessary information (e.g., the patient was lost to follow-up)
Recurrence	Development of new or worsened signs or symptoms of UTI at the LFU visit in those patients who had a clinical response of cure or improvement at their TOC visit
Bacteriologic outcome	
Eradication	All baseline pathogens present at $\leq 10^4$ CFU/ml at the TOC visit
Persistence	Presence of any baseline pathogen at $>10^4$ CFU/ml at TOC
Presumed persistence	No culture results at TOC but a clinical response of failure at TOC
Superinfection	Emergence of a new (nonbaseline) pathogen at $\geq 10^5$ CFU/ml at or before TOC, together with signs or symptoms of UTI
Colonization (low-level bacteriuria)	Emergence of a new (nonbaseline) pathogen after the start of treatment, but at $<10^5$ CFU/ml or not accompanied by signs or symptoms of UTI
Relapse	Eradication of baseline pathogen(s) at TOC, with subsequent appearance of the same pathogen at $>10^3$ CFU/ml
Reinfection	Eradication of baseline pathogen(s) at TOC, with subsequent appearance of a new pathogen at $\geq 10^5$ CFU/ml accompanied by signs or symptoms of UTI
Indeterminate	No information available
Overall Outcome	
Success	Clinical response of cure or improvement plus bacteriologic response of eradication without changing or adding to the antibiotic regimen
Failure	All other outcomes

QT syndrome or were taking antiarrhythmic agents or other medications known to cause QTc prolongation; or had shown previous hypersensitivity or photosensitivity to fluoroquinolones.

The protocol and study site-specific procedures were reviewed and approved by Chesapeake Research Review, Inc. (Ellicott City, Md.), a central, independent institutional review board; all patients enrolled in the study gave appropriate written informed consent.

Study design. The study was a randomized, open-label, observer-blinded, multicenter comparative trial conducted from February to July 1995 by investigators at 29 centers across the United States. Patients were randomized in a 1:1 ratio to receive either a 3-day sparfloxacin regimen (a 400-mg loading dose on day 1, followed by 200 mg/day on days 2 and 3) or a 3-day ofloxacin regimen (200 mg every 12 h for 3 days). Patients were allowed to take all other medications required to manage underlying illnesses unrelated to their episode of UTI with the exception of other antibiotics, antacids, or medications known to cause QT prolongation.

Microbiologic methods. Urine specimens were obtained by clean-catch midstream collection; samples were transported without delay to a central laboratory (SciCor Laboratories, Indianapolis, Ind.) for isolation and identification of the etiologic pathogen(s) by standard methods. All aerobic bacteria identified were further tested for their susceptibilities to both sparfloxacin and ofloxacin according to National Committee for Clinical Laboratory Standards guidelines (17, 18). Susceptibility was evaluated by the broth dilution (MIC) and disk (Kirby-Bauer) methods for sparfloxacin and by MIC testing for ofloxacin.

Patient monitoring. During the baseline visit, eligible patients underwent a complete history and physical examination, including vital signs and 12-lead electrocardiogram (ECG); dipstick urine leukocyte esterase and screening pregnancy tests were performed; a blood sample was taken for hematology and serum chemistry analyses; and a urine specimen was collected for microscopy, urinalysis, culture, and susceptibility testing. Therapy was begun within 48 h of collection of a baseline specimen for culture. A patient's clinical progress was assessed by phone contact on day 4 ± 1; an investigator blinded to the treatment assignments evaluated the patient's clinical response during a visit on day 10 ± 2 (test of cure [TOC]), and recurrence of infection was assessed by the same investigator during a visit on day 38 ± 7 (late follow-up [LFU]). In addition, a blood sample was collected during the TOC visit, and urine specimens were collected at both the TOC and LFU visits for laboratory evaluation as described above. Patients prematurely dropped from the study were evaluated at the time of discontinuation as would have been appropriate for their next scheduled visit (TOC or LFU). Patients were questioned about adverse events at each contact. Although ECGs were performed at the baseline to exclude patients with electrocardiographic QTc interval prolongation, ECGs were not performed while the patients were receiving study medication because of the short duration of exposure in this study.

Evaluability criteria and definitions. To be clinically evaluable a patient must have presented with appropriate signs and symptoms of uncomplicated UTI as given above, had a positive urine dipstick test for leukocyte esterase, and completed all TOC (or appropriate dropout) procedures such that an assessment of the clinical response could be made; a patient must not have received other systemic antibiotic therapy, provided a baseline urine specimen for culture more than 48 h before the start of therapy, missed any drug doses, or received an incorrect diagnosis. To be bacteriologically evaluable, a patient must have been clinically evaluable and also have had a urinary tract pathogen identified by culture at $\geq 10^5$ CFU/ml (see above), additional culture results for a TOC or posttherapy dropout urine sample, and results for susceptibility of the baseline pathogen to both study drugs; a patient was not bacteriologically evaluable if her baseline pathogen was resistant to the study drug to which she was assigned. Clinical outcomes as assessed by the blinded investigator were defined as shown in Table 1; definitions used for the by-patient analysis of bacteriologic response (based on culture results) and for the analysis of overall response, considered the primary efficacy parameter, are also listed in Table 1.

Statistical analysis. Differences between the two treatment groups in the distribution of demographic variables, baseline characteristics, and changes in ECGs were tested by two-way analysis of variance methods for continuous variables. The equivalence of the efficacy responses between the sparfloxacin and ofloxacin groups was evaluated by the two-sided 95% confidence interval method; assuming that 100 patients were enrolled in each arm, there was a 90% probability of determining that sparfloxacin treatment statistically was not more than 10% worse than ofloxacin treatment, given that the sparfloxacin success rate was at least as good as the ofloxacin success rate. The Cochran-Mantel-Haenszel test was used to analyze adverse events stratified by investigator and was also used to analyze categorical variables in the analyses of demographic data. In addition, logistic regression analyses were performed to evaluate the effects of variables such as investigator, age, race, baseline symptoms and signs, and type and number of baseline pathogens that might also be related to the clinical response.

RESULTS

Study population. A total of 419 patients were enrolled in the study; 204 patients (mean age, 35.8 years) received sparfloxacin, and 215 patients (mean age, 36.1 years) received ofloxacin. The demographic and clinical characteristics of the two treatment groups were comparable, except that there were slightly more Hispanic and slightly fewer black patients in the sparfloxacin group than in the ofloxacin group. There were no

TABLE 2. Clinical and bacteriologic success rates at TOC

Efficacy measurement (population, time point)	No. of responses/total no. in population (%)		
	Sparfloxacin	Ofloxacin	95% CI[a]
Clinical success rate			
All-treated[b]	181/196 (92.3)	196/207 (94.7)	−7.2, 2.5
Clinically evaluable	173/187 (92.5)	185/196 (94.4)	−6.8, 3.1
Bacteriologically evaluable	89/93 (95.7)	74/81 (91.4)	−3.0, 11.7
Bacteriologic success rate			
All-treated[c]	111/116 (95.7)	100/103 (97.1)	−6.3, 3.5
Bacteriologically evaluable	91/93 (97.8)	80/81 (98.8)	−4.7, 2.9
Overall success rate			
All-treated[c]	105/114 (92.1)	91/102 (89.2)	−4.9, 10.7
Bacteriologically evaluable[d]	88/93 (94.6)	73/81 (90.1)	−3.5, 12.5

[a] CI, confidence interval (sparfloxacin-ofloxacin).
[b] Excluding patients with indeterminate response.
[c] Baseline pathogen at $\geq 10^5$ CFU/ml.
[d] Primary efficacy parameter.

statistically significant differences between the two treatment groups with respect to age, weight, and baseline characteristics such as sexual activity, history of prior UTIs, diaphragm use, menopausal status, estimated creatinine clearance, prior hospitalization, cigarette or alcohol use, severity or type of signs and symptoms of current UTIs, or urine tests, although a difference approaching statistical significance was noted for diabetes mellitus ($P = 0.059$).

The disposition of patients with respect to clinical and bacteriologic evaluability was similar across treatment groups. One hundred sixty-five (39.4%) patients completed the study. Reasons for premature discontinuation included no pretherapy pathogen, ineffective therapy, and adverse events. Overall, 91.5% of the patients were clinically evaluable and 41.5% were both clinically and bacteriologically evaluable.

Treatment outcome at TOC. The sparfloxacin and ofloxacin treatment regimens produced clinical success rates of 92.5 and 94.4%, respectively, in the clinically evaluable population, with similar results for the subsets of the all-treated and bacteriologically evaluable populations (Table 2). Improvement accounted for approximately 20% of the outcomes for each regimen in each of the populations. Logistic regression analyses showed no significant dependence of these clinical success rates on variables associated with demographics, medical history (e.g., prior episode of UTI), or underlying conditions in either treatment group. There were no significant differences between the clinical success rates for the two treatment groups in any of the populations.

The sparfloxacin and ofloxacin treatment regimens produced by-patient bacteriologic success rates of 97.8 and 98.8%, respectively, in the bacteriologically evaluable population; bacteriologic success rates in the all-treated population were similar.

The most common pathogen isolated was *Escherichia coli*, which accounted for approximately 86% of the organisms from each treatment group; other less common isolates included *Staphylococcus saprophyticus*, *Proteus mirabilis*, and *Enterococcus faecalis*. The bacteriologic response rates in the two treatment groups, evaluated according to causative pathogen, are shown in Table 3.

The overall success rates (both a positive clinical outcome and a positive bacteriologic response) in the bacteriologically evaluable population were 94.6% for the sparfloxacin group and 90.1% for the ofloxacin group. The 95% confidence interval (−3.5, 12.5) for the difference between the two groups strongly supports the equivalence of the two treatments (Table 2); the enrolled populations and the mean difference were such that the statistical power of the study design was, in fact, 94% rather than the projected 90%.

TABLE 3. Bacteriologic success rates for the all-treated population by pathogen

Pathogen	No. eradicated/no. isolated (%)	
	Sparfloxacin	Ofloxacin
All pathogens	111/116 (95.7)	100/103 (97.1)
E. coli	97/100 (97.0)	87/88 (98.9)
S. saprophyticus	5/6 (88.3)	4/4 (100)
P. mirabilis	5/5 (100)	3/3 (100)
E. faecalis	2/3 (66.7)	6/8 (75.0)

Recurrence, relapse, and reinfection. Clinical recurrence was observed at LFU for 9.8% (9 of 92) and 12.5% (10 of 80) of the patients in the sparfloxacin and ofloxacin treatment groups, respectively. Bacteriologic relapses occurred in nine patients in the sparfloxacin group and five patients in the ofloxacin group; the organisms responsible were *E. coli* (sparfloxacin group, $n = 8$; ofloxacin group, $n = 5$) and *Staphylococcus aureus* (sparfloxacin group, $n = 1$). Fifteen patients in the sparfloxacin group and 26 patients in the ofloxacin group had low-level bacteriuria after a bacteriologic response of eradication at the TOC visit. In addition, one patient in the ofloxacin group had a response of reinfection with *Enterobacter aerogenes* at LFU.

Adverse events. The entire study population of 419 patients was included in the safety evaluation; the results are summarized by treatment regimen in Table 4. At least one adverse event was experienced by 43.2% of the patients in the study; most of these adverse events were of mild or moderate severity: 134 of 149 (89.9%) patients in the sparfloxacin group and 117 of 135 (86.7%) patients in the ofloxacin group. The proportion of patients reporting adverse events which investiga-

TABLE 4. Safety summary

Safety parameter	No. (%) of patients	
	Sparfloxacin[a]	Ofloxacin[b]
One or more adverse clinical events	97 (47.5)	84 (39.1)
Adverse clinical events related to study drug[c]	57 (27.9)	48 (22.3)
Nausea	14 (6.9)	14 (6.5)
Photosensitivity	14 (6.9)	1 (0.5)
Diarrhea	6 (2.9)	7 (3.3)
Insomnia	2 (1.0)	8 (3.7)
Dizziness	6 (2.9)	4 (1.9)
Headache	4 (2.0)	5 (2.3)
Adverse clinical events leading to discontinuation	7 (3.4)	3 (1.4)
Serious adverse clinical events[d]	1 (0.5)	2 (0.9)
Adverse laboratory events	4 (2.0)	7 (3.3)

[a] The sparfloxacin group had a total of 204 patients.
[b] The ofloxacin group had a total of 215 patients.
[c] Considered by the investigator to have a possible or probable relationship to study medication.
[d] Any adverse event that was fatal or life-threatening, that was permanently or severely disabling, that required or prolonged inpatient hospitalization, or that was a congenital anomaly, cancer, or overdose.

tors possibly or probably attributed to study drug was 25.0%; the most common of these events were nausea, photosensitivity reaction, diarrhea, insomnia, dizziness, and headache. Ten patients were discontinued from the study by the investigators as a result of adverse events, 7 of which were considered to be related to study medication; the majority of these were either central nervous system (sparfloxacin group, $n = 2$; ofloxacin group, $n = 1$) or gastrointestinal (sparfloxacin group, $n = 3$) in nature.

Eleven of the 419 patients (2.6%) experienced laboratory abnormalities which, in an investigator's assessment, were clinically significant. These adverse laboratory events included elevated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels and decreased creatinine clearance, each of which occurred in three patients. Otherwise, the mean changes in hematology and serum chemistry parameters from the baseline to any subsequent evaluation time point were minor and were comparable for both groups.

DISCUSSION

The current study conforms with the accepted criteria for a well-designed clinical trial. In particular, the patient population was well defined with respect to disease state (2, 4, 30), enrollment was sufficient to allow a statistically significant null hypothesis test of equivalence, and patients were monitored for both clinical and bacteriologic efficacies in both the short and long term after treatment (10, 21). In addition, considerable emphasis was placed on subject safety in the stringency of enrollment criteria, although data for all enrolled patients who met the inclusion and exclusion criteria were used.

The characteristics of the study population described here are similar to those reported in other recent short-course clinical trials for acute uncomplicated UTI in younger females. For example, although mean ages in such studies have varied widely, from 24 to more than 48 years (5, 6, 10, 24, 28), the mean age of 36 years in this study is typical of the narrower range of 30 to 40 years for multicenter studies with an upper age limit for enrollment (7, 12, 19, 20) and is appropriate for the disease population (2). In addition, the organisms isolated here, predominantly *E. coli* (188 of 219; 85.8%) and *S. saprophyticus* (4.6%), are consistent with the spectrum of pathogens expected in acute uncomplicated UTI (4, 31), although a relatively high percentage of *E. faecalis* (5.0%), which is more commonly associated with nosocomial UTIs (8), was also found.

The two 3-day therapeutic regimens evaluated in this study (for sparfloxacin, a 400-mg loading dose on day 1 followed by 200 mg once daily thereafter, and for ofloxacin, 200 mg twice daily) were statistically equivalent in terms of both clinical and bacteriologic efficacies. Furthermore, when the effects of treatment were evaluated 5 to 9 days after therapy, both drugs provided marked improvement or relief from the signs and symptoms of UTI in more than 92% of all patients treated, including those who were not evaluable because of low urine colony counts ($<10^5$ CFU/ml) at study entry (2).

The clinical and bacteriologic outcome rates in the ofloxacin arm of this study are similar to those reported previously for the drug used for this indication (5, 24). Clinical findings and bacteriologic results in this study were in agreement for all but a few patients; one in each group was deemed a success clinically but had a bacteriologic response of failure, while three in the sparfloxacin group and seven in the ofloxacin group had positive bacteriologic responses but were designated clinical failures.

For the clinically evaluable patient population, the clinical cure rates 4 to 6 weeks after therapy were 78.3 and 76.9% in the sparfloxacin and ofloxacin groups, respectively. For the bacteriologically evaluable population, urine colony counts were significantly reduced in approximately 98% of the patients in each group when they were tested 5 to 9 days after therapy; eradication rates remained high 4 to 6 weeks after therapy, at 88.2 and 92.6% for the sparfloxacin and ofloxacin groups, respectively.

It is of interest that both study drugs in this trial provided a high degree of success in treating patients infected with *S. saprophyticus*, because high rates of failure of short-course therapy with other fluoroquinolones for the treatment of infections caused by this organism have been reported previously (9), in particular, treatment with ofloxacin (5, 6, 24).

The frequency of adverse events was comparable between the two treatment groups. There was a relatively high level of adverse events reported in both arms of the study (43.2% of patients overall), but this level was not atypical given the active method used for elicitation (5, 20). The incidence of adverse events possibly or probably related to study drug, 27.9%, was also high, but again, it was not atypical for a conservative causative analysis (9). The adverse events reported here are those common to the fluoroquinolones, primarily nausea, diarrhea, headache, insomnia, and photosensitivity (15, 26, 29); and almost 90% of these were categorized as being of mild to moderate in severity. The incidence of photosensitivity in this study was higher in sparfloxacin-treated patients, and the incidence of insomnia was higher in ofloxacin-treated patients; the frequency of side effects associated with the cardiovascular, digestive, and nervous systems was similar between the two groups.

Photosensitivity reactions have been reported in patients exposed to direct or indirect sunlight or to artificial UV light (e.g., sunlamps) during or following sparfloxacin treatment (25). Therefore, patients should avoid exposure to the sun, bright natural light, and UV rays throughout the duration of treatment and for 5 days after the completion of treatment. Patients whose employment or lifestyle precludes adherence to these safety precautions should not receive sparfloxacin.

QTc prolongation has been observed in patients treated with sparfloxacin (11); rare instances of torsade de pointes have been reported, primarily in patients at risk because of concomitant therapy with QTc-prolonging antiarrhythmic agents. In this study, changes in the QTc interval were not measured because of the short duration of therapy. Concomitant prescription of sparfloxacin and other QTc-prolonging agents, especially antiarrhythmic agents, should be avoided.

In conclusion, a 3-day course of treatment with sparfloxacin with a 400-mg loading dose on day 1 and 200 mg once per day on the following 2 days was found to be effective and generally well tolerated in women with community-acquired acute uncomplicated UTI. In addition, this three-dose regimen of sparfloxacin was found to be as effective as the six-dose regimen of ofloxacin, providing a more convenient alternative to currently available regimens for patients who are not at risk for photosensitivity reactions or adverse events associated with a prolonged QTc interval.

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