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Effect of Dose Size on Bioavailability of Ciprofloxacin

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We evaluated the bioavailability of ciprofloxacin at two dose sizes in eight healthy volunteers. Each volunteer was given 200 mg of ciprofloxacin both orally and intravenously in a randomized crossover fashion and 750 mg orally. Bioavailability at the two doses was similar: 69 and 69.1% for the 200- and 750-mg doses, respectively. However, the bioavailability observed with the 750-mg dose was significantly more variable than that observed with the 200-mg dose. Between 375 and 700 mg of ciprofloxacin reached the systemic circulation after administration of the 750-mg dose, with no evidence of adverse reactions.

Ciprofloxacin is a quinoline carboxylic acid antimicrobial agent with a broad spectrum of in vitro activity, including activity against methicillin-susceptible and -resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The current dosages available for clinical testing are up to 300 mg intravenously (i.v.) and up to 1 g orally. Previous work at the University of Maryland with healthy subjects given 200 mg orally has revealed that the drug is reliably (approximately 70%) bioavailable (2). Because of the discrepancy in dose sizes available for the i.v. and oral routes of administration and because an assessment of bioavailability with large oral doses has not previously been reported, we believed it necessary to determine the influence of dose size on the bioavailability of ciprofloxacin.

Eight healthy, nonobese male volunteers between 22 and 30 years of age received 200 mg of ciprofloxacin both orally and i.v. in a randomized crossover fashion and 750 mg orally. Ciprofloxacin was obtained from Miles Pharmaceuticals. All volunteers were participating in concurrent studies evaluating the effect of renal function on the disposition of ciprofloxacin (A. Forrest, M. Weir, K. Plaisance, G. Drusano, J. Caldwell, C. Bustamante, J. Leslie, and H. Standiford, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1002, 1985) and the absolute bioavailability of ciprofloxacin (2). Each subject had normal hepatic and renal function indices and gave written informed consent in accordance with institution guidelines. At least 1 week elapsed between studies. All subjects received each of the three regimens on an empty stomach after an overnight fast. The 200-mg i.v. dose of ciprofloxacin was administered as an infusion in 100 ml of normal saline over 10 min. The oral dose was either two 100-mg tablets or one 750-mg tablet administered with 180 ml of tap water. Water was allowed as desired, but the volunteers continued fasting for 3 h after the administrations. The volunteers were questioned about possible adverse reactions, and vital signs were obtained preadministration and at 0, 2, 8, and 24 h postadministration.

For the oral-dose study, blood samples were obtained before drug administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after administration. For the i.v. study, blood samples were obtained before administration, at the end of the infusion, and at 0.083, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the end of the infusion. Serum samples were promptly stored at −20°C or less until the time of assay.

Ciprofloxacin was measured in serum by previously described methods (2). Interday percent coefficients of variation for the assay were 5.5% or less.

Serum data were modeled with either zero-order (i.v.) or first-order (peroral [p.o.]) absorption with a lag time by using iterative, nonlinear, least-squares regression (1). The reciprocal of the assay variance was used for weighting.

The area under the serum concentration-time curve (AUC) was calculated by the linear trapezoidal rule, with extrapolation to infinity accomplished by adding the last observed concentration divided by the terminal elimination rate constant. The elimination rate constant was determined by iterative, weighted, least-squares regression of the terminal portion of the serum concentration-time curve. Total serum clearance was calculated as the dose divided by the AUC from zero hour to infinity ($AUC_{0-\infty}$). The volume of distribution in the postdistributional phase was determined as the dose divided by the product of AUC times the elimination rate constant. Bioavailability (F) was calculated as: $F = AUC_{p.o.} \times dose_{i.v.}/(AUC_{i.v.} \times dose_{p.o.})$.

Statistical comparisons of pharmacokinetic parameter estimates between treatments were accomplished with a one-way analysis of variance, and an F test was used to compare variances.

Demographic data for our subjects are shown in Table 1. Pertinent pharmacokinetic parameter values for the three

TABLE 1. Demographic characteristics of male volunteers

Volunteer	Age (yr)	Wt (kg)	CL_{CR}[a] (liters/h per 1.73 m^2)
1	28	88.2	6.2
2	28	74.5	7.5
3	28	81.9	9.0
4	28	60.5	6.9
5	30	74.1	6.1
6	26	89.4	6.1
7	22	68.5	7.9
8	27	81.6	7.0
$\bar{x}$ (SD)	27.1 (2.4)	77.3 (9.9)	7.1 (1.0)

[a] CL_{CR}, Creatinine clearance.

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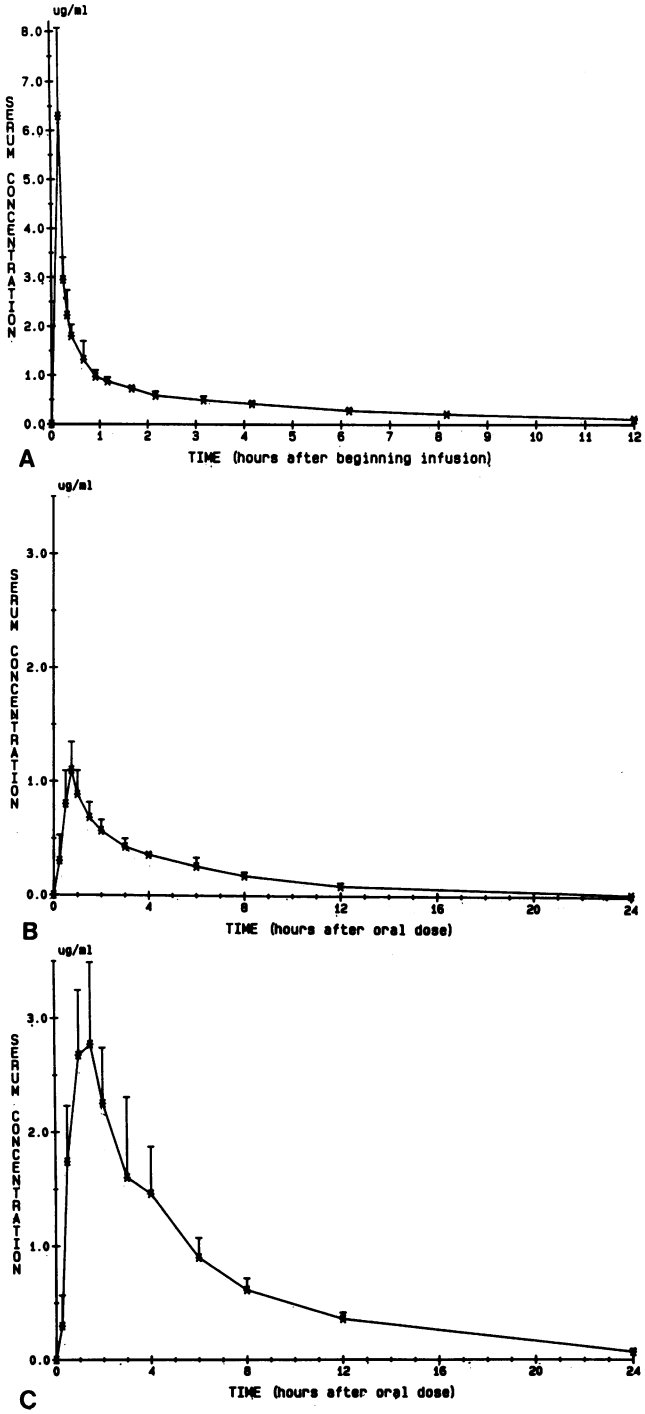

FIG. 1. Mean concentrations of ciprofloxacin in sera of eight healthy volunteers after a 10-min i.v. infusion (A) and 200-mg (B) and 750-mg (C) oral doses. The vertical lines indicate standard deviations.

studies are shown in Tables 2 and 3. The maximum mean (standard deviation) concentration in serum samples observed after i.v. administration was 6.3 (1.77) μg/ml, with a 12-h concentration of 0.1 (0.009) μg/ml (Fig. 1A). After oral administration of 200 mg, a mean peak concentration of 1.18 (0.20) μg/ml was achieved at 0.69 (0.18) h, with 8- and 12-h concentrations of 0.17 (0.03) and 0.09 (0.03) μg/ml, respectively (Fig. 1B). The peak concentration, observed at a mean time of 1.38 (0.35) h after oral administration of 750 mg, was 2.97 (0.65) μg/ml, and 8- and 12-h concentrations were 0.61 (0.10) and 0.36 (0.06) μg/ml, respectively (Fig. 1C).

TABLE 2. Model independent pharmacokinetic parameter values for ciprofloxacin in normal volunteers[a]

Regimen	V_{area}/F (liters/kg)	CL/F (liters/h per 1.73 m^2)	AUC (mg/h per liter)	$t_{1/2}$ (h)
200 mg i.v.	2.55 (0.44)	26.8 (5.71)	5.97 (0.91)	4.27 (0.84)
200 mg p.o.	3.87 (1.12)	39.1 (7.28)	4.18 (1.10)	4.11 (0.73)
750 mg p.o.	4.62 (1.05)	42.2 (8.05)	15.3[b] (3.77)	5.19[b] (0.68)

[a] V_{area}, Volume of distribution in the postdistributional phase; CL, clearance; $t_{1/2}$, half-life. Values are means, with standard deviations in parentheses.

[b] Value significantly different from those for the other regimens (one-way analysis of variance; $P < 0.05$).

A significantly longer elimination half-life was observed after administration of the 750-mg dose (5.19 h) than with either the i.v. (4.27 h) or oral (4.11 h) administration of the 200-mg dose (Table 2). The percentage of the total area which was extrapolated in the calculation of $AUC_{0-\infty}$ ranged from 0.3 to 11%, with a mean of 3.6%. The influence of the longer elimination half-life with the larger dose on the calculation of area was therefore minimal. Apparent serum clearance (CL/F, where CL is total clearance and $F = 1$ after i.v. administration) of the 200- and 750-mg oral doses was not significantly different.

The mean bioavailability of ciprofloxacin at the two doses studied was equivalent (69.0 and 69.1% [Table 3]). The bioavailability of the 750-mg dose, however, was significantly more variable than that observed with the 200-mg dose (Fig. 2; $F = 4.06$; $P < 0.05$). The slower absorption rate constant (k_a) observed with the larger dose (Table 3) may

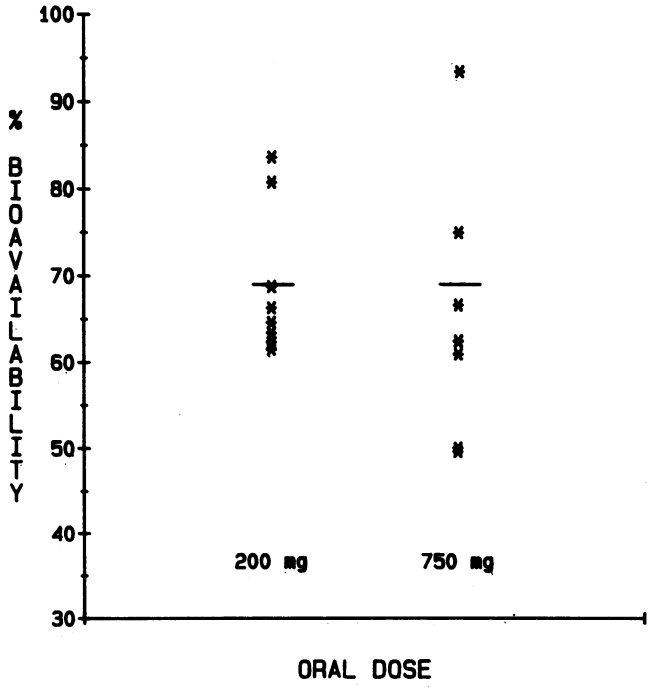

FIG. 2. Bioavailability of 200- and 750-mg oral doses of ciprofloxacin. For the 750-mg dose, $n = 2$ at 94%. Means are indicated by horizontal lines.

TABLE 3. Effect of dose on absorption of ciprofloxacin administered orally[a]

Dose (mg)	C_{max} (mg/liter)	T_{max} (h)	k_a (h^{-1})	T_{lag} (h)	F (%)
200	1.18[b] (0.20)[c]	0.69[b] (0.12)[c]	8.58[b] (7.37)[c]	0.22 (0.04)[c]	69.0 (8.59)[c]
750	2.97[b] (0.64)[c]	1.38[b] (0.35)[c]	1.48[b] (0.50)[c]	0.30 (0.11)[c]	69.1 (17.3)[c]

[a] C_{max}, Maximum concentration in serum; T_{max}, time to maximum concentration in serum; k_a, absorption rate constant; T_{lag}, lag time. Values are means, with standard deviations in parentheses.
[b] Difference between regimens significant by a one-way analysis of variance at $P < 0.05$.
[c] Difference between regimens significant by an F test at $P < 0.05$.

have contributed to this variability. The time to reach maximum concentrations of the drug in serum was significantly longer with the 750-mg dose than with the 200-mg dose (1.38 versus 0.69 h). As expected, peak concentrations with the two oral regimens were significantly different (Table 3). However, the peak concentrations normalized for dose to 750 mg were significantly higher with the smaller dose (4.4 versus 3.0 μg/ml).

Within subjects, the bioavailability of the 200-mg dose was poorly correlated with the bioavailability of the 750-mg dose ($r^2 = 0.208$; $P < 0.05$). The minimum amounts of drug absorbed with the 200- and 750-mg doses were 123 and 372 mg, respectively.

The mean bioavailability of ciprofloxacin with both the 200- and 750-mg oral doses was consistent at 69%. The calculation of bioavailability was based on the assumption that ciprofloxacin clearance did not change between the study periods. However, the elimination half-life observed with the 750-mg dose was significantly longer than with the 200-mg dose, whereas the apparent clearance and the renal clearance (2; Forrest et al., 25th ICAAC) remained the same. Our study was conducted in normal volunteers with no alterations in either renal or hepatic function between the studies. Clearance is a physiologic parameter which depends on the function of the eliminating organs, whereas half-life depends on both distributive and elimination functions. Therefore, we believe this perturbation in half-life more likely reflected a shift in partitioning between volume and half-life than an actual change in drug clearance between the study days. Normalization of the area for half-life changes, however, produced similar results.

Although the mean bioavailability observed in the two studies was nearly identical, the bioavailability observed with the 750-mg dose was significantly more variable. The much slower absorption rate constant observed with the larger dose and the possible influence of changing gastrointestinal motility and blood flow may have contributed to this variability (3, 4). The prolongation of absorption and the variability in bioavailability observed with the larger dose most likely reflected variable disintegration/dissolution rates with the 750-mg tablet versus the 100-mg tablets. The presence of a saturable process involved in the oral absorption of ciprofloxacin appears less probable.

Our volunteers absorbed between approximately 375 and 700 mg of ciprofloxacin after administration of the 750-mg dose, an amount greater than the largest i.v. dose currently used in clinical trials. Our subjects experienced no signs of adverse reactions. A larger dosage than the recommended 200 mg i.v. every 12 h may be necessary to treat infections with difficult pathogens such as *S. aureus* and *P. aeruginosa* (5).

The clinical relevance of these observations are two-fold. First, because the 750-mg dose was associated with a large variability under controlled conditions in healthy volunteers, the bioavailability with these clinically useful larger doses must be determined in populations of patients. Second, as much as 700 mg of ciprofloxacin reached the systemic circulation with the 750-mg dose with no evidence of adverse reactions. Hence, larger i.v. doses than those currently used may be useful in treating serious infections with less susceptible pathogens.

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