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Pharmacokinetics and Penetration into Inflammatory Fluid of Trovafloxacin (CP-99,219)

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A single 200-mg oral dose of trovafloxacin (CP-99,219) was given to each of eight healthy male volunteers, and the concentrations of the drug were measured in plasma, cantharides-induced inflammatory fluid, and urine over the subsequent 36 h. The mean maximum concentration observed in plasma was 2.9 μg/ml at a mean time of 0.75 h postdose. The mean maximum concentration observed in inflammatory fluid was 1.2 μg/ml at 4.0 h postdose. The mean elimination half-life in plasma was 7.8 h. The overall penetration into inflammatory fluid was 64%, as assessed by determining the ratio of the area under the concentration-time curves. Recovery of the dose in urine within the first 36 h postdose was 5.0% of the administered dose. Our results indicate that trovafloxacin, at a dosage of 200 mg once or twice daily, should be adequate for the treatment of systemic infections caused by most common bacterial pathogens.

Trovafloxacin (CP-99,219) is a new azabicyclo naphthyridone agent with a broad spectrum of antibacterial activity (1, 6) which includes the family *Enterobacteriaceae* and the major respiratory pathogens, including *Streptococcus pneumoniae*, and has a high degree of activity against *Staphylococcus aureus*.

In the single-dose study described here, the pharmacokinetics of 200 mg of trovafloxacin were investigated in eight healthy volunteers. The level of penetration into a chemically induced mild inflammatory exudate (14) was also studied.

MATERIALS AND METHODS

Volunteers. Eight healthy male volunteers gave written, informed consent to participate in the study after hospital Ethical Committee approval had been obtained. They had a mean age of 26 years (range, 18 to 43 years), a mean weight of 73.1 kg (range, 60.0 to 87.0 kg), and a mean height of 1.76 m (range, 1.67 to 1.83 m). The medical histories and physical examinations of all volunteers were normal. Hematological and biochemical profiles of all the volunteers were normal, as were urinalyses. On the night before each trial day, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the forearm of each volunteer. After overnight fasting each subject was given a tablet of 200 mg of trovafloxacin with 150 ml of water. A light meal was served 2 h after dosing, and fluids were allowed ad libitum. Blood samples were taken prior to (0 h) and at 30 min and 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h following administration. The blisters were sampled at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after administration by puncture with a butterfly needle, with approximately 50 μl being removed; the integrity of the blisters was maintained by spraying them with a fast-drying plastic dressing (Opsite; Smith and Nephew Medical Ltd., Hull, United Kingdom). A predose urine sample was collected, as was all urine over 0 to 12, 12 to 24, and 24 to 36 h postdose; the volumes were measured and an aliquot was taken for antibiotic assay.

At 48 h postdose a further hematological and biochemical profile was performed.

Drug analysis. Assays were performed within 1 h of sample collection by a plate diffusion method with a 5-mm-diameter well. The indicator organism was *Escherichia coli* 4004, which was flooded onto the surface of the assay plates containing Iso-Sensitest agar (Unipath, Basingstoke, United Kingdom) after dilution in distilled water to give an optical density at 630 nm of 0.004. Calibrators of 0.125, 0.25, 0.5, 1, and 2 μg/ml and internal controls of 1.5 and 2.0 μg/ml were prepared in human serum (Bradsure Biological, Market Harborough, United Kingdom), it having previously been shown that plasma and serum controls gave identical results; these controls were 70% human serum in phosphate buffer (pH 7), and phosphate buffer (pH 7) for the assay of trovafloxacin in plasma, blister fluid, and urine, respectively. The urine samples were diluted volumetrically in the phosphate buffer (pH 7) to bring the expected concentration within the standard range. After overnight incubation at 30°C, the zone sizes were measured by an image analyzer (Vidas Image Associates, Thame, United Kingdom). The between-assay coefficients of variation were 6.4, 6.5, and 6.5% at a concentration of 1.5 mg/liter for plasma, 70% human serum, and pH 7 buffer, respectively; and the within-assay coefficients of variation were 6.0, 5.0, and 6.3% at concentrations of 1.5, 1.3, and 0.3 mg/liter for plasma, 70% human serum, and pH 7 buffer, respectively. The lower limit of sensitivity of the assay was 0.12 μg/ml.

Pharmacokinetic analysis of the plasma and blister fluid samples was performed by the GPHARM program (8) by using a Powell algorithm that uses a weighted least-squares procedure with the error variance model with a weight of $1/Y$ calc., the calculated observation. Following inspection of the individual concentration-time curves and the Akaike value to support the model choice, the plasma data were fitted to a two-compartment model with first-order elimination from the central compartment. The blister data were fitted to a one-compartment model with first-order input. The maximum concentration of drug in serum (C_{max}) at the time of the maximum concentration in serum (T_{max}) was determined by inspection. The degree of penetration into blister fluid was based on the comparison of the area under the concentration time curve from time zero to infinity ($AUC_{0-\infty}$) in blister fluid to that in plasma.

RESULTS

The mean concentrations of trovafloxacin found in plasma and inflammatory fluid are shown in Fig. 1, and the derived pharmacokinetic parameters are provided in Table 1. For the plasma data the correlation between the observed and the predicted values was ≥0.96 in all but one volunteer. This indicated that in these seven volunteers the model accounted for 96% of the variation in the concentration and that 4% of the variation was attributable to error. In one volunteer the correlation was 0.88.

Inspection of the individual graphs of the plasma data suggested that there was a short initial distribution phase of 1.5 to 2 h; this was followed by a log-linear decline of concentration with time. This fell from a mean C_{max} of 2.9 μg/ml to a mean concentration of 0.7 μg/ml at 12 h and 0.26 μg/ml at 24 h. Trovafloxacin appeared to be rapidly absorbed, with the mean T_{max} being 0.75 h and occurring at 0.5 h in five of the eight volunteers. Although there was a modest amount of individual variation in the concentrations in plasma at the early time points (for example, the mean concentration at 0.5 h, 2.6 μg/ml; standard deviation [SD], 1.2 μg/ml), there was little individual variation after 3 h (for example, the mean concentration at 4 h, 1.5 μg/ml; SD, 0.2 μg/ml).

The mean plasma elimination half-life ($t_{1/2\beta}$) was 7.8 h, with the range being from 6.1 to 9.6 h. The total clearance of

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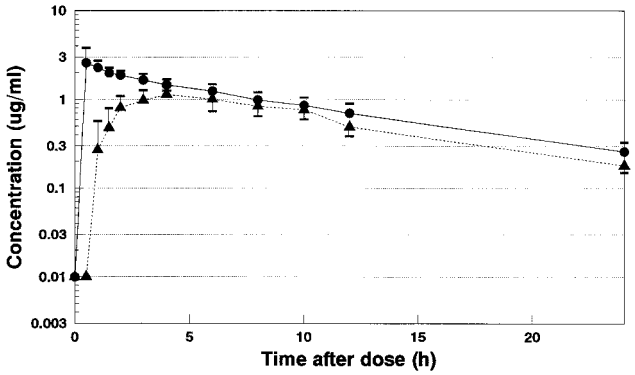

FIG. 1. Mean concentrations in plasma (●) and blister fluid (▲) following the administration of 200 mg of trovafloxacin to eight volunteers. Note that blister fluid data are for five volunteers. Bars indicate SDs.

trovafloxacin from the body varied from 170.9 to 116.7 ml/min (mean, 140.6 ml/min). The mean volume of distribution of the compound, as measured in the elimination phase, was 94.2 liters or 1.31 liters/kg of body weight, assuming complete absorption and complete systemic availability.

In one volunteer no blister formation occurred, and for two volunteers only five samples were available for assay; hence, the pharmacokinetic parameters in this fluid were derived from data for five volunteers. Trovafloxacin penetrates moderately rapidly into the inflammatory exudate, with the mean T_{max} being at 4 h (range, 3 to 6 h). The mean peak concentration achieved was 1.2 μg/ml, being 41% of the mean peak concentration in plasma. The rate of elimination of trovafloxacin from the inflammatory fluid was similar to the elimination rate from plasma, with the inflammatory fluid half-life being 7.1 h (range, 5.3 to 7.9 h). The level of penetration of trovafloxacin into the inflammatory exudate, calculated by comparison of the $AUC_{0-\infty}$ for measurements in inflammatory fluid with that for measurements taken in plasma, was 62.6% (range, 50.7 to 77.4%). Over 0 to 12 h, 3.6% (SD, 0.62%) trovafloxacin was eliminated in the urine. Over the 36-h collection period, a mean of 5.0% (SD, 0.98%) was recovered by this route.

Physical examination revealed no abnormalities that had developed over the trial period. Three of the eight volunteers complained of light-headedness, which they ascribed to being fasted, and the complaint resolved on eating breakfast. No hematologic or biochemical abnormalities were observed.

DISCUSSION

There are few published data on the pharmacokinetics of trovafloxacin. The $t_{1/2\beta}$ in monkeys was reported to be 14 h (2).

Trovafloxacin appears to be rapidly absorbed when it is administered to humans. In studies with doses of between 30 and 1,000 mg, the C_{max} appears to be about 1 μg/ml per 100 mg of an administered dose (11). After the administration of a 200-mg dose we determined the C_{max} to be 2.9 μg/ml. The earlier study described the $t_{1/2\beta}$ to be 7.1 to 12.4 h for 30- and 1,000-mg doses, respectively, and 9.6 h for the 300-mg dose. We found the value to be somewhat lower at 7.8 h, which might reflect methodological variations in calculating this parameter.

Trovafloxacin differs from many other fluoroquinolones in the low amount recovered in the urine. In the present study 5% was recovered by this route in 36 h, by which time elimination must be considered essentially complete. This value accords well with those obtained in a recent multiple-dose study (12): 100 and 300 mg of trovafloxacin when less than 10% of the administered dose was recovered in the urine. In this regard trovafloxacin was similar to pefloxacin, 4.9% of which is recovered in the urine (10); however, pefloxacin is extensively metabolized to norfloxacin. The metabolism of trovafloxacin is under study. Preliminary investigations in animals (7) suggest only minor urinary glucuronide formation, but the glucuronide lacks antimicrobial activity. The major route of elimination in humans is the fecal route, with 63.3% of the administered drug being recovered by this route (4).

Trovafloxacin, in comparison with other fluoroquinolones, apparently has a reduced level of penetration into the inflammatory exudate. Although the rate of penetration is as rapid as those of ciprofloxacin (T_{max}, 3.5 h [3]) and sparfloxacin (T_{max}, 5 h [9]), the proportion that penetrated was lower at 64%, compared with 102.8 and 117% for ciprofloxacin and sparfloxacin, respectively. However, the value of the AUC per 100-mg dose administered for inflammatory fluid is 5.1 μg · h/ml for ciprofloxacin and 8.1 μg · h/ml for trovafloxacin. A possible explanation for this observation may be related to the higher level of protein binding of trovafloxacin (87.9% at 1 μg/ml) (5), compared with those of ciprofloxacin (20% [13]) and sparfloxacin (45% [unpublished data]). Multiple-dose studies on penetration into inflammatory fluid would be

TABLE 1. Pharmacokinetic parameters following administration of 200-mg oral dose of trovafloxacin

Subject no.	Plasma							Inflammatory fluid					
	C_{max} (μg/ml)	T_{max} (h)	K_a (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg · h/liter)	V_β/kg (liters/kg)[a]	Total clearance (ml/min)	C_{max} (μg/ml)	T_{max} (h)	K_a (h^{-1})	$t_{1/2\beta}$ (h)	$AUC_{0-\infty}$ (mg · h/liter)	% Penetration
1	2.92	0.5	1.89	9.6	27.4	1.40	121.6	1.44	3.0	0.76	5.3	13.9	50.7
2	3.88	0.5	24.0	7.5	19.8	1.82	168.3	—[b]	—	—	—	—	—
3	2.16	0.5	0.41	8.4	28.6	1.15	116.7	—	—	—	—	—	—
4	1.79	1.5	1.93	7.71	19.5	1.31	170.9	1.24	4.0	3.6	7.1	15.1	77.4
5	2.48	1.0	12.6	8.4	32.1	1.17	103.8	1.32	6.0	0.45	7.3	19.4	60.4
6	2.64	1.0	3.1	6.1	20.9	1.14	159.6	0.96	3.0	1.41	7.9	13.4	64.1
7	2.92	0.5	14.7	8.0	24.7	1.20	134.7	1.1	4.0	0.56	7.7	14.9	60.3
8	4.2	0.5	11.1	7.0	22.4	1.32	149.0	—	—	—	—	—	—
Mean	2.9	0.75	8.7	7.8	24.4	1.31	140.6	1.2	4.0	1.4	7.1	15.3	62.6
SD	0.82	0.4	8.3	1.0	4.6	0.22	24.2	0.19	1.2	1.3	1.0	2.4	9.7

[a] V_β, volume of distribution in the elimination phase.
[b] —, incomplete data.

needed to assess accurately the steady-state penetration of a moderately highly bound agent such as trovafloxacin.

The MIC of trovafloxacin at which 90% of isolates are inhibited for members of the family *Enterobacteriaceae*, streptococci (including *Streptococcus pneumoniae*), methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, *Haemophilus influenzae*, and *Moraxella catarrhalis* is ≤0.5 μg/ml (1, 6). This concentration was exceeded in inflammatory fluid for about 12 h and in plasma for about 16 h. This would support the use of the drug at a once-daily dosage for the therapy of infections caused by many pathogens. Treatment of less susceptible pathogens, such as *Pseudomonas aeruginosa* and methicillin-resistant (and ciprofloxacin-resistant) *Staphylococcus aureus*, may require a higher dose or more frequent dosing.

In conclusion, the present study supports the continuing investigation of trovafloxacin for the treatment of a wide range of systemic infections by a once- or twice-daily dosing regimen.

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