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Pharmacokinetics and Serum Bactericidal Titers of Ciprofloxacin and Ofloxacin following Multiple Oral Doses in Healthy Volunteers

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Fourteen adult males participated in a randomized three-way crossover study to compare the pharmacokinetics and serum bactericidal titers (SBTs) of 500 mg of ciprofloxacin (regimen A), 750 mg of ciprofloxacin (regimen B), and 400 mg of ofloxacin (regimen C) administered every 12 h for seven doses. Mean steady-state peak concentrations in serum for regimens A, B, and C were 3.0, 4.4, and 6.5 μg/ml, respectively ($P < 0.01$, all comparisons) and mean half-lives were 4.5, 4.3, and 6.5 h, respectively ($P < 0.05$, C versus A and B). Mean steady-state areas under the concentration-time curve were 14.1, 21.1, and 48.1 μg/h/ml for regimens A, B, and C, respectively ($P < 0.05$, all comparisons). SBTs were determined at different times postdose for three isolates each of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*. Mean steady-state peak SBTs for regimens A, B, and C, respectively, were as follows: *S. pneumoniae*, <1:2, 1:8, 1:8; *S. aureus*, 1:16, 1:16, 1:16; *E. coli*, 1:≥128, 1:≥128, 1:64; *E. cloacae*, 1:≥128, 1:≥128, 1:64; *P. aeruginosa*, 1:8, 1:8, 1:2. These differences in SBTs within each genus were statistically significant. The majority of predicted SBTs were within one dilution of measured SBTs. Areas under the serum bactericidal time curves for *E. coli*, *E. cloacae*, and *P. aeruginosa* were significantly higher for ciprofloxacin; areas under the serum bactericidal time curves for *S. pneumoniae* and *S. aureus* were significantly greater for ofloxacin. Ofloxacin achieved higher concentrations in serum than ciprofloxacin, but differences in in vitro activity were a more important determinant of SBTs.

Ciprofloxacin and ofloxacin are fluoroquinolone antibiotics which are well absorbed by the oral route and are active against a broad range of pathogenic bacteria (7). Since these quinolones differ in both pharmacokinetics and in vitro activity, measurement of serum bactericidal titers (SBTs) integrates both characteristics and allows for direct comparison of their pharmacodynamic properties (1, 4, 16). The purpose of this study was to compare the pharmacokinetics and SBTs of ciprofloxacin and ofloxacin in healthy volunteers after multiple-dose oral administration.

(A portion of this manuscript appeared as an abstract in the program of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, Calif., October 1992 [6a].)

MATERIALS AND METHODS

Study subjects. Fourteen healthy male volunteers participated in this study after providing informed consent. This study was approved by the Committee on the Conduct of Human Research of the Medical College of Virginia, Virginia Commonwealth University. The mean age ± standard deviation was 25 ± 3.6 years, and the mean weight ± standard deviation was 76.2 ± 11.6 kg. Exclusion criteria included known hypersensitivity to quinolones, abnormalities on physical examination or prestudy serum biochemical tests, including hematology, electrolytes, and liver and renal function, or an abnormal electrocardiogram. Each subject was required to abstain from any medications, including vitamins, mineral supplements, and antacids, the week prior to and throughout the duration of the study. Alcohol (maximum of two drinks per day) was permitted during washout weeks; subjects were required to refrain from alcohol at least 48 h prior to each study period. Subjects were allowed two cups of caffeinated beverages per day.

Drug administration and sample collection. Subjects reported to the Medical College of Virginia's BioClin Research Center the evening prior to the first dose of each study period. The morning of day 1, after an overnight fast, subjects received in random order one of the following three regimens (each administered every 12 h for seven doses): 500 mg of ciprofloxacin (lot 1ABP; Miles, Inc., West Haven, Conn.), 750 mg of ciprofloxacin (lot OJCST), or 400 mg of ofloxacin (lot HA2974; Ortho Pharmaceuticals, Raritan, N.J.). One hour prior to each dose, subjects consumed 240 ml of tap water. Four hours after the first dose, subjects consumed a standard meal. Subjects remained in the research unit until after they received their second dose of study drug; they then returned to receive each subsequent dose. Subjects were also housed overnight before the final dose for each regimen. There was a 10-day washout between each regimen. All 14 subjects completed the three regimens.

Blood samples. Serial blood samples (approximately 3 ml) for concentrations of ciprofloxacin and ofloxacin in serum were collected through an indwelling catheter kept patent by periodic injections of heparin. Blood was obtained on day 1

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immediately before dosing (baseline) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 h postdose. The 12-h sample was obtained just prior to administration of the second dose. Blood was obtained before and after dose 7 at the same times as dose 1, with additional samples obtained at 16, 20, 24, 28, and 32 h postdose. SBTs for the measured peak concentration and at 4, 8, and 12 h postdose were determined. After the seventh dose, SBT determinations were repeated at the same times as before and an additional sample was obtained at 24 h.

Samples for serum drug concentration and SBTs were collected in red top tubes, allowed to clot for 30 min, centrifuged for 20 min at 1,000 × *g*, and then transferred to sterile polypropylene tubes. Samples for serum drug concentration were stored at −35°C, and samples for SBTs were stored at −70°C until the assay.

Urine samples. Baseline urine was collected prior to dose 1 and from 0 to 4 h, 4 to 8 h, and 8 to 12 h. After dose 7, urine was similarly collected, with an additional collection from 12 to 24 h. The total volume of urine collected during each interval was recorded, and aliquots (5 ml) of each sample were transferred to polypropylene tubes and frozen at −35°C until assay.

Ciprofloxacin and ofloxacin assay. Ciprofloxacin and ofloxacin concentrations in serum were measured by a procedure developed in our laboratory involving a reversed-phase high-performance liquid chromatography method. A mobile phase consisting of 0.05 M potassium phosphate buffer (pH 2)–tetrahydrofuran (90:10, vol/vol) was pumped through a C18 column (5-μm particle size, 250 by 4.6 mm [Nucleosil; Alltech Associates, Inc., Applied Science Division, State College, Pa.) at a flow rate of 1.5 ml/min. The signal was recorded by fluorescence detection with excitation at 277 nm and a 417-nm cutoff filter on the emission side.

Serum standards, controls, and patient specimens were thawed and vortexed, and 500 μl was transferred to borosilicate glass tubes (16 by 100 mm) to which 100 μl of internal standard was added. The internal standard for ciprofloxacin was ofloxacin (5 μg/ml; lot 18489-000-AC, R. W. Johnson Pharmaceuticals), and the internal standard for ofloxacin was norfloxacin (5 μg/ml; lot vR1275, Merck Sharp & Dohme, West Point, Pa.). After vortexing for 5 s, 400 μl of sodium phosphate buffer (0.2 M, pH 7.0) was added, and this mixture was vortexed for an additional 5 s. Ciprofloxacin (or ofloxacin) and internal standard were extracted into 5.5 ml of dichloromethane-isopropyl alcohol (90:10, vol/vol) by rotation for 25 min. The tubes were then centrifuged for 25 min at 580 × *g*. The aqueous layer was aspirated, and the lower organic layer was transferred to a clean glass culture tube and evaporated to dryness under nitrogen at 40 to 50°C. The residue was reconstituted with 200 μl of mobile phase and vortexed for 10 s at high speed. The sample was transferred to an autosampler vial, and 20 μl was injected onto the column. Retention time for ofloxacin was approximately 6 min. Both ciprofloxacin and norfloxacin had retention times of 8 min. The limit of detection for both the ciprofloxacin assay and the ofloxacin assay was 0.05 μg/ml. The standard curve for ciprofloxacin had a linear range of 0.05 to 1.25 μg/ml, and the linear range for ofloxacin was 0.05 to 1.5 μg/ml; samples were diluted as required. Between-day coefficients of variation ranged from 3 to 9%. Recovery was 73 and 83% for ciprofloxacin and ofloxacin, respectively.

Urine was assayed for antibiotic concentrations by a method similar to that used for serum, with the following modifications. The flow rate was 1.0 ml/min, and the integrator measured peak heights instead of peak area (for ciprofloxacin only). Urine standards, controls, and unknowns were thawed, vortexed, and centrifuged, and 100 μl of each sample was transferred to a clean glass culture tube. The internal standard for ciprofloxacin was ofloxacin (25 μg/ml; lot 18489-000-AC, R. W. Johnson Pharmaceuticals), and the internal standard for ofloxacin was norfloxacin (25 μg/ml; lot vR1275, Merck Sharp & Dohme). Internal standard (200 μl) was added to each tube, and then the mixture was diluted to 5 ml (1:50 dilution) and vortexed. The sample was transferred into an autosampler vial, and 15 μl was injected. Retention times for ciprofloxacin and internal standard (ofloxacin) were 10 and 8 min, respectively. Ofloxacin and its internal standard (norfloxacin) had retention times of 6 and 8 min, respectively. The range of linearity for both drugs was 10 to 200 μg/ml. Between-day coefficients of variation ranged from 1 to 6% for ciprofloxacin and 1 to 4% for ofloxacin.

TABLE 1. MBCs for clinical isolates and American Type Culture Collection strains

Organism[a]	MBC (μg/ml) of:	
	Ciprofloxacin	Ofloxacin
S. aureus		
Isolate 1	0.78	0.19
Isolate 2	0.78	0.39
Isolate 3	0.19	0.19
S. pneumoniae		
Isolate 1	0.39	0.78
Isolate 2	0.78	1.56
Isolate 3	0.39	0.78
E. coli		
Isolate 1	0.012	0.048
Isolate 2	0.012	0.048
Isolate 3	0.012	0.048
E. cloacae		
Isolate 1	0.024	0.048
Isolate 2	0.024	0.048
Isolate 3	0.048	0.097
P. aeruginosa		
Isolate 1	0.78	6.2
Isolate 2	0.78	3.1
Isolate 3	0.097	1.56

[a] For each organism, isolate 1 is the American Type Culture Collection strain.

SBT procedure. Three isolates (one American Type Culture Collection strain and two clinical specimens) of each of the following organisms were tested: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*. To select clinical specimens, we determined MICs of ciprofloxacin and ofloxacin for five clinical isolates of each of the preceding species, and from these we selected two susceptible isolates (when possible) with the broadest range of MICs of each drug. MICs and MBCs of both drugs against each isolate were determined by the microdilution method recommended by the National Committee for Clinical Laboratory Standards (14), and the MBCs are shown in Table 1. The MIC for each isolate (data not shown) was the same as the MBC or was 1 dilution lower. SBTs were determined in serial twofold dilutions of Mueller-Hinton broth plus human serum (50:50) with the standard microdilution method recommended by the National Committee for Clinical Laboratory Standards (13). The range in measured SBTs was from ≤1:2 to ≥128. A total of 5,670 SBTs were determined, representing 405 SBTs per subject.

Pharmacokinetic analysis. The pharmacokinetic parame-

ters for ciprofloxacin and ofloxacin were determined by noncompartmental and compartmental methods. The maximum concentration and the time of maximum concentration were determined by visual inspection of the observed concentration-versus-time profiles for each subject. Serum concentrations versus time were analyzed by PCNONLIN (19) by using both one- and two-compartment, multiple-dose models with first-order absorption and elimination and no lag time. The goodness of fit of the one- or two-compartment body model to the data was determined by using the Schwartz criterion. Weighting of 1/concentration provided the best fit to the data. The elimination rate for each subject was estimated from PCNONLIN-generated least-squares regression. The areas under the plasma concentration-time curve from time zero to 12 h (AUC_{0-12}) after the final dose were determined by the linear trapezoidal rule. Renal clearance was estimated as the amount recovered (0 to 12 h, dose 7) divided by the AUC_{0-12} (dose 7). Accumulation for each regimen was estimated from the AUC_{0-12} for the first and seventh doses and an accumulation factor, AUC_1/AUC_2, was calculated.

SBT evaluations. Each SBT was converted to its $\log_2$-transformed value to allow use of parametric statistical tests (see below). For example, reciprocal SBTs of ≤2, 2, 4, 8, etc, were converted to log values of 0, 1, 2, 3, etc. The arithmetic mean SBT was then calculated and rounded to the nearest integer; the mean SBT is reported from the antilog. For example, an arithmetic mean SBT of 5.3 results in a mean SBT of 1:32.

The area under the SBT-versus-time curve (AUBC) was calculated at steady state. The reciprocal of the log SBT was plotted as a function of time for each subject, regimen, and isolate. AUBCs were calculated by the trapezoidal rule from the baseline, measured peak, and 4-, 8-, and 12-h reciprocal log SBTs. (When the SBT was ≥7, a value of 7 was used for calculation of AUBC.) The mean AUBC for each bacterial species and regimen was then determined.

Predictability of SBTs. An investigator blinded to measured SBTs calculated a predicted SBT for each subject and each organism for the final dose at the measured peak and at 4, 8, 12, and 24 h. The predicted SBT is the quotient of the measured serum concentration and MBC rounded to the nearest integer. The percentage of predicted SBTs that were within ±1 dilution of measured SBTs is reported. A total of 210 pairs of measured and predicted SBTs were possible for each bacterial species. When predicted and measured SBTs were both ≤1:2 or ≥1:128, this was interpreted as agreement (within ±1 tube). A predicted SBT of 1:128 with a measured SBT of ≥1:128 was also interpreted as agreement. Bias was calculated as the mean of the log difference between predicted and measured SBTs.

Statistical analysis. Statistical comparisons of the differences in pharmacokinetic parameters, SBTs for organisms and regimens, and AUBCs were tested by two-way analysis of variance. Scheffe's test was used for post hoc comparisons. Variability is expressed as standard deviation. Statistical significance was defined as $P < 0.05$.

RESULTS

All 14 subjects completed each phase of the study. Adverse reactions to ciprofloxacin included nausea, diarrhea, left flank pain (one subject, 500 mg of ciprofloxacin), and headache, nausea, and flatus (one subject each, 750 mg of ciprofloxacin). During ofloxacin treatment, two subjects reported nausea and vomiting (temporally unrelated to administration time) and one complained of headache.

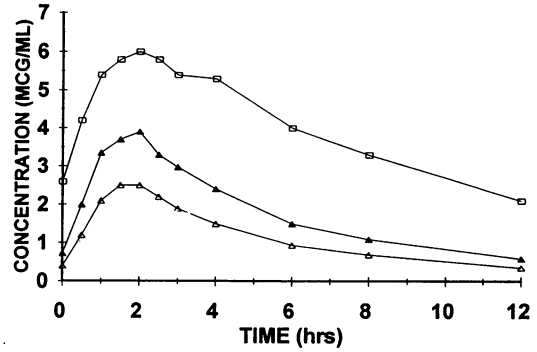

FIG. 1. Mean steady-state concentrations in serum of 500 mg of ciprofloxacin (△), 750 mg of ciprofloxacin (▲) and 400 mg of ofloxacin (□) in 14 adults.

Pharmacokinetics. Mean steady-state serum concentrations of all regimens are shown in Fig. 1. Pharmacokinetic parameters are listed in Table 2. Concentrations of ciprofloxacin and ofloxacin immediately prior to the final dose were not significantly different from the concentrations 12 h after the final dose (Fig. 1), indicating that steady-state conditions had been attained for all three regimens by the seventh dose. Compared with both ciprofloxacin regimens at steady state, ofloxacin had a significantly higher mean peak serum concentration, longer half-life, and a greater AUC_{0-12}. Accumulation was significantly greater for ofloxacin, and more ofloxacin was recovered in urine over 24 h. The volume of distribution for ciprofloxacin was greater than that for ofloxacin.

SBTs. Reciprocal mean SBTs versus time for each organism and regimen are shown in Table 3. In general, SBTs at steady state were the same as or were 1 tube dilution higher than those observed after the first dose (data not shown). Against *S. pneumoniae*, mean steady-state peak SBTs for 750 mg of ciprofloxacin and 400 mg of ofloxacin were equal (1:4) and were significantly greater than that for 500 mg of ciprofloxacin (<1:2). For *S. aureus*, there was no difference between steady-state peak titers for all three regimens (1:16). For *E. coli* and *E. cloacae*, peak steady-state SBTs of both ciprofloxacin regimens (≥1:128) were significantly greater than that for ofloxacin (1:64). SBTs of ciprofloxacin and for *E. coli* were more often ≥1:128 (55 and 44% of all SBTs of 750 and 500 mg of ciprofloxacin, respectively) than were those of ofloxacin (26% of SBTs). Similarly, SBTs for *E. cloacae* and of ciprofloxacin were more often ≥1:128 (35 and 25% for 750 and 500 mg of ciprofloxacin, respectively) than was that of ofloxacin (6%). SBTs for *P. aeruginosa* were significantly higher with both ciprofloxacin regimens (1:8 for each) than was that of ofloxacin (1:2).

AUBCs. The mean AUBCs for each organism and regimen are shown in Table 3. The mean steady-state AUBCs for *S. pneumoniae* and *S. aureus* were significantly greater for ofloxacin than both regimens of ciprofloxacin. Against *E. coli* and *E. cloacae*, mean steady-state AUBCs were significantly higher for 500- and 750-mg ciprofloxacin regimens than for ofloxacin. Since SBTs of ciprofloxacin were more often ≥1:128 than were those of cofloxacin for these two organisms (as shown above), the true difference in AUBCs between regimens is greater than the reported values (Table 3). For *P. aeruginosa*, the two ciprofloxacin regimens were

TABLE 2. Pharmacokinetic parameters for the first and seventh doses of ciprofloxacin and ofloxacin[a]

Parameter	500 mg of ciprofloxacin		750 mg of ciprofloxacin		400 mg of ofloxacin	
	Dose 1	Dose 7	Dose 1	Dose 7	Dose 1	Dose 7
Serum peak concn (μg/ml)	2.5 (0.6)	3.0 (0.6)[b]	3.3 (0.7)	4.4 (1.1)[b]	4.5 (1.3)	6.5 (1.5)[b]
Time of peak concn (h)	1.4 (0.4)	1.6 (0.7)	1.5 (0.3)	1.6 (0.8)	1.5 (0.5)	1.8 (0.8)
Terminal half-life (h)	4.0 (1.6)	4.5 (1.2)	4.2 (0.6)	4.3 (1.5)	4.6 (1.5)	6.5 (0.7)[c]
AUC_{0-12} (μg/h/ml)	10.6 (2.3)	14.1 (2.7)[d]	15.6 (3.1)	21.1 (6.1)[d]	26.7 (5.3)	48.1 (12.3)[c]
Vol of distribution area/F (liter)	254.3 (56.3)	295.6 (76.6)	256.1 (57.3)	295.1 (107)	103.4 (21.0)	60.7 (11.5)[c]
Renal clearance (ml/min)[e]	NC[f]	226.5 (94.8)	NC	192.6 (87.4)	NC	107.7 (36.9)[c]
Urinary recovery (% dose/12 h)[e]	NC	36.9 (13.1)	NC	32.2 (9.7)	NC	68.0 (29.6)[c]
Accumulation factor		1.4 (0.2)		1.3 (0.2)		1.8 (0.2)[c]

[a] Mean predicted values are in parentheses. (Note that statistical significance was determined only for values at dose 7.)
[b] $P < 0.01$.
[c] Ofloxacin value significantly different from those of both ciprofloxacin regimens ($P < 0.01$).
[d] $P < 0.05$.
[e] Values are for renal clearance and urinary recovery from 13 subjects.
[f] NC, not calculated.

not significantly different, but 750 mg of ciprofloxacin resulted in significantly higher AUBCs than did ofloxacin. There was no significant difference between the 500-mg ciprofloxacin regimen and the ofloxacin regimen for *P. aeruginosa*.

The AUBCs described above represent mean values; within a species, however, there were occasionally large differences in AUBCs, depending on the MBC for a particular isolate. This was most clearly seen for *P. aeruginosa*, in which there was a large difference in MBCs of ciprofloxacin for isolates 1 and 3 (0.78 versus 0.097 μg/ml). There was a greater than threefold difference in mean AUBCs for these two isolates and the 500-mg ciprofloxacin regimen (9.8 ± 4.8 and 32.4 ± 14.5 [$P < 0.05$], respectively). In contrast, differences in AUBCs resulting from pharmacokinetic differences were less pronounced. For example, AUBCs after 500- and 750-mg ciprofloxacin regimens for *P. aeruginosa* (isolate 1) were less than twofold (9.8 ± 4.2 versus 15.2 ± 8.0 [$P > 0.05$]). Figure 2 shows the inverse relationship between MBCs and AUBCs for all organisms and regimens. The deviations from this relationship (at MBCs of ciprofloxacin and ofloxacin of 0.78 and 3.1 μg/ml, respectively) occurred primarily for *S. aureus* and *P. aeruginosa*, for which SBTs were greater than expected (Table 2 and below).

Predictability of SBTs. Figure 3 shows the predictability of SBTs at steady state. The majority of measured SBTs were within one tube of the predicted SBTs. However, calculation of bias revealed that predicted SBTs of ciprofloxacin were generally lower than measured (underpredicted or negative bias), whereas predicted SBTs of ofloxacin were greater than measured (overpredicted or positive bias). The means of the difference in log SBTs (predicted − measured) for the three regimens, i.e., 500 mg of ciprofloxacin, 750 mg of ciprofloxacin, and 400 mg of ofloxacin, respectively, were as follows: *S. aureus*, −0.61, −0.62, +0.80; *S. pneumoniae*, +0.36, +0.44, +0.36; *E. coli*, −0.48, −0.40, +0.04; *E. cloacae*, −0.89, −0.90, +1.00; *P. aeruginosa*, −0.20, −0.17, −0.69.

DISCUSSION

Other trials have compared the pharmacokinetics of ciprofloxacin and ofloxacin (2, 11, 17, 25–27), although this is the first to compare multiple oral doses. Results from the present study are consistent in finding that ofloxacin (400 mg) achieves higher serum concentrations and has a longer half-life, higher AUC, and greater urinary recovery after oral administration than ciprofloxacin (500 and 750 mg). We found that accumulation was significantly greater for ofloxacin, reflecting its longer half-life. The steady-state mean AUC over 12 h for ofloxacin was approximately two and one-half times that of 750 mg of ciprofloxacin. As in other studies, the volume of distribution for ciprofloxacin was significantly larger than that for ofloxacin.

Characterization of the pharmacodynamic properties of an antibiotic must consider not only pharmacokinetic features, but in vitro activity as well. In general, ciprofloxacin is more active for members of the family *Enterobacteriaceae* and for *P. aeruginosa*, ofloxacin is more active for *S. aureus*, and both have similar activities for *S. pneumoniae* (7). The susceptibilities of the organisms in this study (Table 1) are consistent with reported values for these two drugs.

SBTs integrate both differences in pharmacokinetics and in vitro activity, allowing for direct comparisons between drugs. Calculation of AUBCs from serial measurement of SBTs has been proposed to be a rational method to compare antibacterial drugs (1, 16). A number of investigators have determined SBTs after administration of ofloxacin or ciprofloxacin (5, 9, 18, 24), and three investigations have directly compared the SBTs of ciprofloxacin and ofloxacin after single-dose intravenous or oral administration (12, 25, 28). The overall results of the present study are consistent with previous investigations in finding SBTs and AUBCs for *E. coli* and *E. cloacae* to be very high for both drugs, lower for *S. aureus* and *P. aeruginosa*, and poorest for *S. pneumoniae*.

We found a number of statistically significant differences between SBTs and AUBCs for the three regimens. The clinical significance of the differences in SBTs and AUBCs (Table 3) is unknown, since specific SBTs and AUBCs of quinolones have not been correlated to clinical outcome in prospective human trials (as described below). However the rank order of SBTs and AUBCs in this trial correlates well with clinical experience. For example, published clinical trials indicate that both drugs are highly effective for treatment of infections caused by members of the family *Enterobacteriaceae* (7).

Ciprofloxacin is more effective for infections caused by *P. aeruginosa*, although emergence of resistance has been reported (7). Both ciprofloxacin and ofloxacin appear effective for infections caused by *S. aureus*, although methicillin-resistant *S. aureus* may rapidly become resistant (22). There has been considerable controversy regarding the efficacy of

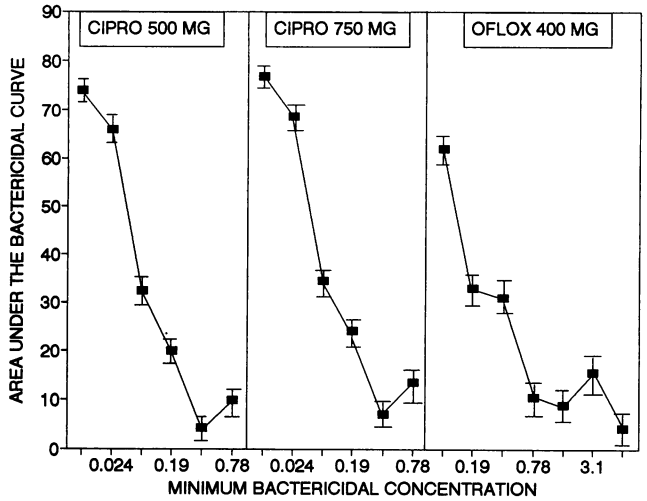

FIG. 2. Relationship between the MBCs and AUBCs of 500 mg of ciprofloxacin, 750 mg of ciprofloxacin, and 400 mg of ofloxacin.

TABLE 3. Mean measured SBTs at steady state

Organism	Measured (predicted) SBT and $AUBC_{0-12}$ for regimen:											
	500 mg of ciprofloxacin					750 mg of ciprofloxacin					400 mg of ofloxacin				
	Peak	4 h	8 h	12 h	24 h	$AUBC_{0-12}$ (mean ± SD)	Peak	4 h	8 h	12 h	24 h	$AUBC_{0-12}$ (mean ± SD)	Peak	4 h	8 h	12 h	24 h	$AUBC_{0-12}$ (mean ± SD)
S. pneumoniae	<2 (4)	<2 (2)	<2 (0)	<2 (0)	<2 (0)	3.3 ± 1.3	8 (4)	2 (4)	<2 (2)	<2 (0)	<2 (0)	6.1 ± 1.9	8 (4)	4 (4)	2 (2)	<2 (2)	<2 (0)	10.1 ± 3.8
S. aureus	16 (4)	4 (2)	2 (0)	<2 (0)	<2 (0)	17.5 ± 4.9	16 (8)	4 (4)	2 (2)	<2 (0)	<2 (0)	21.2 ± 8.9	16 (16)	8 (16)	4 (8)	4 (8)	<2 (2)	32.3 ± 8.1
E. coli	>128 (>128)	>128 (64)	64 (32)	32 (16)	16 (8)	74.0 ± 3.8	>128 (>128)	>128 (>128)	64 (64)	64 (32)	16 (8)	77.3 ± 4.5	64 (>128)	64 (64)	32 (32)	32 (32)	16 (8)	68.3 ± 5.5
E. cloacae	>128 (64)	64 (32)	32 (16)	16 (8)	4 (2)	65.9 ± 3.4	>128 (64)	64 (32)	32 (16)	4 (4)	4 (4)	69.8 ± 10.1	64 (64)	32 (64)	16 (32)	8 (32)	4 (8)	54.7 ± 3.2
P. aeruginosa	8 (8)	4 (2)	2 (2)	<2 (0)	<2 (0)	16.1 ± 6.4	8 (8)	4 (4)	2 (2)	<2 (0)	<2 (0)	19.5 ± 7.5	2 (2)	2 (0)	2 (0)	<2 (0)	<2 (0)	11.4 ± 6.2

quinolones for infections caused by *S. pneumoniae*, in part because of the relatively poor ratio of concentrations in serum to MICs (10).

The pharmacodynamic determinants of efficacy for the fluoroquinolones have recently been investigated. Experimental evidence in neutropenic mice (3, 23), theoretical arguments (16), and retrospective analysis of clinical trial data (6) indicate that either the peak concentration/MIC ratio or the daily area under the inhibitory time curve (AUIC) is most predictive of response. Specifically, daily AUICs of 25 to 125 have been reported to correlate with optimal response (6, 16, 23). Since the quinolones are bactericidal, our AUBCs should be similar to AUICs, or slightly lower. When the steady-state AUBCs (Table 3) are doubled to yield AUBCs over a full day, only *E. coli* and *E. cloacae* would be considered fully susceptible. Some *S. aureus* and *P. aeruginosa* strains would also be susceptible, depending on the specific MBC as discussed above. All of the *S. pneumoniae* strains in this study would be considered resistant. Similarly, the mean AUCs from the pharmacokinetic analysis (Table 2) can be used to calculate MIC breakpoints for each regimen required to produce AUICs of 125. Breakpoints for 500 and 750 mg of ciprofloxacin and 400 mg of ofloxacin, each given every 12 h, would be 0.19, 0.28, and 0.64 μg/ml, respectively. These breakpoints are more conservative than those usually recommended, but would be closer to the approved breakpoints if a less-stringent AUIC were used. However intriguing these concepts are, the true significance of differences in AUBCs and designation of appropriate breakpoints must be verified by prospective clinical trials.

SBTs primarily reflect the interaction of the antibiotic and the in vitro susceptibility (MBC) of the organism (20). SBTs should be predictable if these two variables are known, and limited data for other classes of antibiotics suggest this to be true (4, 21), although not all agree (8, 15). One previous investigation evaluated the predictability of SBTs from quinolones. Dudley et al. found that measured SBTs for ciprofloxacin after single-dose infusion were greater than predicted (5). They attributed this to a bioactive metabolite of ciprofloxacin which is transiently present at concentrations above the MBC for highly susceptible organisms (29). We also found that measured SBTs for ciprofloxacin were fre-

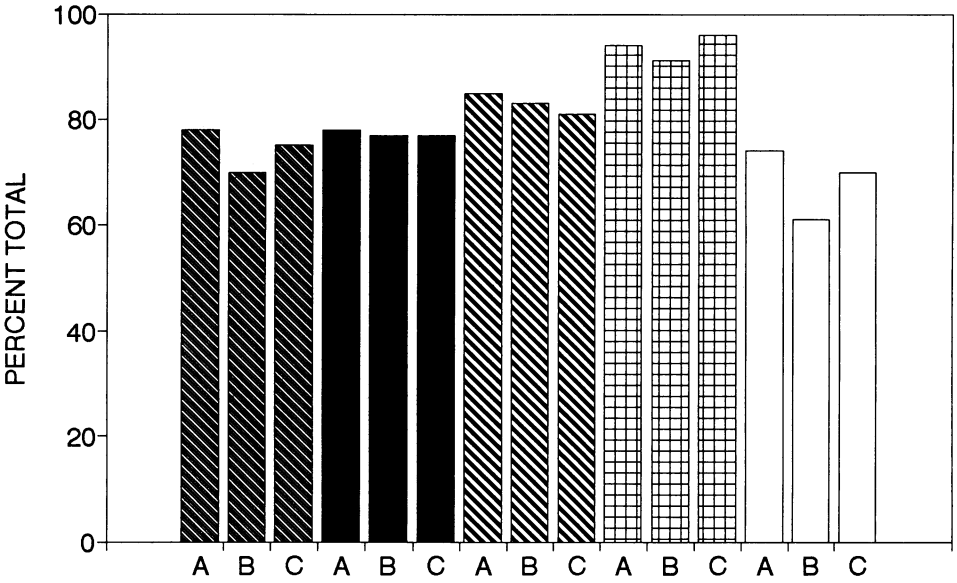

FIG. 3. Predictability of serum bactericidal titers at steady state for each organism. Each bar represents the proportion of measured SBTs which are within ±1 dilution of the predicted SBT. From left to right: A, 500 mg of ciprofloxacin; B, 750 mg of ciprofloxacin; C, 400 mg of ofloxacin. □, *S. aureus*; ■, *E. coli*; ▨, *P. aeruginosa*; ■, *S. pneumoniae*; □, *E. cloacae*.

quently greater than predicted, whereas measured and predicted values for ofloxacin showed closer agreement (Table 3 and Fig. 3).

When comparing two antibiotics, a one-tube disadvantage in MBC offsets a twofold advantage in concentration in serum. Within a class of antibiotics, it is more common to find marked differences in in vitro activity than to find similarly large differences in pharmacokinetics. This is especially true for fluoroquinolones, since peak concentrations in serum for all of the available drugs range from 3 to 8 μg/ml, approximately a threefold difference. In contrast, it is not unusual to find differences in MIC_{90}s of 5- to 10-fold as discussed above (7). The data from this study indicate that these differences in in vitro activity have a greater impact on SBTs and AUBCs than do differences in pharmacokinetic parameters. The strong inverse relationship between the AUBC and the MBC across organisms (Fig. 2) suggests that the MBC is the major determinant of the SBT and that differences in SBTs between organisms primarily reflect differences in MBCs. However, it is ultimately the ratio of serum concentration to MBC which determines the measured SBT.

In the present trial, ciprofloxacin's greater in vitro activity for *E. coli*, *E. cloacae*, and *P. aeruginosa* offset its lower concentrations in serum and resulted in SBTs and AUBCs greater than those of ofloxacin. In contrast, ofloxacin's greater activity for *S. aureus* and its higher concentrations in serum resulted in greater AUBCs, although peak SBTs were not different. SBTs for *S. pneumoniae* were relatively poor for all three regimens, but the persistently higher concentrations of ofloxacin in serum resulted in a greater AUBC.

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