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Pharmacokinetics and Tissue Penetration of the New Fluoroquinolone Grepafloxacin

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A single 400-mg oral dose of grepafloxacin (OPC-17116) was given to each of six healthy male volunteers, and the concentrations of the drug in plasma, cantharides-induced inflammatory fluid, and urine were measured over the subsequent 12 h. The mean peak concentration in plasma of 1.5 μg/ml was attained at a mean time of 2.0 h postdose. The mean peak concentration in inflammatory fluid of 1.1 μg/ml was attained at a mean time of 4.8 h postdose. The mean elimination half-life in plasma was 5.2 h, and that in inflammatory fluid was 12.7 h. The overall penetration into inflammatory fluid was 180.6% (or 133% if one aberrant result from one volunteer is excluded). Recovery of the drug in urine during the first 24 h postdose was 8.3% of the administered dose. Our results indicate that a once- or twice-daily dosage of grepafloxacin should be adequate to treat systemic infections caused by most bacterial pathogens.

Grepafloxacin (OPC-17116) is a new, oral fluoroquinolone which is characterized as having an N-1 cyclopropyl group, a C-5 methyl group, and a C-7 piperazinyl moiety to which a 3-methyl group is attached. In vitro studies suggest that in comparison with the earlier quinolones, grepafloxacin has enhanced activity against gram-positive cocci, including *Streptococcus pneumoniae*, *Enterococcus* species, and methicillin-susceptible *Staphylococcus aureus* (5, 8, 9, 12). It also appears to be more active against anaerobes, particularly *Bacteroides* species. One study demonstrated activity against chlamydial species, including *Chlamydia pneumoniae*, that was greater than that of ciprofloxacin or tetracycline (12).

The purpose of this study was to investigate the pharmacokinetics of grepafloxacin in healthy volunteers following a single 400-mg dose and to investigate the penetration into inflammatory fluid with a chemically induced blister as a model (13).

MATERIALS AND METHODS

Approval for this study was obtained from the Hospital Ethical Committee. Six healthy, Caucasian male volunteers with a mean age of 28 years (range, 22 to 37 years), a mean weight of 73.08 kg (range, 60 to 89.4 kg), and a mean height of 1.77 m (range, 1.69 to 1.85 m) were selected. None had a history of atopy or of allergy to antibiotics or had taken any prescribed or over-the-counter medication in the 4 and 2 weeks, respectively, prior to the study. Results of physical examinations, biochemical and hematological profiles, and urinalyses were within normal limits in the 9 days prior to the study. Vital signs, including sitting blood pressure, pulse, respiratory rate, and oral temperature, were checked immediately prior to dosing and after the study.

Two 1.5-cm^2 plasters impregnated with 0.2% cantharides were taped to the forearm of each volunteer approximately 12 to 16 h prior to dosing. After an overnight fast, the volunteers were given 400 mg of grepafloxacin (provided by Otsuka Pharmaceutical Company, London, United Kingdom) to be taken orally with 200 ml of water. They fasted for a further 2 h after the dose, at which time they were permitted to have a light breakfast of toast. They were then allowed to drink fluids freely for a further 4 h; thereafter, food and fluids were taken ad libitum. No caffeinated beverages were permitted during the course of the study.

Blood samples for grepafloxacin determination were taken via an indwelling peripheral intravenous cannula. Between samplings, the cannulae were kept patent by being flushed with 5 ml of saline. Drug levels in plasma were measured immediately before the dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h postdose. Samples of blister fluid were taken by puncturing the blister with a sterile needle and then aspirating fluid with a sterile micropipette at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 h postdose. After the sampling, the blisters were resealed with Nobecutane aerosol spray (Astra Chemicals Ltd., Watford, United Kingdom). Urine was collected over the periods 0 to 4, 5 to 8, 9 to 12, and 12 to 24 h postdose. The volume collected was recorded, and aliquots of each sample were saved for measurement of levels of grepafloxacin in urine.

The concentrations of grepafloxacin in plasma, blister fluid, and urine were measured by using a microbiological plate assay method. The assay was externally validated by the Otsuka Pharmaceutical Company, Tokyo, Japan. An overnight culture of *Escherichia coli* 4004 (from Bayer Pharmaceutical Co., Newbury, United Kingdom), diluted to give an optical density of 0.004 at a wavelength of 630 nm, was used as the test organism on Iso-Sensitest agar (Unipath, Basingstoke, United Kingdom). Standards for plasma, blister fluid, and urine were prepared by diluting grepafloxacin in human serum, 70% human serum in phosphate buffer (pH 7), and phosphate buffer (pH 7), respectively. The internal controls used were 0.8 and 0.1 μg/ml. Samples of plasma and blister fluid were tested both undiluted and diluted 1:5 in human serum. Urine was diluted in phosphate buffer to bring the drug concentration within the range of the standard curve.

The plates were incubated overnight in air at 30°C. The resulting zones of inhibition were measured with a magnifying zone reader (Lee Brook Instruments, Strood, United Kingdom), and antibiotic concentrations were calculated with Bennett's correction (2). The lower limit of sensitivity of the assay was 0.03 μg/ml, and the between-assay coefficient of variation was 8.0% (standard deviation [SD], 2.3%) for the internal controls of 0.8 and 0.1 μg/ml.

Pharmacokinetic analysis was done with the GPHARM (4) program, using a Powell minimization algorithm and a unitary weighted least-squares parameter estimation procedure after assessment of results by inspection of the Akaike value. The plasma samples were analyzed by assuming a two-compartment model with first-order input. The data for blister fluid were fitted to a one-compartment model with first-order input and elimination. The maximum concentration of drug in plasma or blister fluid and the time at which this was attained were determined by inspection.

RESULTS

The mean concentrations of grepafloxacin in plasma and blister fluid are shown in Fig. 1. The derived pharmacokinetic parameters are given in Table 1. One of the six volunteers showed poor blister formation in response to application of the cantharides plasters; therefore, only five sets of blister fluids were available for analysis. Following a single 400-mg dose, grepafloxacin reached a mean peak in plasma of 1.5 μg/ml at 2.0 h postdose in all six volunteers. Thereafter, the levels declined, with a mean plasma elimination half-life of 5.2 h (range, 4.3 to 6.6 h), and by 12 h had reached a mean value of 0.4 μg/ml.

In the inflammatory blister fluid, the concentration of grepafloxacin showed much more variation among volunteers. In all of the volunteers, two peaks were evident; the first peak occurred at a mean time of 4 h (mean concentration, 0.9 μg/ml), and the second peak occurred at 8 h (mean concentration, 1.0 μg/ml). This phenomenon was observed in the blister fluids

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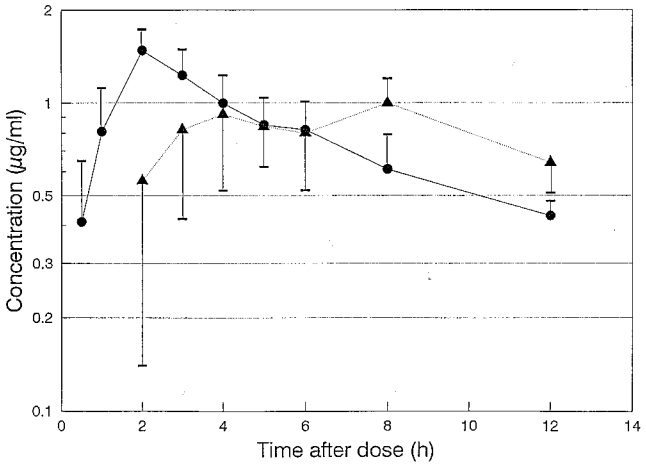

FIG. 1. Mean grepafloxacin levels in plasma (●) and inflammatory fluid (▲) following 400 mg of grepafloxacin by mouth. Bars, SDs.

from all five volunteers but not in their plasma samples. The blister fluid elimination half-life was 12.7 h, but the range was very broad (4.3 to 27.8 h).

The mean percent penetration of grepafloxacin into blister fluid, calculated from the ratio of the area under the curve for blister fluid to that for plasma, was 180.6%. However, one volunteer (with a blister fluid elimination half-life of 27.8 h) had a percent penetration of 369%; if this result is omitted, the mean percent penetration was 133%. The apparent volume of distribution of the drug (as measured for the elimination phase) was high, at a mean of 253.2 liters.

The volunteers excreted a mean total of 33.17 mg of grepafloxacin in urine over 24 h, representing 8.3% (SD, 3.18%) of the total 400-mg dose ingested. The mean concentrations of grepafloxacin in urine at 8 to 12 and 12 to 24 h after the dose were 15.1 and 15.4 μg/ml, respectively.

The results of routine hematological and biochemical investigations and urinalyses remained within normal limits following the single 400-mg dose. One volunteer complained of a headache some 12 h after taking the dose. This did not require medication and resolved spontaneously; otherwise, no adverse effects were reported.

DISCUSSION

The data obtained for the concentration of grepafloxacin in plasma were similar to those previously published (7).

Grepafloxacin appears to be rapidly absorbed from the gastrointestinal tract. Compared with that of the other quinolones, the excretion of the drug in urine is low, with 8.3% (SD, 3.18%) of the total dose being recovered from the urine. This is similar to results previously reported (7). It is in contrast to the case for ciprofloxacin and ofloxacin, 27.8 and 98.5% of which, respectively, are excreted in the urine (3, 11).

Animal studies suggest that the main route of excretion of this drug is in feces, either via the bile or transmucosally (1).

It is difficult to account for the observation of the double peaks in the inflammatory exudate. Inspection of the individual blister fluid data shows large inter- and intrasubject variation. The mean peak drug concentrations in blister fluid at 4, 6, and 8 h are 0.95 (SD, 0.44) 0.80 (SD, 0.27), and 1.0 (SD, 0.20) μg/ml, respectively, and a one-way analysis of variance shows no significant differences ($P = 0.60$) between these values. There is no obvious pharmacokinetic explanation. The mean

TABLE 1. Pharmacokinetic parameters of grepafloxacin following a single 400-mg oral dose[a]

Sample	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2\beta}$ (h)	$t_{1/2\alpha}$ (h)	V_β (liters)	$AUC_{0-\infty}$ (mg · h/liter)	% Penetration[b]
Serum	2.0	1.5 ± 0.3 (1.0–1.8)	5.2 ± 0.8 (4.3–6.6)	0.6 ± 0.2 (0.4–0.9)	253.2 ± 58.0 (185.9–355.0)	12.4 ± 2.4 (9.0–16.0)	
Blister fluid[c]	4.8 ± 1.9 (3.0–8.0)	1.1 ± 0.3 (0.9–1.7)	12.7 ± 10.6 (4.3–27.8)			22.0 ± 12.98 (10.3–43.2)	180.6 ± 114 (92.5–369)

[a] Results are reported as means ± SDs, with ranges given in parentheses. T_{max}, time at which maximum drug concentration was achieved; C_{max}, maximum drug concentration; $t_{1/2\beta}$, elimination half-life; $t_{1/2\alpha}$, absorption rate half-life; V_β, volume of distribution, elimination phase; $AUC_{0-\infty}$, area under the concentration-time curve from 0 h to infinity.

[b] ($AUC_{0-\infty}$ for blister fluid/$AUC_{0-\infty}$ for plasma) × 100.

[c] Results for one volunteer were omitted (see text).

percent penetration into the inflammatory exudate (excluding the aberrant result from the volunteer with the protracted elimination of the drug from this site) of 133% is similar to that found with other quinolones, for example, 113% for sparfloxacin (6) and 100% for lomefloxacin (10). It is recognized, however, that the half-lives (and hence the area under the concentration-time curve) for blister fluid are not robustly estimated here, since the half-life interval in some volunteers is close to the sampling interval.

Grepafloxacin is a quinolone with a high level of tissue distribution, penetrating well into inflammatory exudates. The MIC of grepafloxacin at which 90% of the isolates are inhibited is $\leq$0.25 μg/ml for the majority of members of the family *Enterobacteriaceae* and for *S. aureus* and is 0.5 μg/ml for *S. pneumoniae. Haemophilus influenzae* and *Moraxella catarrhalis* are more susceptible (MIC at which 90% of the isolates are inhibited, $\leq$0.03 μg/ml) (12). Since concentrations achieved in plasma and exudate exceed 0.5 μg/ml for more than 10 to 12 h after a single oral dose of grepafloxacin, it is probable that this agent will be efficacious in a wide range of bacterial infections.

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