Pharmacokinetics and Inflammatory Fluid Penetration of Clinafloxacin

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A single 200-mg dose of clinafloxacin was given orally to each of nine healthy male volunteers, and the concentrations of the drug were measured in plasma, cantharidin-induced inflammatory fluid, and urine over the following 24 h (48 h in the case of urine). The mean maximum concentration in plasma was 1.34 μg/ml at a mean time of 1.8 h postdose. The mean maximum concentration in the inflammatory fluid was 1.3 μg/ml at 3.8 h postdose. The mean elimination half-life of clinafloxacin in plasma was 5.65 h. The overall penetration into the inflammatory fluid was 93.1%, as assessed by determining the ratio of area under the concentration-time curves. Recovery of clinafloxacin in urine was 58.8% by 24 h and 71.8% by 48 h postdose.

Clinafloxacin (PD127,391, CI-960) is a dihalogenated quinolone which has an enhanced antibacterial spectrum and is particularly active against gram-positive cocci (5, 8). In this study, the pharmacokinetics of a single 200-mg oral dose of clinafloxacin were studied in nine volunteers with the following characteristics: mean age, 34 years (range, 22 to 41 years); mean weight, 77.5 kg (range, 64.5 to 88.5 kg); and mean height, 178 cm (range, 171 to 184 cm). The volunteers agreed to participate after informed consent had been obtained. The extent of penetration into a chemically induced inflammatory exudate (7) was investigated.

Approval by the hospital’s Ethical Committee was obtained, and medical histories and physical examinations of all volunteers were normal. Hematological and biochemical profiles of all volunteers were normal, as were urinalyses. On the night before each trial day, three 0.2% cantharidin-impregnated plasters (1 by 1 cm) were applied to the forearm of each volunteer. One additional patch was applied at 12 h for the 24-h sample. After overnight fasting each subject was given a capsule of 200 mg of clinafloxacin with 240 ml of water. All volunteers applied a factor 30 sunblock (Ambre Solaire; Laboratoire Garnier, Paris, France) preparation to light-exposed areas of skin, as phototoxicity has been observed following exposure to sunlight (data on file; Parke-Davis). A single 200-mg dose of clinafloxacin was given orally to each of nine healthy male volunteers, and the concentrations of the drug were measured in plasma, cantharidin-induced inflammatory fluid, and urine over the following 24 h (48 h in the case of urine). The mean maximum concentration in plasma was 1.34 μg/ml at a mean time of 1.8 h postdose. The mean maximum concentration in the inflammatory fluid was 1.3 μg/ml at 3.8 h postdose. The mean elimination half-life of clinafloxacin in plasma was 5.65 h. The overall penetration into the inflammatory fluid was 93.1%, as assessed by determining the ratio of area under the concentration-time curves. Recovery of clinafloxacin in urine was 58.8% by 24 h and 71.8% by 48 h postdose.

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The mean concentration-time curve from time zero to infinity (AUC\text{0–}\infty) for the inflammatory fluid to that for plasma. The AUC was determined by a log linear trapezoidal method. Apparent oral clearance (CL/F) was determined by dividing the dose by the AUC\text{0–}\infty. The apparent volume of distribution was calculated by dividing the CL/F by the elimination constant.

The mean concentrations of clinafloxacin, following the 200-mg oral dose, in plasma and inflammatory fluid are shown in Fig. 1, and the derived pharmacokinetic parameters are provided in Table 1. The correlation coefficient between the time and the log of the concentration, in the plasma elimination (or log linear) phase, was 0.988, and the regression coefficient for the same phase was 0.977.

Inspection of the individual graphs of plasma data suggested that distribution was essentially completed during the absorption phase, as no biphasic response was noted. Absorption was rapid, the mean time to maximum concentration of the drug in plasma (T\text{max}) being 1.78 h and ranging from 1 to 3 h. The mean maximum concentration of the drug (C\text{max}) in plasma was 1.34 μg/ml, with little individual variation (SD, 0.32 μg/ml).

The mean elimination half-life in plasma (t\text{1/2}) was 5.65 h, and the range was 4.9 to 7.31 h. The total clearance of that fraction of the drug absorbed was 341.7 ml/min. Over 24 h, 58.8% of the drug was recovered in the urine, and the recovery increased to 71.8% by 72 h. The mean concentration of the drug in urine in the final sample assayed (24 to 48 h postdose) was 3.0 μg/ml (SD, 1.04 μg/ml).

Clinafloxacin penetrated moderately rapidly into the inflammatory exudate, achieving a maximum at a mean time of 3.8 h postdose (SD, 1.3 h), and the mean maximum concentration was 1.13 μg/ml, 77% of the mean peak concentration in plasma. The mean rate of elimination of clinafloxacin from the inflammatory exudate was apparently higher (4.6 h) than that for plasma but more variable (1.5 h) than that for plasma. The degree of penetration into the inflammatory exudate, calculated from a comparison of the AUC\text{0–}\infty in the exudate with that in plasma, was 93.1% (range, 70.5 to 117.2%).

![FIG. 1. Mean plasma and inflammatory fluid clinafloxacin concentrations following a 200-mg dose of the drug. Vertical bars, SDs.](image)

| TABLE 1. Pharmacokinetic parameters following a 200-mg oral dose of clinafloxacin |
|---------------------------------|---------------------------------|-------------------------------------------------|---------------------------------|-------------------------------------------------|---------------------------------|-------------------------------------------------|---------------------------------|-------------------------------------------------|
| Pharmacokinetic parameter       | Plasma                          | Inflammatory fluid                           |                    |                      |                  |                      |                  |                      |
|                                  | C\text{max} (μg/ml)            | T\text{max} (h)                              | t\text{1/2} (h)   | AUC\text{0–}\infty (μg · h/liter) | Apparent vol of distribution (liter) | CL/F (ml/min)       | % of drug recovered in urine 0–24 h | % of drug recovered in urine 0–48 h | C\text{max} (μg/ml)            | T\text{max} (h)                              | t\text{1/2} (h)   | AUC\text{0–}\infty (μg · h/liter) | % Penetration  |
| Mean                            | 1.34                            | 1.78                                        | 5.65             | 9.86                        | 166.3                         | 341.7                  | 58.8                         | 71.8                         | 1.13                            | 3.8                                        | 4.6                                        | 9.22                        | 93.1                                        |
| SD                              | 0.32                            | 0.83                                        | 0.72             | 1.13                        | 19.4                          | 41.7                    | 3.16                         | 3.3                          | 0.51                            | 1.3                                        | 1.5                                        | 2.21                        | 16.1                                        |
| Minimum                         | 1.01                            | 1                                           | 4.90             | 7.98                        | 138.6                         | 301.7                   | 55.2                         | 66.2                         | 0.78                            | 3                                           | 2.2                                        | 6.80                        | 70.5                                        |
| Maximum                         | 1.95                            | 3                                           | 7.31             | 11.04                       | 198.4                         | 418.3                   | 63.1                         | 75.7                         | 1.69                            | 6                                           | 5.2                                        | 12.63                       | 117.2                                       |
One of the nine volunteers complained of a moderate headache and photophobia which developed 28 h after dosing and lasted approximately 12 h; it was difficult to assess if this was associated with the study drug.

No hematological or biochemical abnormalities were encountered.

There is little published data on the pharmacokinetics of clinafloxacin. A report of a dose range study (2) suggested that the agent was rapidly absorbed, with a \( C_{\text{max}} \) of about 1 \( \mu \text{g/ml} \) for each 100-mg dose, and was eliminated from plasma with a \( t_{1/2} \) of 4.6 to 6.1 h; between 44 and 65% of the dose given was recovered in the urine over the 72 h after administration.

The present study confirmed that clinafloxacin is rapidly absorbed. The plasma \( C_{\text{max}} \) achieved (1.34 \( \mu \text{g/ml} \)) is lower than that in the earlier report for the same dose. The highest value we noted (1.95 \( \mu \text{g/ml} \)) was less than the mean value previously reported (2.5 \( \mu \text{g/ml} \)). The mean AUC\(_{0-\infty}\)s in both studies were similar, 10.2 \( \mu \text{g} \cdot \text{h/ml} \) in the earlier study and 9.86 \( \mu \text{g} \cdot \text{h/ml} \) in the present study. The urinary recovery in our study was also greater, with a mean of 71.8% over 48 h.

The rapid and extensive penetration of clinafloxacin into the inflammatory exudate contrasts with that of trovafloxacin, for which the mean percent penetration was reported as 62.6% (9) and possibly reflects the high protein binding of trovafloxacin (87.9%) (3) compared with that of clinafloxacin (2 to 7%) (8). The mean penetration of clinafloxacin, 93.1%, was not significantly different from that described for sparflloxacin (113%) (4) or lomefloxacin (100%) (6).

In conclusion, the concentration in both plasma and inflammatory fluid was greater than the MIC at which 90% of the isolates are inhibited for the majority of the \( \text{Enterobacteriaceae}, \text{Streptococcus pneumoniae}, \) methicillin-susceptible \( \text{Staphylococcus aureus}, \) and \( \text{Bacteroides fragilis} \) for approximately 20 h following the single 200-mg oral dose. This suggests that this dose should be efficacious in the treatment of systemic infections caused by such pathogens.

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