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Pharmacokinetics of Three Oral Formulations of Ciprofloxacin

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We compared the absorption of three formulations of ciprofloxacin after oral administration in 18 normal adult male volunteers. Each subject received 500 mg of ciprofloxacin as two 250-mg tablets, one 500-mg tablet, or a solution in a randomized crossover sequence. Pharmacokinetic parameters were determined by model independent methods. Because a solution is considered to be the ideal oral dosage form, the results determined for the tablets were compared to those for the solution. Mean values for the maximum concentration of drug in serum, the time to maximum concentration of drug in serum, and the elimination half-life were 3.23 μg/ml, 1.00 h, and 5.04 h, respectively, for the solution. The mean renal clearance of ciprofloxacin was 372 ml/min and accounted for at least 50% of the total clearance. We recovered 44.4, 48.6, and 55.8% of the administered ciprofloxacin from the urine as unchanged drug within 24 h after dosing with the 250-mg tablets, 500-mg tablets, or solution, respectively. The 500-mg tablets were found to be bioequivalent to the solution with regard to all pharmacokinetic parameters. The 250-mg tablet was not bioequivalent to either of the other formulations; the relative bioavailability values were 78.7 and 74.1%, respectively, for the 500-mg tablet and the solution. The clinical significance of this difference in bioavailability is yet to be determined.

Ciprofloxacin is a quinoline carboxylic acid which possesses superior activity in vitro in comparison to other quinoline carboxylic acids against both gram-positive and gram-negative organisms. Its antimicrobial spectrum includes activity against aminoglycoside- and cephalosporin-resistant *Enterobacteriaceae* organisms, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (1, 3, 6, 8).

Ciprofloxacin is water soluble and can be formulated as a solution or as a tablet. Since absorption is not reduced or delayed by disintegration or dissolution, a solution is considered the optimal oral dosage form to which other forms are compared. Slower or less-complete absorption of tablets may result in lower peak antibiotic concentrations in the serum or a shorter time during which the serum concentration exceeds the MIC of a susceptible organism. Because of the lack of studies done in children, there are no plans to manufacture the solution formulation of ciprofloxacin at this time. The purpose of this study was to investigate the pharmacokinetic properties of ciprofloxacin after single-dose oral administration and to compare the absorption characteristics of the tablets to those of the solution.

MATERIALS AND METHODS

Study population. Eighteen healthy male volunteers (aged 24 to 40 years) were enrolled into the study after informed consent was obtained. The study protocol was approved by the University of Washington Human Subjects Review Board. All subjects had normal physical examinations and urinalysis, and the hematological and chemical studies were also normal. All were within 20% of their ideal body weight (mean weight, 78 kg), and all were nonsmokers. The subjects abstained from alcohol-containing beverages and medications for 72 h before and 48 h after administration of the study drug. All subjects were reexamined, and laboratory tests were repeated within 72 h after the final dose of ciprofloxacin.

Drug administration. In a randomized crossover sequence, volunteers received a single dose of ciprofloxacin orally as two 250-mg tablets, one 500-mg tablet, or a solution containing 500 mg. A 1-week washout period separated each dose. Subjects fasted after 7 p.m. the evening before each study period but were allowed to drink water as desired. The tablets were ingested along with 120 ml of water. The solution was prepared immediately before ingestion. Ciprofloxacin hydrochloride (500 mg) was mixed with 30.0 g of a sucrose vehicle (total volume, 50 ml). Subjects drank the entire volume, and the bottle containing the solution was rinsed with an additional 70 ml of water which was also ingested by the subjects. Immediately after all formulations were given, 80 ml of orange juice was swallowed over a 5-min period, bringing the entire fluid intake to 200 ml for all dosage forms. Subjects abstained from solid food for 4 h after receiving the drug but were allowed to drink clear fluids as desired.

Sample collections. Blood was taken from an indwelling intravenous cannula immediately before and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after drug administration. The blood was allowed to clot at room temperature; the samples were then centrifuged for 15 min at 800 × *g*, and the serum was collected. Urine was collected just before and from 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h after each dose. The urine volume was noted, and a portion from each collection was saved for assay. A 2-ml sample of parotid saliva was collected immediately before and 1, 2, 4, and 8 h after each dose; the pH was noted for each sample. Saliva was collected by placing a suction device over the duct of the parotid gland and stimulating salivation with citric acid crystals. All blood, urine, and saliva samples were frozen within 1 h of collection and were stored at −20°C until assayed.

Assays. Samples were allowed to thaw at room temperature on the day of assay. Ciprofloxacin concentrations in plasma, urine, and saliva were assayed by high-pressure liquid chromatography. A mobile phase which consisted of 32.5% methanol and 0.8% tetrahydrofuran in 67 mM phos-

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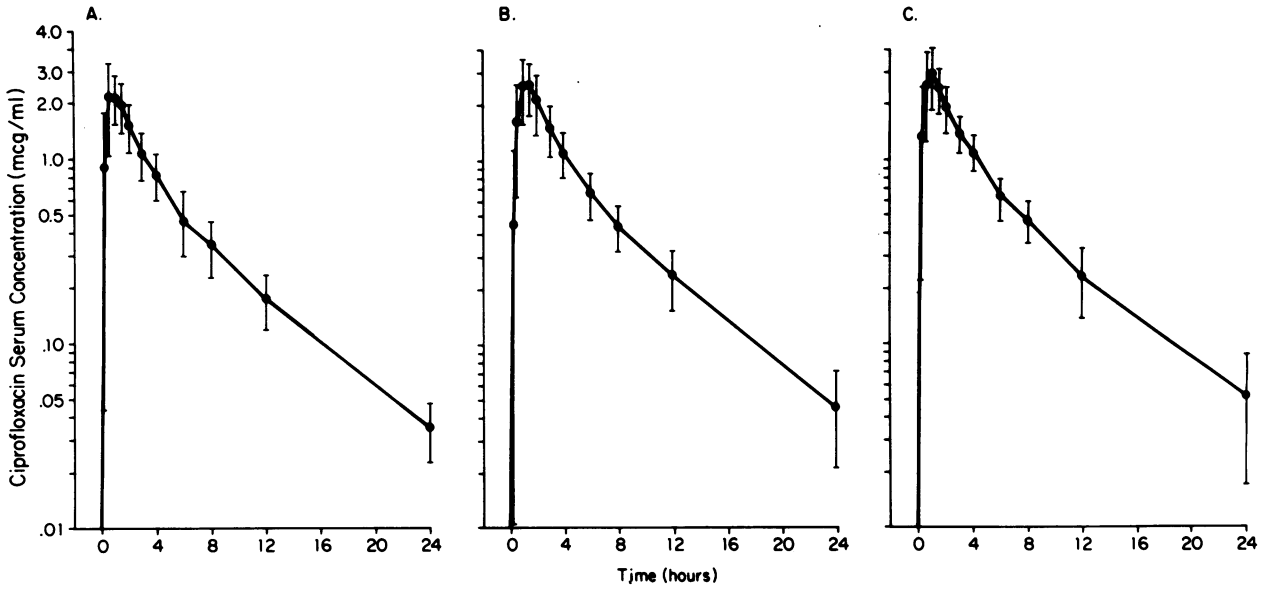

FIG. 1. Ciprofloxacin concentrations in serum during the first 24 h after the administration of two 250-mg tablets (A), one 500-mg tablet (B), or solution (C).

phate buffer at pH 3.0 was delivered to a 10-μm C_{18} μBondapak Radial-Pak column under radial compression at 1,600 lb/in^2 (Waters Associates, Inc.). Fluorescence of the eluent was monitored by UV excitation at 277 nm and emission detection at 445 nm. UV absorbance was monitored at 277 nm. Fifty microliters was diluted with an equal volume of acetonitrile, mixed, and centrifuged. The clear supernatant (20 μl) was injected into the mobile phase at a flow rate of 2.0 ml/min. The assay was linear for concentrations varying from 5 ng/ml to 5 μg/ml. The sensitivity limit of the assay was 5 ng/ml. The intraday coefficient of variation was 1.8% for the high control (500 ng/ml) and 3.1% for the low control (100 ng/ml); the interday coefficient of variation was 7.2% for the high control and 7.9% for the low control.

Pharmacokinetic analysis. Pharmacokinetic analysis was performed by using model independent methods. The terminal elimination rate constant was calculated from the slope of the line made by the logs of the 8-, 12-, and 24-h ciprofloxacin concentrations in serum divided by 2.303. The area under the concentration-versus-time curve (AUC) was calculated by using the trapezoidal rule plus the quotient obtained by dividing the last concentration in serum by the terminal elimination rate constant (5).

Total clearance (CL) was calculated by dividing the dose by the AUC. The volume of distribution (V) during the terminal elimination phase was calculated by dividing the total clearance by the elimination rate constant. These estimations of clearance and V assume 100% bioavailability (f). In the case of an oral agent such as ciprofloxacin in which the absolute bioavailability is unknown, these equations generate estimates of CL/f and V/f. Renal clearance was calculated by dividing the amount of unchanged drug excreted in the urine in the first 24 h after drug administration by the AUC during that time interval. The bioavailability of the tablets compared to the solution was calculated by dividing the AUC for the tablet by the AUC for the solution (5).

Statistical analysis. Statistical analysis of the data was performed by using analysis of variance (ANOVA) for repeated measures. Observations found to vary to a significant extent were further tested by Tukey's A test to determine differences between formulations (7). Probability values of <0.05 were considered significant.

RESULTS

Ciprofloxacin was well tolerated in all subjects after oral administration of each dosage form. No subjects reported any adverse effects, and physical examinations and labortory studies done at the completion of the protocol were within normal limits.

The mean concentrations in serum for each formulation from 0 to 24 h are shown in Fig. 1. Urinary excretion data is listed in Table 1. Ciprofloxacin was rapidly absorbed after oral administration of all three dosage forms, and significant concentrations were achieved in the urine in the first 2 h after dosing.

Multivariate analysis was conducted for the following parameters: maximum concentration of drug in serum, time to maximum concentration of drug in serum, AUC, elimination half-life, elimination rate constant, V, total clearance, renal clearance, urinary recovery of unchanged drug, and concentration in saliva. The results of these analyses are shown in Table 2. When significant variation due to dosage form was observed, a posteriori testing (using Tukey's A test) was performed to identify differences between formulations.

TABLE 1. Mean urinary excretion data for all ciprofloxacin formulations

Time (h) post dose	Ciprofloxacin concn (μg/ml) in urine			Cumulative % dose excreted	
	Mean	SD	Range	Mean	SD
0 to 2	464	357	28–1,847	18.6	7.4
2 to 4	304	225	60–1,219	29.6	8.8
4 to 8	189	141	31–731	40.3	10.9
8 to 12	111	84	19–486	45.4	11.9
12 to 24	41	30	8–128	51.0	12.2
24 to 48	7.2	7.2	0.7–45	52.6	12.4

TABLE 2. Pharmacokinetic data for all three ciprofloxacin formulations

Ciprofloxacin formulations	Pharmacokinetic parameters (mean ± SD)[a]				
	C_{max} (μg/ml)	T_{max} (μg/ml)	AUC (mg · h/liter)	k_{el} (h^{-1})	$t_{1/2}$ (h)
2 250-mg tablets	2.83 ± 0.68	0.99 ± 0.56	10.0 ± 2.18[b]	0.143 ± 0.02	4.91 ± 0.53
1 500-mg tablet	2.91 ± 0.74	1.25 ± 0.55	12.7 ± 2.89	0.147 ± 0.02	4.82 ± 0.69
Solution	3.23 ± 1.13	1.00 ± 0.62	13.5 ± 3.01	0.143 ± 0.03	5.04 ± 1.07
All formulations	3.00 ± 0.88	1.08 ± 0.58	12.2 ± 3.00	0.144 ± 0.02	4.92 ± 0.78

[a] Abbreviations: C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum; AUC, area under the concentration-versus-time curve; k_{el}, elimination rate constant; $t_{1/2}$, elimination half-life; V, volume of distribution; f, bioavailability; CL, total clearance; CL_R, renal clearance; X_{u24}, ciprofloxacin recovered in the urine within 24 h after administration of drug.

[b] Statistically different ($P < 0.05$) from solution and 500-mg tablet.

[c] Statistically different ($P < 0.05$) from solution only.

The time to maximum concentration of drug in serum, concentration in the saliva, elimination rate constant, and renal clearance were not influenced by dosage form. Although higher maximum concentrations were achieved with the solution, this was not statistically different from the other formulations. The 500-mg tablets were not found to be statistically different from the solution in any pharmacokinetic parameter. The V/f and the nonrenal clearance/bioavailability (CL_{NR}/f) (defined as CL/f minus renal clearance) were significantly greater, and the AUC and the amount of unchanged drug excreted in the urine were significantly smaller for the 250-mg tablets compared to the solution. These differences ranged from 20 to 31%. The V/f and nonrenal clearance of the 250-mg tablets were also found to be significantly different from those of the 500-mg tablets. These differences ranged from 17 to 25% with respect to the 500-mg tablets.

The mean values and ranges for the ratio of ciprofloxacin concentration in saliva to that in serum are shown in Table 3. These ratios varied widely between and within subjects but were not dependent on the formulation administered. Ciprofloxacin concentrations in saliva averaged 21.2% (range, 5.8 to 62.8%) of simultaneous concentrations in serum, with poorer penetration at more alkaline pHs ($r = -0.2442$, $P < 0.0003$). Ciprofloxacin concentration in saliva declined more rapidly than it did in serum; thus, the ratio of ciprofloxacin concentration in saliva to that in serum was highest early after drug ingestion ($r = 0.3994$, $P < 0.00001$). Although these correlations achieved statistical significance, only 6 and 16% of the variation of the saliva/serum concentration ratio could be explained by pH and time after dose, respectively.

DISCUSSION

Ciprofloxacin was well absorbed in all subjects after the administration of each formulation. The mean concentrations in serum from 0 to 24 h for each formulation are shown in Fig. 1. Mean maximum concentrations in serum were between 2.83 and 3.23 μg/ml, which are many times greater than the MICs for most susceptible organisms.

Our data indicate that ciprofloxacin is eliminated at least 50% by the kidney as unchanged drug, with a mean renal clearance of 365 ml/min. This value is much greater than the normal rate of glomerular filtration (4) and indicates that tubular secretion contributes to renal excretion. We found no correlation between urine flow rate and renal clearance ($r = 0.0008$, $P = 0.63$), suggesting that ciprofloxacin does not undergo significant flow-dependent tubular reabsorption.

Total body clearance and V could not be reliably estimated in our subjects since the bioavailability of orally administered ciprofloxacin is unknown. In a recent report by Wise et al. (9), the bioavailability of ciprofloxacin in five subjects was reported to be 71.7 ± 13.2% after a 500-mg oral dose and a 100-mg intravenous dose. Bioavailability was calculated by using AUC ratios corrected for dose. In that study, mean total body clearance was 34.0 liters/h after a 100-mg intravenous dose. The higher total clearance (CL/f) for all formulations found in our study suggests that ciprofloxacin was incompletely absorbed. Solving for f in our subjects using a dose-corrected AUC from the study of Wise et al. (9) yields a bioavailability of 58.9, 74.7, and 79.4% for the 250-mg tablets, the 500-mg tablets, and the solution, respectively; this is in good agreement with the Wise data for the latter two formulations.

The mean V/f of 277 liters in our subjects after administration of the oral solution was probably also influenced by incomplete absorption. Our V/f estimates cannot be directly compared at steady-state of 177 liters found after intravenous administration (8), since these parameters were calculated by different methods. Nonetheless, this large V indicates that ciprofloxacin distributes to an apparent volume which is much larger than total body water (42 liters in a 70-kg adult (4). Studies of distribution of radioactive drug in animals reveal higher concentrations in the kidney, liver, and cartilagenous tissue relative to concentrations in the rest of the body (personal communication, George Arcieri, Miles Pharmaceuticals). A similar distribution of ciprofloxacin in humans may account for the large V that has been found in studies in normal volunteers.

We also measured the ciprofloxacin content in parotid saliva. In our subjects, the mean concentration was 25.5% of the simultaneous concentration in serum. This finding cannot be explained by a high degree of plasma protein binding since ciprofloxacin is only 20% bound to plasma proteins (8). Ciprofloxacin is a large dipolar ion (molecular weight, 348) that is poorly lipophilic (9) and thus would not be likely to diffuse into saliva. Our data indicate that ciprofloxacin content in saliva, relative to that in serum, may be greater early in the dosing interval. The reason for this is unclear; the ratio should be constant unless some process (i.e., diffusion or protein binding) is nonlinear. It was not a result of unrinsed drug left in the mouth early after dosing since we collected saliva directly from the parotid gland with the aid of a suction device, and the phenomenon occurred with tablets as well as solution.

We also found a statistically significant relationship between the concentration of ciprofloxacin in saliva and the pH. As a result of this observation, we investigated the effect of pH on the solubility of ciprofloxacin in octanol in our laboratory. Using this technique, we were unable to show significant changes in lipophilicity at physiological pH ranges (5.4 to 8.0). Our values for penetration into saliva were lower

TABLE 2.—*Continued*

Pharmacokinetic parameters (mean ± SD)[a]						
V/f (liter)	*V/f* per kg (liter)	CL/*f* (liter/h)	CL/*f* per kg (liter/h)	CL_R (liter/h)	CL_R per kg (liter/h)	X_{u24} (mg)
361 ± 98[b]	5.00 ± 1.56[b]	50.2 ± 11.8[b]	0.69 ± 0.20[b]	22.2 ± 4.02	0.31 ± 0.07	222 ± 65[c]
288 ± 64	3.99 ± 1.06	42.0 ± 10.2	0.58 ± 0.16	20.5 ± 3.55	0.29 ± 0.06	243 ± 57
277 ± 66	3.78 ± 0.80	38.8 ± 9.05	0.53 ± 0.13	22.3 ± 3.73	0.31 ± 0.06	279 ± 51
308 ± 85	4.26 ± 1.28	43.7 ± 11.3	0.60 ± 0.18	21.6 ± 3.78	0.30 ± 0.06	247 ± 61

than what has been found for blister fluid (57.9% [2]). Unlike saliva, blister fluid represents an inflamed environment with increased capillary permeability. Blister fluid also contains plasma proteins which could result in slightly higher drug concentrations.

The 250-mg tablets were statistically different from the other formulations for the following parameters: AUC, CL/*f*, and *V/f*. These parameters are interdependent when calculated by the methods used here and are all influenced by differences in the extent of absorption. Parameters such as elimination half-life and time to maximum concentration of drug in serum, which are not affected by the extent of absorption, were similar for all three formulations. Therefore, it can be concluded that the relative bioavailability of the 250-mg tablets is 74.1% that of the solution and 78.7% that of the 500-mg tablets. The 500-mg tablet was not statistically different from the solution in any parameter and can be considered bioequivalent.

The clinical significance of these slight differences in bioavailability between formulations is unknown at the present time. The optimal dosage regimen for ciprofloxacin is yet to be established, and these differences in bioavailability between formulations should be considered when patients are being treated with ciprofloxacin.

TABLE 3. Comparison of ciprofloxacin concentrations in saliva and in serum

Time (h) post dose	Ratio of saliva/serum concn			
	Mean	SD	Minimum	Maximum
1	0.255	0.114	0.078	0.628
2	0.247	0.098	0.095	0.587
3	0.193	0.086	0.072	0.481
4	0.158	0.067	0.028	0.332

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