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Pharmacokinetics and Inflammatory Fluid Penetration of Sparfloxacin

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A single 400-mg oral dose of sparfloxacin was given to each of six healthy male volunteers, and the concentrations of the drug were measured in plasma, cantharides-induced inflammatory fluid, and urine over the subsequent 52 h. The mean peak concentration in plasma of 1.6 μg/ml was attained at a mean time of 2.7 h postdose. The mean peak concentration in inflammatory fluid of 1.3 μg/ml was attained at a mean time of 5 h postdose. The mean elimination half-life in plasma was 17.6 h, and that in inflammatory fluid was 19.7 h. The overall penetration into inflammatory fluid was 117%. Urinary recovery within the first 52 h postdose was 8.8% of the administered dose. Our results indicate that a once-daily dosage of sparfloxacin should be adequate to treat systemic infections caused by most common bacterial pathogens.

Sparfloxacin [AT-4140; 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-7(*cis*-3,5-dimethyl-1-piperazinyl)-4-oxoquinolone-3-carboxylic acid] is a new difluorinated quinolone antimicrobial agent. In vitro studies have shown it to have greater activity than most other quinolones against gram-positive species and only slightly less activity than ciprofloxacin against gram-negative species (1). It also has good activity in vitro against many atypical pathogens, such as *Chlamydia trachomatis* (1), legionellae, mycobacteria, mycoplasmas (9), and rickettsiae (11).

The purpose of this study was to investigate the pharmacokinetics of sparfloxacin and its penetration into a chemically induced blister, which is similar in composition to a mild inflammatory exudate (14), following a single oral dose.

MATERIALS AND METHODS

Six healthy male volunteers gave written, informed consent after hospital Ethical Committee approval had been obtained. They had a mean age of 30 (range, 23 to 40) years, a mean weight of 72.8 (range, 64.2 to 85.0) kg, and a mean height of 1.74 (range, 1.63 to 1.85) m. The medical histories and physical examinations of all were normal; in particular, none reported any previous episode of convulsions, allergy, or intolerance to any antibiotics. Hematological and biochemical profiles were normal, as was urinalysis. On the night before the trial, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the anterior forearm of each volunteer. After overnight fasting, each subject was given a single 400-mg tablet of sparfloxacin with 200 ml of water. Thereafter, water was taken ad libitum. Food was taken after 2 h. Blood was taken before the dose and then 0.5, 1, 2, 3, 4, 6, 8, 12, 26, and 52 h after the dose via an intravenous cannula kept patent with heparinized saline. The blisters were sampled at the same times postdose as the blood samples by using a micropipette; the integrity of the blisters was maintained by spraying with a fast-drying plastic dressing (Nobecutane; Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom). All urine was collected (protected from light) at 0 to 4, 4 to 8, 8 to 12, 12 to 26, and 26 to 52 h postdose, the volumes were measured, and an aliquot was taken for antibiotic assay.

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Antibiotic assays were performed within 1 h of sample collection by using a plate diffusion method; the test organism was *Escherichia coli* 4004 (Bayer AG, Wuppertal, Germany); the medium used was Iso-Sensitest agar (pH 7.2; Oxoid Ltd., Basingstoke, United Kingdom). Standards were prepared by using human serum (Bradshaw Biologicals, Leicester, United Kingdom) for serum samples, 70% human serum (to simulate the protein content of the inflammatory fluid) in pH 7 phosphate buffer for inflammatory fluid samples, and phosphate buffer at pH 7 for urine samples. Samples were applied by filling 5-mm-diameter wells cut into the plates, which were then incubated in air overnight at 30°C. The coefficient of variation within the assay was 9.4% at 0.75 μg/ml and 6.5% at 0.1 μg/ml. The coefficients of variation between assays were 5.9 and 7.9%, respectively. The lower limit of sensitivity was 0.1 μg/ml. The standard range for the assay was 0.06 to 1 μg/ml, and the assay was linear between these values.

Physical examinations and measurements of initial signs were repeated 3 and 7 days after the dose was administered.

Pharmacokinetic analysis of the plasma samples was performed by using the GPHARM program (4), assuming a two-compartment model using a weighted least-squares algorithm. Pharmacokinetic analysis of blister fluid samples was based on standard graphical methods (3, 5). The area under the curve for time zero to infinity ($AUC_{0-\infty}$) was derived from the knowledge of the AUC for time zero to 52 h, the elimination constant, and the concentration at $t = 52$ h.

RESULTS

The mean concentrations in plasma and inflammatory fluid obtained are shown in Fig. 1. The derived pharmacokinetic data are listed in Table 1.

The rate of absorption of sparfloxacin was very variable, the time at which the maximum drug concentration (T_{max}) in plasma was achieved ranging from 0.5 to 6 h, but generally was fairly slow, with a mean T_{max} in plasma of 2.7 h. This is reflected in the low but varied absorption rate constant (K_a) of 0.1 to 1.8 h^{-1}. Peak concentrations in plasma were much less varied, with a mean of 1.6 (range, 1.2 to 1.9) μg/ml. The drug penetrated inflammatory fluid well but also slowly, with a mean peak concentration of 1.3 μg/ml at a mean time of 5

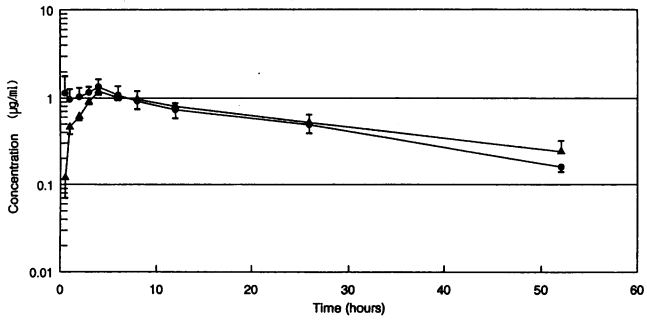

FIG. 1. Mean concentrations of sparfloxacin in plasma (●) and inflammatory fluid (▲) following a single 400-mg oral dose. The bars show standard deviations.

h postdose. The mean elimination half-life of sparfloxacin in plasma was 17.6 (range, 15.1 to 20.9) h, while that in inflammatory fluid was much more varied (range, 12.2 to 32.6 h) but was generally slightly longer, with a mean value of 19.7 h.

The mean percentage of sparfloxacin penetration into inflammatory fluid, calculated from individual ratios of $AUC_{0-\infty}$ for inflammatory fluid and $AUC_{0-\infty}$ for plasma, was 117% (range, 91 to 155%). Urinary recovery of microbiologically active sparfloxacin over the first 52 h after administration of the drug was 8.8% (range, 6.7 to 11.6%) of the dose. The mean urinary concentration between 8 and 12 h postdose was 10.8 (range, 6.8 to 14.7) μg/ml, between 12 and 26 h it was 11.7 (range, 5.4 to 19.9) μg/ml, and between 26 and 52 h it was 5.2 (range, 2.9 to 7.9) μg/ml. Physical examination revealed no abnormalities that had developed during the trial period, although one volunteer complained of pruritis for 5 days and another complained of dry skin for 4 days after taking sparfloxacin.

TABLE 1. Pharmacokinetic parameters of sparfloxacin

Parameter[a] in fluid indicated (unit)	Mean value (SD)	Range
Plasma		
T_{max} (h)	2.7 (2.1)	0.5–6
C_{max} (μg/ml)	1.6 (0.3)	1.2–1.9
$t_{1/2\beta}$ (h)	17.6 (2.0)	15.1–20.9
$AUC_{0-\infty}$ (mg · h/liter)	32.3 (4.0)	27.6–38.5
K_a (h^{-1})	0.8 (0.7)	0.1–1.8
Inflammatory fluid		
T_{max} (h)	5.0 (1.7)	4–8
C_{max} (μg/ml)	1.3 (0.3)	1.0–1.7
$t_{1/2\beta}$ (h)	19.7 (7.6)	12.2–32.6
$AUC_{0-\infty}$	37.4 (6.3)	27.3–45.0
% Drug penetration into inflammatory fluid ($AUC_{0-\infty}$ inflammatory fluid/$AUC_{0-\infty}$ plasma)	117 (21)	91–155
Urinary recovery (mg)		
0–4 h	3.9 (1.3)	2.7–5.8
4–8 h	4.6 (1.5)	2.6–6.6
8–12 h	5.9 (2.0)	4.4–9.6
12–26 h	11.0 (2.1)	8.7–14.4
26–52 h	9.7 (2.9)	4.5–12.3
Total (0–52 h)	35.1 (6.9)	26.8–46.4

[a] C_{max}, maximum concentration in plasma; $t_{1/2\beta}$, elimination half-life; K_a, absorption rate constant.

DISCUSSION

Most of the currently available data on the pharmacokinetics of sparfloxacin have been collected following a dose of 200 mg given orally. The results of these studies show slightly shorter elimination half-lives in plasma than we obtained, i.e., 14.1 h (13), 14.9 h (7), and 15.2 h (12), compared with our result of 17.6 h. The reason for this difference is not known, but it is of note that these other studies took place in Japan and consequently the patients and volunteers used were probably of a different ethnic group than those in our study. A microbiological assay method such as the one we used may give a longer half-life than other assay methods if there is a bioactive metabolite present that has a longer half-life than the parent compound. Sparfloxacin, however, does not have an active metabolite. Other results (elimination half-lives of 16.28 h after 200 mg and 16.02 h after 400 mg of sparfloxacin [data on file at Rhone-Poulenc Santé]) lie between our result and those of the Japanese workers. The maximum concentration in plasma of 1.6 μg/ml attained in our study was slightly higher than the 1.4 μg/ml (data on file at Rhone-Poulenc Santé) previously reported following a 400-mg dose of sparfloxacin. The time taken to reach the peak concentration in plasma was shorter in our study than has previously been found; other workers have reported values of T_{max} ranging from 4 (7) to 5.6 (13) h, but as has already been noted, there was great variation in our results for T_{max} (range, 0.5 to 6 h). In retrospect, there should have been more sampling points over 0 to 2 h for more accurate determination of the absorption rate constant.

The spectrum of activity of sparfloxacin most closely resembles those of ciprofloxacin and temafloxacin. These two drugs are absorbed more quickly than sparfloxacin (ciprofloxacin T_{max}, 1.25 h [2]; temafloxacin T_{max}, 1.5 h [10]), have slightly higher maximum concentrations in plasma (ciprofloxacin, 2.3 μg/ml following a 500-mg oral dose [2]; temafloxacin [400 mg], 3.3 μg/ml [10]) but much shorter half-lives (ciprofloxacin, 3.9 h [2]; temafloxacin, 6.8 h [10]). All three agents penetrate inflammatory fluid well, the percentages of penetration being 117% for ciprofloxacin (2) and sparfloxacin and 104.5% for temafloxacin (10).

Detailed information on the bioavailability of sparfloxacin in humans is not available. The major portion excreted in the urine is in the microbiologically inactive glucuronide-conjugated form (8). The value we obtained for excretion of microbiologically active sparfloxacin in urine is in close agreement with the previous report of 10.9% for a 400-mg dose excreted within the first 72 h postadministration (8).

Our study shows that even 26 h after a single 400-mg oral dose of sparfloxacin, concentrations in plasma and inflammatory fluid exceed the MICs for 90% of the strains of almost all common bacterial pathogens (1). Despite the relatively small amount excreted unchanged in the urine, urinary concentrations exceed the MICs for 90% of the strains of all common urinary pathogens for more than 26 h after a single dose. Other tissues that have shown high concentrations of sparfloxacin are lung (6), prostate (13), and gynecological (15) tissues. With these concentrations in tissue plus its high in vitro activity and excellent pharmacokinetics, sparfloxacin should prove to be a useful antimicrobial agent for the treatment of chest, genitourinary, soft tissue, and systemic infections, with the added advantage of a once-daily oral dosage regimen.

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