Pharmacokinetics and Distribution in Tissue of FK-037, a New Parenteral Cephalosporin

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Received 21 March 1994/Returned for modification 18 June 1994/Accepted 20 July 1994

A single 1-g or 2-g intravenous dose of the cephalosporin FK-037 was given over 30 min in a cross-over-designed study, to each of six healthy male volunteers, and the concentrations of the drug were measured in plasma and cantharides-induced blister fluid over the subsequent 12 h. Urine was collected over 24 h. After a washout period of 6 weeks, during which the blisters healed, the study was repeated at the other dose level. Following the 1-g dose, the mean peak concentration in plasma was 83.8 μg/ml, and after the 2-g dose it was 142.6 μg/ml. The mean peak concentrations in the inflammatory fluid were 37.9 and 63.3 μg/ml, respectively. The mean elimination half-lives from plasma and inflammatory fluid were 2.0 and 2.5 h, respectively, after 1 g and 2.0 h and 3.7 h, respectively, after 2 g. The amounts of penetration into inflammatory fluid (as assessed by ratios of areas under the concentration-time curves) were 109.9 and 110.5% following doses of 1 and 2 g, respectively. The proportions of the administered drug recovered in the urine by 24 h were 87.6 and 85.7%, respectively. Our results indicate that FK-037 should prove to be efficacious in the treatment of a wide range of systemic infections.

FK-037 is a new parenteral aminothiazolyl cephalosporin with a 1-hydroxyethyl-5-aminopyrazole moiety at the 3 position (4). This compound has a broad spectrum of antibacterial activity; staphylococci and Pseudomonas aeruginosa are more susceptible to FK-037 than to cepfepime or ceftazidime, and its activity against members of the family Enterobacteriaceae is comparable to that of cefepime (3).

In this open-label, double-dose paired-design study, the pharmacokinetics of 1-g and 2-g doses of FK-037 in healthy volunteers were compared. The penetration into a chemically induced blister, which is similar in composition to a mild inflammatory exudate (7), was also studied.

MATERIALS AND METHODS

Volunteers. Six healthy male volunteers gave written, informed consent after hospital Ethical Committee approval had been obtained. They had a mean age of 28 (range, 22 to 37) years, a mean weight of 73.1 (range, 69 to 89.4) kg, and a mean height of 1.77 (range, 1.69 to 1.83) m. The medical histories and physical examinations of all were normal; in particular, none reported any previous history of allergy or intolerance to any antibiotic. Hematological and biochemical profiles of all the volunteers were normal, as was urinalysis. On the night before each trial day, two 0.2% cantharides-impregnated plasters (1 cm by 1 cm) were applied to the forearm of each volunteer. After overnight fasting, each subject was given either 1 or 2 g of FK-037 reconstituted in 100 ml of 0.9% saline. This was administered intravenously by a constant-infusion pump over 30 min. A light meal was served 2 h after dosing, and fluids were taken ad libitum. Blood samples were taken prior to (0 h) and at 15, 30 (end of infusion), and 45 min and 1.0, 1.5, 2.3, 4.5, 6, 8, and 12 h following the start of infusion via an intravenous cannula inserted into the arm opposite that receiving the infusion and kept patent with heparinized saline. The blisters were sampled at 0, 0.5, 1, 2, 4, 6, 8, and 12 h postinfusion by puncture with a micropipette, approximately 50 μl being removed; the integrity of the blisters was maintained by spraying with a fast-drying plastic dressing (Nobecutane; Astra Pharmaceuticals Ltd., Kings Langley, United Kingdom [UK]). All urine was collected at 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose, the volumes were measured, and an aliquot was taken for antibiotic assay.

After a washout period of 6 weeks, during which the blisters healed, the study was repeated at the other dose level. Physical examinations were repeated 24 h after each dose administration.

Drug analysis. Antibiotic assays were performed within 1 h of sample collection by a plate diffusion method. The indicator organism was Escherichia coli NCTC 10418, which was flooded onto the surface of Antibiotic Medium No. 1 (Unipath, Basingstoke, UK) after dilution in distilled water to an optical density of 0.004 at a wavelength of 630 nm. Calibrators (0.5, 1, 2, 4, and 8 μg/ml) were prepared in human serum (Bradshure Biologicals, Leicester, UK), in 70% human serum in pH 6.6 phosphate buffer (to simulate the protein content of inflammatory fluid), and in pH 6.6 phosphate buffer for the assays of plasma, blister fluid, and urine, respectively. Urine samples were diluted volumetrically in pH 6.6 phosphate buffer to bring them within the calibrator range. Two internal controls, 6 and 0.8 μg/ml, were also assayed on every plate. Samples were applied to the plates on blotting paper discs (6 mm diameter). Assay plates were incubated overnight at 30°C, and after incubation, zones were measured with a zone viewer (Leebrook Instruments, Strood, Kent, UK). The lower limit of detection of the assay was 0.25 μg/ml. Intra-assay coefficients of variation of the assay for the internal controls were 8.3% (at 6 μg/ml) and 5.9% (at 0.8 μg/ml) for human serum, 6.1% (at 6 μg/ml) and 6.9% (at 0.8 μg/ml) for simulated blister fluid, and 7.0% (at 6 μg/ml) and 5.6% (at 0.8 μg/ml) for pH 6.6 phosphate buffer. Interassay coefficients of variation for the internal controls were 8.8% (at 6 μg/ml) and 4.7% (at 0.8 μg/ml) for human serum, 7.1% (at 6 μg/ml) and 9.6% (at 0.8 μg/ml) for phosphorylated blister fluid, and 7.0% (at 6 μg/ml) and 5.6% (at 0.8 μg/ml) for pH 6.6 phosphate buffer. Interassay coefficients of variation for the internal controls were 8.8% (at 6 μg/ml) and 4.7% (at 0.8 μg/ml) for human serum, 7.1% (at 6 μg/ml) and 9.6% (at 0.8 μg/ml) for phosphorylated blister fluid, and 7.0% (at 6 μg/ml) and 5.6% (at 0.8 μg/ml) for pH 6.6 phosphate buffer.

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μg/ml) for simulated blister fluid, and 10.5% (at 6 μg/ml) and 7.6% (at 0.8 μg/ml) for pH 6.6 phosphate buffer.

The plasma and blister fluid concentration data were analyzed by noncompartmental and model-dependent methods. The model-dependent analysis was conducted via NONLIN pharmacokinetic software (Statistical Consultants, Lexington, Ky.) (maximum concentration in plasma or blister fluid) was determined by inspection, and the area under the concentration-time curve from 0 to 12 h (AUC₀₋₁₂) was determined by standard trapezoidal summation. The plasma data were fitted to a two-compartment model with zero-order input and first-order elimination through the central compartment. The blister data were fitted to a one-compartment model with first-order input and elimination. Tₗ₉₉, the lag time for absorption to commence in blister fluid, was a specific parameter delineated in the system of equations of the model. Within the equations, observed time postdose was modified to time post-dose lag-time, where Tₗ₉₉ was a continuous variable from 0 to 1 h. The ratio of penetration into blister fluid was based upon comparison of both Cₘ₉₉ and AUC₀₋₁₂. The parameter Corr (Y, Y') was a measure of the correlation between observed values and those predicted by the model; hence, a Corr (Y, Y') value of 0.975 would indicate that the model accounted for 97.5% of the variation in the concentration and that 2.5% of the variation was attributed to error.

RESULTS

The mean concentrations found in plasma and inflammatory fluid are shown in Fig. 1 and 2. The derived pharmacokinetic data are shown in Table 1.

Inspection of the graphs of the plasma data suggested that there was an initial distribution phase followed by a log-linear decline of concentration with time. The Corr (Y, Y') between the observed and predicted pharmacokinetic values was ≥0.97 in all but one instance (volunteer 2; the Corr (Y, Y') was 0.903 for the blister fluid data following the 2-g dose). The mean Cₘ₉₉ was greatest at the end of the infusion period (0.5 h), and the mean Cₘ₉₉ was 83.8 following a 1-g dose and 142.6 following a 2-g dose.

FIG. 1. Mean concentrations in plasma (solid line) and inflammatory fluid (dashed line) after 1 g of FK-037.

FIG. 2. Mean concentrations in plasma (solid line) and inflammatory fluid (dashed line) after 2 g of FK-037.
dose of FK-037. There was a modest amount of individual variation in $C_{\text{max}}$; the range in the observation was 64.8 to 94.8 µg/ml after a 1-g dose and 109 to 175 µg/ml after a 2-g dose. By 12 h, the concentrations in plasma were <2.0 and <4.3 µg/ml after 1 and 2 g, respectively. The mean AUC$_{0-24}$s were 159.7 and 303.7 µg · h/ml, highly suggestive of linearity of dose response between the two doses. The terminal (β) elimination half-life ($t_{1/2\beta}$) from plasma was 2.0 h for each dose, with very little individual variation (1.7 to 2.3 h). The volume of distribution (at steady state) ($V_{ss}$) did not vary with the dose and displayed a moderate degree of variation between the individuals (range, 13.8 to 21.3 liters).

In one volunteer, who received 2 g of FK-037, no blister formation occurred. In the other volunteers, however, FK-037 penetrated into the inflammatory exudate rapidly and $T_{\text{lag}}$ ranged from 0 to 0.9 h. The mean maximum concentrations attained were 37.9 µg/ml after the 1-g dose and 63.3 µg/ml after the 2-g dose. The mean AUC for measurements taken in the inflammatory fluid was proportional to the dose, 176.3 and 316.8 µg · h/ml, respectively. Elimination of FK-037 from the inflammatory exudate was slower than that from plasma, over the period studied, and showed considerably more individual variation, from 1.9 to 6.2 h. At 12 h, the mean inflammatory fluid concentrations were 2.7 and 6.5 µg/ml following 1- and 2-g doses, respectively. The percentage penetration of FK-037 into the exudate, calculated by comparison of the AUC for measurements taken in inflammatory fluid with that for measurements taken in plasma, was 110%.

Over 0 to 4 h, 64.4% (standard deviation [SD], 9.3%) and 64.7% (SD, 18.2%) of the FK-037 were excreted into the urine following 1- and 2-g doses, respectively. Over 0 to 24 h, urinary elimination was 87.6% (SD, 5.3%) and 85.7% (SD, 15.4%) of the administered dose, respectively.

Physical examination revealed no abnormalities that had developed over the trial period, although one volunteer developed a syncopal attack immediately prior to the administration of one dose.

<table>
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<th>Parameter$^a$</th>
<th>Subject no.</th>
<th>Mean</th>
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<tr>
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TABLE 1. Pharmacokinetic parameters following 1- and 2-g intravenous doses of FK-037

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$^a$ $V_c$, volume of central compartment; $V_{ss}$, volume of distribution at steady state; $K_{12}$, distribution rate constant for transfer of drug from central to peripheral compartment. The % penetration is calculated as the ratio of AUC for measurements taken in blister fluid to AUC for measurements taken in plasma.

$^b$ ND, no available data.
DISCUSSION

The pharmacokinetics of FK-037 as determined in this study are remarkably similar to those described in preliminary communications (2, 6); the only exception is that both earlier studies found the elimination half-life to be slightly longer, at 2.2 to 2.5 h. FK-037 would appear to be a typical cephalosporin exhibiting linear pharmacokinetics over the limited dose range studied, the plasma data fitting well with the two-compartment model employed.

Following a single intravenous injection of 1 or 2 g of FK-037, the antimicrobial agent is rapidly distributed (t1/2α, ca. 0.1 h) to an apparent mean volume of distribution of 15 to 17 liters. The availability of the drug in inflammatory fluid was high, with a percent penetration of 110%. FK-037 is eliminated predominantly by the kidneys, with less than 15% of the agent not accounted for in the urine in the 24 h following the dose.

A comparison of the pharmacokinetic data we have obtained with the in vitro activity of FK-037 (3) would suggest that against the less-susceptible bacterial pathogens, such as P. aeruginosa (MIC for 90% of the strains tested [MIC90], 4 μg/ml) and Enterobacter cloacae (MIC90, 8 μg/ml), the levels in serum and inflammatory fluid will be inhibitory for 8 to 10 h following a 2-g intravenous dose. For more susceptible species such as E. coli (MIC90, 0.06 μg/ml) and methicillin-susceptible Staphylococcus aureus (MIC90, 2 μg/ml), a lower dose administered once or twice daily may be clinically efficacious.

Other extended-spectrum or so-called fourth generation cephalosporins, cefpirome and cefepime, have pharmacokinetics very similar to those of FK-037; the elimination half-life of cefpirome was 2.3 h and the penetration into inflammatory exudate was 123% (1), and those of cefepime were 2.1 h and 80.4%, respectively (5). With these concentrations in inflammatory exudate plus its high in vitro activity and good pharmacokinetics, FK-037 should prove to be a useful antimicrobial agent for the treatment of a wide range of systemic infections.

ACKNOWLEDGMENT

This study was supported by a grant from the R. W. Johnson Pharmaceutical Research Institute.

REFERENCES