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Ciprofloxacin Penetration into Extravascular Spaces in a Rabbit Model

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Ciprofloxacin penetration into extravascular spaces was studied in a rabbit Visking chamber model. The drug was administered (7 mg/kg) intramuscularly every 4 h for eight doses. Peak and trough drug levels by dose 8 were 1.3 and 0.35 μg/ml in serum and 0.61 and 0.50 μg/ml in extravascular sites. The ratio of extravascular site to serum free drug area under the drug curve by dose 8 was 91.1%. This potent, new antimicrobial agent appears to distribute freely to extravascular spaces in this animal model.

Ciprofloxacin is a new quinolone carboxylic acid derivative with an extremely broad spectrum of antimicrobial activity against aerobic and anaerobic cocci and bacilli (1–4, 6–8, 12–14). Previously it has been shown that when given to human volunteers, ciprofloxacin is rapidly absorbed after oral administration, has a relatively long half-life, and achieves levels in serum and blister fluid which exceed MICs for many pathogenic organisms (5). The present study was designed specifically to examine the pharmacokinetics of extravascular penetration of ciprofloxacin in a rabbit model.

The rabbit model used has been described previously (9). The extravascular fluid chambers consisted of Visking tubing (Union Carbide Corp., Chicago, Ill.) tied around the tubing of a 21-gauge, rubber-stoppered intermittent infusion set (Abbott Laboratories, North Chicago, Ill.) at one end and sealed at the other end. Six such chambers were implanted subcutaneously along the flanks of each of four female New Zealand white rabbits weighing approximately 3 kg each. The chambers were implanted 3 to 4 days before the first drug dose, while the rabbits were under anesthesia with ketamine plus xylazine hydrochloride. Before the first ciprofloxacin dose, each chamber was flushed with sterile saline, cultured to confirm sterility, and filled with 3 ml of sterile commercial rabbit serum. Ciprofloxacin was obtained in standard powder form (Miles Pharmaceuticals, West Haven, Conn.) and mixed in sterile water for intramuscular injection. Each rabbit received 7 mg of ciprofloxacin per kg intramuscularly every 4 h for a total of eight doses.

Blood samples of 0.2 ml each were obtained from mammary or ear veins at 0, 15, 30, 60, 120, and 180 min after doses 2 and 8. The Visking chambers were sampled (0.2 ml) at 0, 30, 45, 60, 120, 180, and 240 min after doses 1, 7, and 8. The serum was immediately removed from the blood samples and stored at −80°C with the chamber samples until the drug concentrations were assayed.

Ciprofloxacin concentrations were determined by high-pressure liquid chromatography with a Varian liquid chromatograph (model 5000; Varian Associates, Inc., Palo Alto, Calif.) (C. Fasching and L. Peterson, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 24th, Washington, D.C., abstr. no. 984, 1984). The minimal detectable level of drug by this assay was 0.05 μg/ml.

The areas under the drug curves for serum (AUCS) and extravascular sites (AUCEV) were determined with a compensating planimeter and by the trapezoidal rule (11).

Protein binding of ciprofloxacin to the commercial rabbit serum and fresh rabbit serum was determined by ultracentrifugation as previously described (10).

The average (± standard deviation) ciprofloxacin concentrations in serum after doses 2 and 8 are shown in Table 1. Peak levels occurred after 15 min, with a mean of 1.3 μg/ml after dose 8. The mean trough level was 0.35 μg/ml after dose 8, and the serum half-life was 1.8 h. The average (± standard deviation) ciprofloxacin concentrations in the extravascular chambers after doses 1, 7, and 8 are also shown in Table 1. Peak levels were obtained at 60 min, with a mean of 0.61 μg/ml after dose 8. The mean trough level was 0.50 μg/ml after dose 8. The mean total AUCS after doses 2 and 8 and the mean total AUCEV after doses 1, 7, and 8 are also shown in Table 1. The ratio of mean total AUCEV to AUCS by dose eight was 78%.

Protein binding of ciprofloxacin to commercial rabbit serum and to fresh rabbit serum was determined to be 27.3% and 37.9%, respectively. When corrected for these differences in protein binding, the ratio of free drug AUCEV to AUCS was 91.1% by dose eight.

This study has shown that ciprofloxacin readily diffuses from the intravascular to the extravascular space, reaching equilibrium at least by dose 8, as evidenced by the free drug ratio of AUCEV to AUCS being ≥90% by that dose. Peak and trough drug levels at both sites exceed the MICs necessary to inhibit many pathogenic organisms, as reported elsewhere (1–4, 6–8, 12–14). These findings are consistent with and in most respects confirmatory of findings obtained in human volunteers (5).

The protein binding in fresh rabbit serum was found to be similar to that found in human serum (5). Drug binding to commercially purchased rabbit serum (27.3%) was only 72% of that to fresh rabbit serum (37.9%), which accounted for a significant difference in the total drug AUCEV/AUCS ratio and the free drug AUCEV/AUCS ratio. This illustrates the importance of measuring the degree of drug binding to both intravascular and extravascular fluid for proper interpretation of studies on the distribution of antimicrobial agents.

Ciprofloxacin is a new quinolone carboxylic acid derivative with a broad spectrum of in vitro activity. In this rabbit model, it readily achieved equilibrium between the intravas-

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TABLE 1. Mean concentration of ciprofloxacin, AUCS of ciprofloxacin after doses 2 and 8, and AUCEV of ciprofloxacin after doses 1, 7, and 8

Time after dose (h)	Mean (± SD) ciprofloxacin concn (μg/ml) in:				
	Serum		Extravascular sites		
	Dose 2	Dose 8	Dose 1	Dose 7	Dose 8
0	0.27 ± 0.05	0.35 ± 0.10	0	0.49 ± 0.15	0.47 ± 0.09
0.25	1.9 ± 0.06	1.3 ± 0.33	ND[a]	ND	ND
0.5	1.4 ± 0.38	1.2 ± 0.26	0.06 ± 0.08	0.45 ± 0.09	0.50 ± 0.08
0.75	ND	ND	0.09 ± 0.11	0.58 ± 0.10	0.55 ± 0.10
1	1.1 ± 0.35	0.98 ± 0.16	0.17 ± 0.11	0.60 ± 0.09	0.61 ± 0.12
2	0.68 ± 0.20	0.66 ± 0.11	0.26 ± 0.09	0.58 ± 0.10	0.59 ± 0.12
3	0.48 ± 0.13	0.53 ± 0.06	0.33 ± 0.11	0.54 ± 0.10	0.56 ± 0.11
4	ND	ND	0.31 ± 0.09	0.47 ± 0.09	0.50 ± 0.12
AUC[b]	0.195	0.180	0.06	0.13	0.14

[a] ND, No data available.
[b] AUCS and AUCEV determined with planimeter (milligram · minute per milliliter).

cular and extravascular space. Further studies are necessary to establish the in vivo antimicrobial activity of ciprofloxacin.

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