

Pharmacokinetics and Tissue Penetration of Ciprofloxacin

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A 500-mg dose of the quinoline ciprofloxacin was administered orally to each of six healthy male volunteers, after which the concentrations of this agent in serum and blister fluid were measured. Absorption appeared to be rapid, with a mean peak level of 2.4 $\mu\text{g/ml}$ attained 1.25 h after administration. The serum elimination half-life was 3.9 h. The agent penetrated blister fluid well, the percent penetration being 57%. Urinary recovery of ciprofloxacin was 30%.

Ciprofloxacin is a new quinoline carboxylic acid derivative which is well absorbed when administered orally (1, 6). It has high in vitro activity against a broad spectrum of organisms such as *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Bacteroides* spp., including strains resistant to aminoglycosides and other commonly used agents such as the broad-spectrum β -lactams. Because of its high activity, it may be possible to use this antimicrobial agent to treat systemic rather than urinary tract infections, as is the case with nalidixic acid and norfloxacin (5).

The purpose of this study was to investigate the pharmacokinetic properties of this compound after oral administration and also to determine the penetration of the agent into chemically induced blister fluid, which has been shown to be similar in composition to the exudate of a mild inflammatory reaction (7).

MATERIALS AND METHODS

Six healthy male volunteers were entered into the study; approval was obtained from the Dudley Road Hospital Ethical Committee, and informed consent was gained. They were aged 23 to 41 (mean age, 29 years) with a mean weight of 78 kg (range, 69 to 83 kg). There were no significant episodes in their past medical histories, and their biochemical and hematological profiles were normal. All underwent physical examination the week before the study and all were normal. On the night before the study, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the volar surface of one forearm and taped in place. The subjects fasted from 10 p.m. of that evening. At 8 a.m. on the day of the study, they were given a single oral dose of a 500-mg ciprofloxacin tablet with 200 ml of water. Thereafter, fluid was taken ad libitum. Solid food was taken after 2 h.

Blood was taken from an indwelling intravenous cannula at 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, and 12 h after the administration of the drug. Urine samples were collected over 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after administration. The two blisters were sampled at 30 and 60 min and then hourly by using a

fine needle. The integrity of the blisters was maintained by spraying with a fast-drying plastic dressing. Approximately 20- μl samples were used to impregnate preweighed sterile 6-mm assay disks, which were then reweighed to accurately measure the quantity of fluid obtained.

The antibiotic assays were performed within 1 h of sample collection, using a plate diffusion assay; the test organism was *Escherichia coli* 4004 (obtained from Bayer AG, Wuppertal, West Germany). The medium used was IsoSensitest, pH 7.4 (Oxoid Ltd., Basingstoke, U.K.). Standards were prepared with human serum for serum samples, 70% human serum for blisters, and a pH 6.6 phosphate buffer for urine. The plates were incubated in air overnight. The blister fluid assay plates were incubated at 30°C, and the serum assays were incubated at 37°C. Appropriate serum and blister standards and controls were used in each plate. The 95% confidence limit for the assay was $\pm 19.3\%$. The lower limit of sensitivity for the assay was 0.01 $\mu\text{g/ml}$.

Repeat hematological and biochemical profiles and physical examinations were performed on the subjects at the conclusion of the study.

Pharmacokinetic analysis was performed by analysis of individual data and routine graphical methods (3, 4).

RESULTS

The concentrations of ciprofloxacin found in sera and blister fluids are shown in Table 1, and the pharmacokinetic data are detailed in Table 2.

The drug appeared to be rapidly absorbed, with maximum serum levels (mean maximum level, 2.4 $\mu\text{g/ml}$) being obtained at a mean time of 1.25 h after administration. The maximum serum level was above 1.6 $\mu\text{g/ml}$ in all cases.

The drug penetrated blister fluid moderately rapidly, the maximum levels being obtained at a mean time of 2.6 h. The mean percent penetration of the drug into the blister fluid (that is, the maximum blister level being expressed as a percentage of the maximum serum level) was 57.9%. The maximum level of the drug attained in blister fluid exceeded 0.82 $\mu\text{g/ml}$ in all volun-

TABLE 1. Mean ciprofloxacin concentrations in serum and blister fluid

Time	Mean concn ($\mu\text{g/ml}$) \pm 1 SD	
	Serum	Blister fluid
15 min	0.3 \pm 0.2	— ^a
30 min	1.0 \pm 0.6	0.4 \pm 0.2
45 min	1.5 \pm 0.8	—
60 min	1.7 \pm 0.5	0.6 \pm 0.5
90 min	1.9 \pm 0.8	—
2 h	1.5 \pm 0.5	0.9 \pm 0.3
3 h	1.0 \pm 0.3	1.2 \pm 0.5
4 h	0.8 \pm 0.2	1.1 \pm 0.4
5 h	0.6 \pm 0.2	1.0 \pm 0.5
6 h	0.5 \pm 0.2	0.8 \pm 0.2
8 h	0.4 \pm 0.1	0.6 \pm 0.2
12 h	0.2 \pm 0.1	0.4 \pm 0.1

^a —, Not tested.

teers. Blister fluid levels exceeded that in serum after 3 h.

The mean terminal elimination half-life of ciprofloxacin in serum was 3.9 h. The elimination half-life from blister fluid was longer (5.6 h) and showed more individual variation. In all individuals the drug levels in both serum and blister fluid exceeded 0.1 $\mu\text{g/ml}$ 12 h after administration. The mean percentages of the recovered active drug in urine during the collection periods were: 0 to 4 h, 20.9%; 4 to 8 h, 5.13%; 8 to 12 h, 2.93%; 12 to 24 h, 1.63%; giving a 0 to 24 h total of 30.6%. The levels of drug found in urine showed great individual variation but exceeded 2.0 $\mu\text{g/ml}$ in all volunteers in the 12 to 24 h sample.

The areas under the concentration-time curves were very similar for the serum and blister fluid data, and calculated volumes of distribution were high (ca. 80 liters). The value of these observations is uncertain in the absence of data concerning the metabolism of the drug, but they suggest that the drug is widely distributed throughout the tissues.

There were no adverse effects of the drug in any subject during this study, and the hematological and biochemical parameters did not vary significantly between the pre- and post-treatment samples.

DISCUSSION

There are limited data available on the pharmacokinetics of ciprofloxacin. Comparisons of our results with those of a previous study (personal communication from Bayer AG) show that we encountered slightly higher mean serum levels (2.3 versus 1.6 $\mu\text{g/ml}$) and a somewhat shorter serum half-life (3.9 versus 4.5 h). It is not known whether these differences relate to differences in food intake, but this is a possibility.

Ciprofloxacin would appear to penetrate blister fluid to an extent similar to that of norfloxacin. In a previous study (Z. Adhami, R. Wise, D. Weston, and B. Crump, in press), the mean percent penetration of norfloxacin was 67%, whereas it was 57% for ciprofloxacin. The longer half-life of ciprofloxacin in blister fluid compared with serum leads to higher levels in blister fluid after about 3 h postadministration.

The 30% urinary recovery suggests that either oral absorption is poor or that considerable metabolism is occurring, as it does for the related compound norfloxacin (2), for which at least one major metabolite and up to six minor metabolites have been found. Another possibility is that rapid tissue distribution occurs with slow release from these tissues. Our study did not attempt to look for metabolites, and it is possible that microbiologically active metabolites, if present, could have interfered with the assay system used.

Studies of the mean inhibitory concentrations required for this drug have been performed on a wide variety of organisms (1, 6). The 90% mean inhibitory concentrations for *Enterobacteriaceae*, *Haemophilus influenzae*, *Neisseria* sp., and *P. aeruginosa* are equal to or less than 0.25 $\mu\text{g/ml}$. The 90% mean inhibitory concentration for *Staphylococcus aureus* is 0.5 $\mu\text{g/ml}$. This study would therefore suggest that serum and inflammatory tissue fluid levels of ciprofloxacin after a 500-mg dose achieve levels that should inhibit systemic infections caused by these strains. However, since the 90% mean

TABLE 2. Pharmacokinetics of ciprofloxacin

Parameter	Value \pm SD
Serum	
T_{max} (h)	1.25 \pm 0.5
C_{max} ($\mu\text{g/ml}$)	2.3 \pm 0.7
$t_{1/2\beta}$ (h)	3.9 \pm 0.8
$K_{\text{e}\beta}$ (h^{-1})	0.18 \pm 0.035
$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	9.9 \pm 2.43
K_a (h^{-1})	2.7 \pm 1.22
Blister fluid	
T_{max} (h)	2.6 \pm 0.97
C_{max} ($\mu\text{g/ml}$)	1.4 \pm 0.36
$t_{1/2\beta}$ (h)	5.6 \pm 2.4
$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{h/ml}$)	11.6 \pm 4.1
Urinary recovery	
24-h excretion (% of dose)	30.6 \pm 9.8

^a Abbreviations: T_{max} , time at which the maximum concentration (C_{max}) in serum or tissue fluid is achieved; $t_{1/2\beta}$, terminal elimination half-life in the serum and blister fluid; $K_{\text{e}\beta}$, overall elimination constant; $\text{AUC}_{0-\infty}$, area under the serum (or blister fluid) concentration-time curve; K_a , absorption rate constant.

inhibitory concentrations for streptococci (including *Streptococcus pneumoniae*) and *Bacteroides fragilis* are 2 and 4 µg/ml, respectively, it would appear that a larger dose would be required. It is suggested that a 12-h dosing interval of ciprofloxacin would be appropriate for initial clinical studies.

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