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Pharmacokinetics of Ro 13-9904, a Broad-Spectrum Cephalosporin

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The pharmacokinetics of the new cephalosporin Ro 13-9904 were studied in six healthy male volunteers receiving a 500-mg dose as a bolus intravenously. Tissue penetration of the antibiotic was estimated by using a cantharides blister method. The data obtained fitted a two-compartment open model. The mean elimination half-life was about 8 h, which is considerably longer than that of other β-lactam compounds. The distribution volume was 4.3 liters in the central compartment. Levels of Ro 13-9904 in blister fluid exceeded those in serum after 6.5 h. Approximately 60% of the antibiotic was excreted in the urine.

A new group of cephalosporins, showing a wide antibacterial spectrum and high potency, has been introduced for investigation over the last few years. This group includes cefotaxime (1), moxalactam (4), and now Ro 13-9904 (8) (Roche Laboratories, Welwyn-Garden-City, England). The spectrum of activity and potency of Ro 13-9904 are similar to those of cefotaxime (8) except that this newer cephalosporin has little activity against *Bacteroides fragilis*. The high activity of Ro 13-9904 against *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and, more modest but possibly clinically useful, *Pseudomonas aeruginosa* are of particular interest.

In this study, the pharmacokinetics of Ro 13-9904 were investigated in healthy volunteers. This investigation included measurement of tissue penetration as estimated in a skin blister model (5).

MATERIALS AND METHODS

The subjects were six healthy male volunteers between the ages of 21 and 37 years. They were of normal body build with a mean weight and height of 78.2 kg and 1.93 m, respectively. At the time of the trial they were not on any medication. They gave no history of previous allergy to β-lactam compounds, atopy, or hepatic or renal diseases. Renal and hepatic functions were normal as assessed by liver enzymes, blood urea, and serum creatinine estimations 1 week before the study. The conduct of the study met the requirements of the Helsinki Agreement, with informed consent being obtained from the volunteers.

The volunteers were instructed to avoid excessive fluid intake for 12 h before the trial. On the evening before the trial, two 0.2% cantharides plasters (1 by 1 cm) were taped to the anterior aspect of a forearm. On the morning of the study, the volunteers consumed a light breakfast (of cereal or toast) with one cup of beverage. A predose sample of blood was taken, and the volunteers emptied their urinary bladders. An intravenous cannula was inserted into an arm vein and kept patent by a small flushing dose of heparinized saline. A 500-mg amount of the hydrated disodium salt of Ro 13-9904 (equivalent to 418 mg of free acid), dissolved in 5 ml of sterile water, was injected intravenously into the contralateral arm for 3 min. The volunteers were allowed normal activity and diet for the next 16 h.

Blood samples were taken from the cannula (after discarding the first 2 ml) at 10, 20, and 40 min and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 26, and 30 h after the dose of Ro 13-9904. Serum was separated within 0.5 h, and the samples taken at up to 16 h were assayed the same day; the remainder was assayed the following day.

Urine samples were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 12, 12 to 24, 24 to 36, and 36 to 48 h after dosage. Volumes were measured, and the samples were taken for assay. Fluid was removed from each of the blisters at 1, 2, 4, 6, 10, 14, 16, and 24 h. The fluid removed was placed onto preweighed, sterile 6-mm assay disks and reweighed to measure the amount of fluid on the disk. Each blister had an appropriate volume of 1 ml.

The assays were performed by a routine agar plate diffusion technique utilizing *Escherichia coli* NCTC 10418 as an indicator organism and Oxoid (Basingstoke, United Kingdom) antibiotic medium 1 (pH 6.5). Serum standards were prepared in pooled human serum, and urine standards were prepared in phosphate-buffered saline (pH 6.6), in which the urine samples were diluted when necessary. Blister fluid sample standards were made in 70% human serum and applied in triplicate on identical disks in the same volume as that calculated by weighing on the test disk. The 95% confidence limit of the serum sample assays was greater than ±13%. The pharmacokinetic analysis of the individual data was performed by graphical methods.

RESULTS

The mean serum and blister levels obtained after the 500-mg dose of Ro 13-9904 are shown in Fig. 1. A mean peak level of 93.25 μg/ml was obtained 10 min after dosing. There was an initial rapid distribution phase followed by a gradual and steady decline over the ensuing 30 h. The mean level at 6 h was 30.7 μg/ml and at

30 h it was 4.1 μg/ml. The serum profiles suggest that the data fit a two-compartment open model.

The pharmacokinetic data are shown in Table 1. β is the first-order rate constant for the elimination and distribution of the drug by all routes. AUC is the area under the concentration-time curve, determined by trapezoidal analysis from 0 to 26 h and then extrapolated to infinite time by adding Cp/β, where Cp is the concentration in plasma at 26 h. T/2(α) and T/2(β) are the serum half-lives of the drug during the distribution and elimination phases, respectively. T/2(α) was calculated by extrapolation as described by Greenblatt and Koch-Wesser (2). Vd_c is the apparent distribution volume of the drug in the central compartment, and Vd_β is the total drug distribution volume as calculated in the β phase. The total clearance of the drug was calculated from dose/AUC(0–∞h), and renal clearance was calculated from drug recovery in urine/AUC(0–∞h). Vd_β was determined from the equation dose/AUC(0–∞h) × β. The drug initially distributes itself to a volume of 4.3 liters, approximately equivalent to the volume of the vascular compartment and about 5% of the body weight. During this distribution phase, Ro 13-9904 has a half-life of 0.56 h, and the distribution is complete after about 3 h. In the elimination, or β phase, the serum half-life is 8.8 h, the total clearance is 14.2 ml/min, and the renal clearance is 8.6 ml/min. Approximately 50% of the drug was excreted in the urine by 24 h (Fig. 2), and 58% was excreted by 48 h.

Ro 13-9904 penetrates blister fluid rapidly. The mean level at 1 h post-administration was 17.2 μg/ml and rose until it equalled that in serum at about 6.5 h. The mean maximum blister level was 32.7 μg/ml, and calculation of AUC for blister fluid showed that the values were not significantly different from serum values. The terminal blister fluid half-life (i.e., between 14 and 24 h) was 10.4 h. Previous studies on the

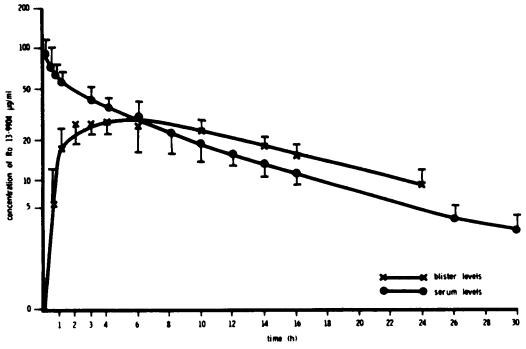

FIG. 1. *Serum levels (●) and blister fluid levels (×) after intravenous injection of 500 mg of Ro 13-9904.* T, *standard deviation.*

TABLE 1. *Pharmacokinetic data on Ro 13-9904*

Volunteer no.	Kinetic parameter										
	C_0 (μg/ml)	β (h^{-1})	AUC: (μg/ml)·h	Total clearance (ml/min)	Renal clearance (ml/min)	Vd_c (liters)	Vd_β (liters)	T/2(α) (h)	T/2(β) (h)	T/2 in blister (h)	Maximum concn in blister (μg/ml)	AUC in blister: (μg/ml)·h
1	92	0.081	600	13.9	8.3	5.4	10.3	0.9	8.5	9.2	32.5	429
2	131	0.088	442	18.8	12.1	3.8	12.9	0.2	7.9	10.7	21.4	435
3	128	0.094	491	17.0	10.6	3.9	10.8	0.6	7.4	10.0	33.0	621
4	122	0.090	673	12.4	6.6	4.0	8.3	0.4	7.5	6.3	39.0	569
5	113	0.066	740	11.3	7.0	4.4	10.2	0.5	10.5	12.5	41.0	794
6	116	0.060	719	11.6	6.8	4.3	11.6	0.8	11.5	14.0	29.6	567
Mean ± SD[a]	117 ± 14.8	0.080 ± 0.013	610 ± 122	14.2 ± 3.1	8.6 ± 2.2	4.3 ± 0.6	10.7 ± 1.5	0.6 ± 0.3	8.8 ± 1.7	10.4 ± 2.7	32.7 ± 7.0	569 ± 134

[a] SD, Standard deviation.

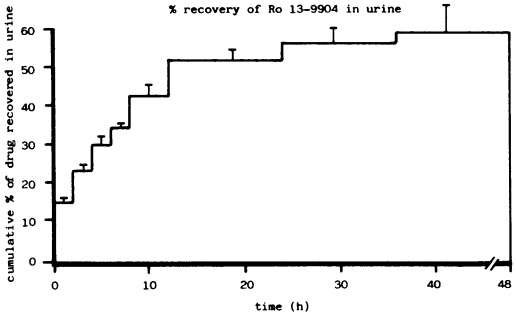

FIG. 2. *The renal excretion of Ro 13-9904. Cumulative percent excreted compared with time.* T, *standard deviation.*

blister fluid (7) have shown that its composition is as follows: total protein, 70% that of serum; leukocyte count, variable (400 to 1,600 cells per mm^3; 85 to 95% polymorphonuclear).

DISCUSSION

The new cephalosporin Ro 13-9904 not only has very broad and potent antibacterial properties but also has pharmacokinetic properties dissimilar to those of other β-lactam compounds. The half-lives of the other "new generation" parenteral cephems are all very much shorter; for example, the half-life of moxalactam is 2.73 h (6), and that of cefotaxime is 1.25 h (3). The data show that about 60% of Ro 13-9904 is excreted by the kidneys in 48 h. There are indications that 40 to 50% is excreted by the biliary-fecal route and that metabolism is minimal (personal communication, L. Lees, Roche Laboratories). As only 1 to 5% of the compound was found in the urine between 36 and 48 h, it could be concluded that renal excretion had virtually ceased by day 2.

The serum clearance of most β-lactam compounds is high. This is usually related to active tubular secretion. The clearance of Ro 13-9904 is about 7% of the glomerular filtration rate, suggesting that it is not actively secreted by the tubule. Alternatively, the low clearance may be explained by the high protein binding of the drug (95% bound [8]) or very efficient tubular reabsorption. Further studies should be performed to study this point.

High protein binding not withstanding, Ro 13-9904 readily penetrated blister fluid, but did so more slowly, however, than such β-lactam compounds as amoxicillin, flucloxacillin, and cefoxitin (9), which attain levels similar to those in serum after 1 to 2 h. The maximum blister level was in excess of the minimum inhibitory concentration of Ro 13-9904 for the majority of susceptible pathogens (50% minimal inhibitory concentration for *P. aeruginosa* is 8 μg/ml or less) (8). This may be of considerable importance as cantharides-induced blister fluid is very similar in nature to a burn blister (9). Ro 13-9904 appears to be eliminated from blister fluid at the same rate as from serum, with a half-life in blister fluid of about 10 h. There is no significant difference for AUCs in the two fluids.

The pharmacokinetic behavior of Ro 13-9904 suggests once- or twice-daily parenteral dosing, which should provide satisfactory serum and tissue levels. As the renal route accounts for only about one-half of the overall elimination, it is possible that only a relatively minor adjustment of dosing may be needed for patients with renal impairment. Direct information is needed, however, before the drug is used in such patients.

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