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Single-Dose Rufloxacin versus 3-Day Norfloxacin Treatment of Uncomplicated Cystitis: Clinical Evaluation and Pharmacodynamic Considerations

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The efficacy and safety of rufloxacin (400 mg, single dose) were compared to those of norfloxacin (400 mg twice a day for 3 days) for the treatment of women with uncomplicated cystitis. In addition, urine levels, drug level/MIC ratio, and urine antibacterial activity 72 to 84 h after treatment initiation were determined in a subgroup of patients for pharmacodynamic assessment. A total of 203 women were included and treated in this open, randomized clinical trial; 100 patients received norfloxacin, whereas 103 received rufloxacin. Of these, 156 (74 and 82 patients in the norfloxacin and rufloxacin groups, respectively) were considered bacteriologically evaluable. At the first follow-up visits (3 to 12 days after starting the treatment), bacteriological cure rates were 99 and 94% for norfloxacin and rufloxacin, respectively. Seventy-nine percent (119 of 150) of bacteriologically cured patients attended a long-term follow-up visit (4 to 6 weeks after starting the treatment), where a relapse rate of 4% (2 of 54) and 5% (3 of 64) were found in the norfloxacin and rufloxacin groups, respectively. The pharmacodynamic evaluation performed in 35 patients showed similar median urine levels (≅25 μg/ml) and urine antibacterial activity for both treatment groups against initial isolates, despite a higher norfloxacin level/MIC ratio due to the lower MIC of norfloxacin. Twenty-one patients (20%) in the rufloxacin group and 12 patients (12%) in the norfloxacin group reported 39 and 16 adverse events, respectively, almost all of them being mild and lasting <24 h. Overall, gastrointestinal reactions were the most frequent adverse events reported. However, 12 patients treated with rufloxacin reported 15 central nervous system adverse events. This study shows that single doses of rufloxacin are as effective as a norfloxacin 3-day standard treatment in uncomplicated cystitis. The results obtained with rufloxacin are consistent with its pharmacodynamic properties.

Uncomplicated cystitis has a narrow spectrum of etiological agents, with *Escherichia coli* in 80% of cases and *Staphylococcus saprophyticus* in 5 to 15% of cases being the most commonly isolated pathogens (31). A 3-day therapy is considered to be the optimal treatment of this disease (29). Although it has been suggested that a single-day therapy which achieves high concentration for at least 12 to 24 h eliminates bladder infection (30), quinolone treatment is more effective when lasting for 3 days (10), particularly with respect to recurrences (31).

Rufloxacin is a broad-spectrum quinolone (27), less active in vitro than norfloxacin against *E. coli* (33), that exhibits a prolonged elimination half-life (28 h) as its major pharmacokinetic feature (34). The in vitro activity (8, 33), in conjunction with the pharmacokinetic profile (11), suggests that rufloxacin may well find clinical use in the treatment of urinary tract infections (UTIs) (33). Reports of high and long-lasting (at least 72 h) urine levels (3) and urine bactericidal activity (4, 5) suggest rufloxacin may be used as a single-dose regimen for the treatment of uncomplicated cystitis. Several studies have reported the efficacy of norfloxacin with the recommended 3-day treatment (19, 30).

The purpose of this study was to evaluate the efficacy and safety of a single dose of rufloxacin (400 mg), compared with those of a norfloxacin standard treatment (400 mg twice a day [BID] for 3 days). In addition, urine levels and urine antibacterial activity were determined in a subgroup of patients, since measurement of ex vivo bactericidal activity allows direct comparison of pharmacodynamic properties (13); furthermore, the measurement of antibacterial activity in urine correlates better with outcome of infection (16) than in vitro susceptibility (7).

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MATERIALS AND METHODS

This open, randomized, parallel-group, phase III clinical trial was performed at Fundación Puigvert Hospital, Barcelona. Approval for the study protocol was provided by the Hospital's Clinical Trials Committee, and informed consent was obtained from each patient before enrollment. No patient entered into the trial on more than one occasion. Female outpatients were entered into the study if they had clinical signs and symptoms of UTI: dysuria, frequency, with or without suprapubic pain, nycturia, or hematuria. Exclusion criteria were a positive pregnancy test, a serum creatinine level of >2 mg/liter, serum glutamic oxalacetic transaminase of >35 U/liter or serum glutamic pyruvic transaminase of >55 U/liter, age over 55 or under 18 years, fever of >37.5°C, presence of clinical symptoms for more than 5 days before entry in the trial, or more than 3 episodes of UTI in the previous 12 months. A clean voided urine sample for culture was collected prior to drug administration. Patients were randomly assigned to one of the treatment regimens: rufloxacin (400 mg) (two 200-mg tablets; Mediolanum farmaceutici S.p.A, Milano, Italy), single dose, or norfloxacin (400-mg tablets; Merck Sharp & Dohme S.A, Madrid, Spain), BID for 3 days (six doses).

Patients were considered evaluable for safety after receiving at least one treatment dose. Similarly, patients were considered evaluable for efficacy if they had at enrollment a positive urine culture with a pure growth of $>10^3$ CFU of uropathogen (members of the family *Enterobacteriaceae*, enterococci, or *Staphylococcus saprophyticus*) per ml and pyuria (>5 leukocytes per high-power field) (29) and complied with the study treatment assigned.

Because of the long half-life of rufloxacin (34), clinical, safety, and bacteriological assessments were performed twice between the third and twelfth day after inclusion (3 to 7 and 8 to 12 days) in all patients. The second early-date evaluation (8 to 12 days) was performed to preclude the possibility of a negative urine culture due to the presence of therapeutic levels of rufloxacin in urine (14) in the 3- to 7-day visit. Because of this fact, we considered short-term evaluation the sum of results from the 3- to 7- and 8- to 12-day visits. Safety was assessed by the investigators on these short-term visits performed after the treatment had started, by asking a simple question such as, "How have you felt since your last

visit?" and recording the duration and intensity (as mild, moderate, or severe) of the reported adverse events. Spontaneous adverse events reported by patients during follow-up were also recorded. Long-term follow-up efficacy assessment was scheduled 4 to 6 weeks after treatment for those patients bacteriologically cured in the first follow-up visit. The primary efficacy parameter was the microbiological outcome of treatment (eradication or bacteriological cure was defined as absence in control cultures of the germs isolated in the pretreatment culture; failure was defined as persistence in the first control culture of the germs isolated in the pretreatment culture; reinfection was defined as presence in control cultures of germs different from those isolated in the pretreatment culture; relapse was defined as the same initial isolate reappearing in a control culture with a previous negative control culture). Clinical cure was defined as absence of signs or symptoms at control visits. Clinical failure was defined as presence of signs or symptoms at control visits.

Microbiological determinations. Bacteria were identified by standard methods, MICs were determined by agar dilution standard methods (21) for all isolates.

All patients were asked to bring to the investigators' department a 12-hour urine sample collected 72 to 84 h after the first (or single) treatment dose, until 50 samples were available. That means approximately 3 half-lives (rufloxacin $t_{1/2}$ = 28 h; norfloxacin $t_{1/2}$ = 4 h) (34, 35) after the administration of last dose (the single or the sixth dose for rufloxacin and norfloxacin, respectively). If the pretreatment urine sample yielded an isolate, urine bactericidal titers were determined against the isolate by the microdilution technique (35). In addition, urine drug levels were measured in these latter samples.

Urine bacteriostatic and bactericidal titers were performed by diluting the posttreatment urine sample in liquid media composed 20% of Isosensitest broth and 80% of pretreatment urine obtained from the same patient. Final inoculum was 10^5 CFU/ml of the initial isolate. The inoculated microtiter plates were incubated at 37°C for 20 h and subcultivated in antibiotic-free chocolate agar that was incubated at 37°C for 20 h. The bacteriostatic endpoint was defined as the highest dilution without macroscopic growth. The bactericidal endpoint was defined as the highest dilution killing 99.9% of initial inocula.

Rufloxacin and norfloxacin urine levels were determined by bioassay using *E. coli* ATCC 25922 as indicator organism, in Antibiotic agar no. 3 (Difco). Rufloxacin and norfloxacin standards were prepared with concentrations following the doubling dilution scale that included 1 μg/ml and at least five dilutions. Each sample was tested twice. The lower detection limits were 2.5 mg/liter for rufloxacin and 0.6 mg/liter for norfloxacin.

Sample size and statistical analysis. The sample size was calculated on the basis of the expected norfloxacin cure rate of 96% (28) and a delta value of 10% to show no differences between treatments (22). With type I and II errors of 0.05 and 0.2, respectively, 61 evaluable patients per treatment should be recruited (22). Sample size was, however, extended to 150 evaluable patients, following the IDSA/FDA guidelines for the clinical evaluation of anti-infective drug products (29).

Treatment group comparisons were done with chi-square tests and Fisher's exact test for qualitative parameters and Mann-Whitney and Spearman correlation for quantitative parameters. Two-tailed P values of <0.05 were considered statistically significant.

RESULTS

Two hundred and three women (mean age ± standard deviation [SD] 31.5 ± 10.6 years; mean weight ± SD, 57 ± 7 kg) were randomly allocated to receive either rufloxacin (400 mg, single dose) or norfloxacin (400 mg/12 h for 3 days). No significant differences in demographic features were noted between groups. The first patient was included in the study on 3 July 1992, and the last patient visit was on 10 January 1994. Forty-seven patients were excluded for efficacy analysis because of protocol violation in 32 cases (lack of compliance with treatment or scheduled visit, more than one initial isolate, concomitant infections or other pathology) and negative pretreatment culture in 15 additional cases. One hundred and fifty-six patients were evaluable for the primary efficacy endpoint (74 and 82 in norfloxacin and rufloxacin groups, respectively) and all 203 patients were evaluable for safety analysis (100 and 103 patients in norfloxacin and rufloxacin groups, respectively).

Table 1 shows microbiological evaluation along the follow-up period. No significant differences were found with respect to eradication rates in the short-term control (77 of 82 [94%] versus 73 of 74 [99%] for rufloxacin and norfloxacin, respectively). The only failure in the norfloxacin group was due to *S. saprophyticus* with a MIC of 2 μg/ml, which was considered a relapse (negative culture at the 3- to 7-day visit). The five rufloxacin failures were due to 4 *E. coli* isolates (MIC of 0.5 μg/ml for two isolates, 2 and >16 μg/ml for the others) and 1 *Klebsiella pneumoniae* isolate (MIC of 2 μg/ml). The *E. coli* with MIC of >16 μg/ml was the only strain isolated in the 3- to 7-day visit urine culture after rufloxacin treatment. Seventy-nine percent (119 of 150) of bacteriologically cured patients in the short-term follow-up visit were evaluated in the long-term follow-up visit. As shown in Table 1, no differences were found in the relapse rates (3 of 64 [5%] versus 2 of 54 [4%] for rufloxacin and norfloxacin, respectively). Relapses were due to *E. coli* in all cases: 3 rufloxacin-treated cases, one with and MIC of 0.25 μg/ml and two with MICs of 0.5 μg/ml, and 2 norfloxacin-treated cases, both with MIC of <0.06 μg/ml. At least 94% of microbiological eradication was obtained in the first follow-up visit in all evaluable patients and at the long-term follow-up visit, in patients bacteriologically cured in the first evaluation and followed in the second one.

TABLE 1. Microbiological evaluation along the follow-up period

Drug	Short-term evaluation (8–12 days posttreatment)			Long-term evaluation (4–6 weeks posttreatment)	
	No. of cases	Eradication rate (%)	Persistence rate (%)	No. of cases	Relapse rate (%)
Rufloxacin	82	93.9 (77/82)	6.1 (5/82)	64	4.7 (3/64)
Norfloxacin	74	98.6 (73/74)	1.4 (1/74)	54	3.7 (2/54)

[a] Relapse: negative culture at 3- to 7-day visit.

With respect to clinical evaluation, 5 of 82 (6.1%) and 3 of 74 (4%) of the patients were evaluated as failures at the short-term follow-up visits with rufloxacin and norfloxacin, respectively. The norfloxacin microbiological failure was also assessed as a clinical failure. In the rufloxacin group, three clinical failures were also microbiological failures, whereas two clinical failures had bacteriological eradication. Two microbiological failures in this group were asymptomatic.

With respect to the long-term follow-up visit, clinical evaluation was considered as failure in 5 of 64 (8%) and 4 of 54 (7%) of the patients in the rufloxacin and norfloxacin groups, respectively. In the latter group, two cases were clinical and bacteriological relapses, whereas the other two were only clinical failures (one of these was considered a clinical failure in the first follow-up visit). In the rufloxacin group, two cases were clinical and bacteriological relapses and three were only clinical relapses. One microbiological relapse in this group was asymptomatic.

In vitro susceptibility of initial isolates is shown in Table 2. Despite differences in in vitro susceptibility favoring norfloxacin, no significant differences were found in eradication rates. No differences were found when stratifying patients according to the species isolated. All *S. saprophyticus* were eradicated except in one case in the norfloxacin group.

Seventy-one percent (112 of 156) of the initial positive urine cultures presented with $>10^5$ CFU/ml. No microbiological efficacy differences were found between patients with initial cultures of $>10^3$ to $<10^5$ CFU/ml and these with $\geq 10^5$ CFU/ml.

The 72- to 84-h urine sample plus the initial isolate were obtained from 35 of 156 (22.4%) patients (16 and 19 receiving rufloxacin and norfloxacin, respectively). No differences were found with respect to urinary levels (median values, 24.7 versus 26.5 μg/ml for rufloxacin and norfloxacin, respectively). In Table 3, median bactericidal and bacteriostatic titers, urine

TABLE 2. In vitro susceptibility of initial isolates

Isolate	Rufloxacin				Norfloxacin			
	No. of cases	MIC (μg/ml)[a]			No. of cases	MIC (μg/ml)[a]		
		50	90	Range		50	90	Range
E. coli	70	0.5	1	0.25–16	56	0.03	0.125	0.03–1
P. mirabilis	5			2–2	7	0.03	0.125	0.03–0.125
S. saprophyticus	3			2–4	7	4	4	0.5–4
K. pneumoniae	3			0.25–8	3			0.125–0.25
Enterococcus spp.					1			4
C. diversus	1			0.5				
Total	82				74			

[a] 50 and 90, MICs for 50 and 90% of isolates, respectively.

levels, MICs, and inhibitory quotients (urine level/MIC) are shown for the subgroup of 26 *E. coli* isolates. No differences were found when all isolated species tested for urine bactericidal activity were considered. Similar values were obtained for both groups with respect to urinary levels, bactericidal and bacteriostatic titers (approximately one dilution of norfloxacin above that of rufloxacin). Differences in inhibitory quotients were due to differences in MIC. A statistically significant ($P < 0.05$) intragroup correlation between inhibitory quotients and bacteriostatic titers was found. While intergroup differences in urine bacteriostatic activity were about one dilution, eightfold differences were found with respect to inhibitory quotients.

All 203 patients were assessed for safety. There was no significant difference in the incidence of adverse events between the groups. Among the 103 patients treated with rufloxacin, 21 (20.4%) reported 39 different adverse events. Fifteen of the 39 (38%) adverse reactions involved the central nervous system and were reported by 12 patients; the most common events were dizziness (6 cases), insomnia (3 cases), and anxiety (3 cases). Twelve of the 39 (31%) adverse events were gastrointestinal reactions reported by 9 patients (7 of which reported nausea or vomiting and 3 who reported abdominal discomfort or pain). All adverse events were mild and lasted ≤24 h, except for a patient who reported diarrhea and anxiety which lasted 48 h. Among the 100 patients treated with norfloxacin, 12 (12%) patients reported 16 adverse events; of these, 14 (14 of 16; 89%) were gastrointestinal reactions (9 patients reported nausea/vomiting). All adverse experiences were mild and transient lasting ≤24 h, except for a reported case of nausea and another of diarrhea after each norfloxacin dose. No central nervous system reactions were reported among those treated with norfloxacin. A statistically significant difference ($P = 0.001$) was found when comparing patients reporting adverse reactions related to central nervous system between the groups (rufloxacin, 11.7%, versus norfloxacin, 0%).

DISCUSSION

Uncomplicated cystitis accounts for more than 85% of all patients with UTI who seek medical attention (24). Although the treatment's goal of this disease is to eradicate infection or reduce recurrences (18), duration of the treatment is a controversial issue (23). Three days is the favored duration of treatment (6, 23), as no efficacy differences between quinolones are found with treatments lasting more days, with respect to short- and long-term evaluations (24). This has been also shown in previous norfloxacin (400 mg BID for 3 days) studies (26, 32). Because the potential of higher rates of early recurrences (18), differences may arise when comparing standard therapy with a single-dose treatment, because of differences in half-life (24). Low bacterial eradication rates were obtained with single doses of enoxacin and fleroxacin (2, 24). Agents with adequate spectra of antibacterial activity against etiological microorganisms of uncomplicated cystitis, and prolonged high active concentrations in urine, are suitable for single-dose therapy (12). In vitro activity (33) and long half-life (34) make rufloxacin suitable as a candidate for assessing its efficacy as single-dose therapy, versus standard 3-day norfloxacin treatment.

With respect to the expected cure rates for short course regimens, following the IDSA/FDA guidelines (29), the trial should fulfill the following conditions: (i) at least 50% of the evaluable patients should have had $>10^5$ CFU of the uropathogen per ml in the initial culture, (ii) >75% of infections should end in bacterial eradication at the first follow-up visit, (iii) at least 50% of the patients assessed at this time should be followed at the 4- to 6-week visit, and (iv) >65% of these patients should be cured at this time. This study fulfills all these criteria.

No significant differences were found with respect to the microbiological evaluation at the short-term and long-term follow-up visit. As expected, four of the five rufloxacin microbiological failures were detected in the 8- to 12-day visit, but not in the 3- to 7-day visit, probably because of the presence of therapeutic antibiotic levels in this latter visit (14), and were not considered relapses for this reason. The only rufloxacin failure detected at the 3- to 7-day visit was due to a highly resistant *E. coli* (MIC >16 μg/ml). The norfloxacin failure was indeed an early relapse. Discrepancies between clinical failure rate (4%) and microbiological failure rate (1%) at the short-term follow-up evaluation in the norfloxacin group are probably due to the fact that symptoms persisted for several more days (18).

Eighty percent of the isolates were *E. coli*. Norfloxacin exhibits 8 times higher in vitro bacteriostatic activity than rufloxacin when susceptibilities of *E. coli* isolates to both drugs are compared. Failures at the first follow-up evaluation were independent of MIC values. All five relapses at the long-term follow-up visit were due to susceptible *E. coli.*

Our results confirm the low resistance rate after treatment

TABLE 3. Median and range bactericidal and bacteriostatic titers, urine levels, MICs, and inhibitory quotients of 26 patients with *E. coli* pretreatment isolates

Drug (*n*)	Titer (range)		Urine levels (μg/ml)	MIC (μg/ml)	Inhibitory quotient[a]
	Bactericidal	Bacteriostatic			
Rufloxacin (14)	8 (0–32)	16 (1–64)	24.75 (12.5–52)	0.5 (0.25–8)	55.5 (1.97–191)
Norfloxacin (12)	24 (2–64)	48 (4–128)	24.75 (3.15–160)	0.045 (0.03–0.125)	477.08 (25.2–5333.33)

[a] Inhibitory quotient: urine level/MIC.

of uncomplicated cystitis (25). Resistance emerges when low doses are used (which is not the case in this study, as high urine drug levels were obtained with both treatments) or in chronic or complicated UTI (25), despite the increasing tendency of resistant-strain isolation in Spain (1). Patients who received previous treatments because of complicated or recurrent UTI were excluded from this trial.

Although it is recognized that a single-dose quinolone therapy is generally less effective against *S. saprophyticus* (18), all three cases in the rufloxacin group and six out of seven in the norfloxacin one were bacteriologically cured. The number of *S. saprophyticus* isolates in this study was too small to draw conclusions about the efficacy of these drugs against this uropathogen.

The positive results and the absence of differences in the bacteriological and clinical assessments between single-dose rufloxacin and norfloxacin 3-day standard treatment are consistent with the pharmacokinetic and pharmacodynamic properties of rufloxacin and confirm the rufloxacin single-dose efficacy described in another trial (14). Similar rufloxacin and norfloxacin concentrations in urine were found 72 to 84 h after the initiation of the treatment. High urine concentrations of active Rufloxacin that exceeded MIC values of most isolated uropathogens were found for at least 84 h after the administration of the antibiotic.

From the pharmacodynamic point of view, similar urine bacteriostatic and bactericidal activities were found in both groups against *E. coli* isolates. These urine antibacterial activities are maintained for more than three days after a single dose of rufloxacin. Pharmacodynamic properties are similar for the rufloxacin single-dose regimen when compared with three-day norfloxacin standard treatment, despite the lower in vitro activity of the former. The dichotomy between inhibitory quotient (higher for norfloxacin) and urine antibacterial ex vivo activity (similar for both quinolones) may be explained by the reported (15) presence of low concentration of the rufloxacin's active *N*-demethyl derivative in concentrations ($\cong$5 μg/ml) above the *E. coli* MIC. This metabolite exhibits in vitro activity similar to that of rufloxacin against *E. coli* isolates (33) and may act synergically.

From the results obtained in this study, it can be concluded that both quinolones were well tolerated, as almost all of the adverse events were mild and transient. The percentage of patients reporting adverse events to norfloxacin in this study (12%) was somewhat lower than that found by others (19%) (32) with the same dose regimen. Almost all adverse events were gastrointestinal reactions. Interestingly enough, no central nervous system reactions were reported in our trial, although there have been some found in other studies (26, 28, 32) and with all quinolones (9). Furthermore, central nervous system reactions were the most commonly reported adverse effects in ofloxacin's postmarketing studies performed in Germany (9). With rufloxacin, 20% of patients reported one or more adverse events, a figure similar to those reported by other authors (14 to 21%) after a single dose or 7 to 14 days of treatment (14, 17, 20). This figure is heavily influenced by central nervous system reactions which were reported by 12% of patients, similar to the rate reported (13%) in another trial (14) but much higher than the one observed by Klietman et al. (17), who only reported 5 cases of this kind of adverse event among 127 patients who were treated with rufloxacin for 10 days. The fact that this study was conducted on an open fashion could contribute to explain these results. It should be emphasized that all adverse events but one lasted $\leq$24 h.

Our results show that in the treatment of uncomplicated urinary tract infections, the efficacy of rufloxacin (400 mg, single dose) is similar to that of norfloxacin (400 mg BID, three days) in terms of the clinical, microbiological eradication, relapse rate, 72- to 84-h urine level, and urine antibacterial activity.

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