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Fosfomycin Kinetics After Intravenous and Oral Administration to Human Volunteers

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The pharmacokinetics of fosfomycin, administered intravenously and orally at two different doses (20 and 40 mg/kg of body weight), was studied in seven volunteers. The elimination profile of this antibiotic, when administered intravenously, followed a two-compartment kinetic model, independent of dosage, giving an elimination half-life of 2.23 ± 0.62 h and an average total volume of distribution at steady state of 0.34 liter/kg. Peak serum levels after rapid intravenous administration of 20 and 40 mg/kg were 132.1 ± 31.8 and 259.3 ± 32.5 μg/ml, respectively. Peak serum levels after oral administration were 7.1 ± 1.6 and 9.4 ± 3.6 μg/ml for the 20 and 40 mg/kg doses, respectively. During the first 24 h after administration, an average of 80% of the intravenous doses and less than 25% of the oral doses were recovered in the urine.

Fosfomycin, a broad-spectrum bactericidal agent which inhibits the cell wall synthesis of both gram-positive and gram-negative bacteria (4, 8, 17), was discovered in *Streptomyces fradiae* fermentation broths (15).

Although pharmacokinetic properties of fosfomycin have been studied in humans (1, 12) after intravenous and oral administration of 250- or 500-mg doses, the pharmacokinetics of larger doses employed therapeutically have not been investigated.

The work reported here was undertaken specifically (i) to describe the pharmacokinetics of single relatively larger intravenous and oral doses of fosfomycin and (ii) to utilize these pharmacokinetic data to determine patient dosage schedules and methods of administration.

MATERIALS AND METHODS

Human volunteers. Seven adult male volunteers participated in this study after informed written consent had been obtained. Their ages ranged from 25 to 56 years (mean ± standard deviation, 36.3 ± 12.3 years), and their body weight ranged from 45 to 70 kg (57.9 ± 7.0 kg). Prestudy physical examination and pre- and postdrug laboratory findings were normal. No volunteer had a history of allergy to antibiotics or other drugs. None had taken any drug during the month before the investigational period.

Dosage. Fosfomycin disodium (lot CS-906; Meiji Seika Research Laboratories, Tokyo, Japan) dissolved in 0.9% saline was administered intravenously at a concentration of 100 mg/ml. Fosfomycin calcium salt (lot FOMDHT 2; Meiji Seika Research Laboratories) was administered orally.

Experimental design. Each of the seven volunteers received fosfomycin disodium salt intravenously over 5 min at doses of 20 and 40 mg (potency) per kg. The same volunteers also received fosfomycin calcium salt orally at doses of 20 and 40 mg (potency) per kg. The oral dose was followed by the ingestion of 100 to 120 ml of water. Treatments were randomized and delivered in a crossover fashion, with 2-week intervals separating the respective doses. Subjects fasted overnight before each study; food was also withheld for 2 h after dosage.

Blood samples (5 ml each) were drawn from an arm vein at 0 (1 min after the completion of injection), 0.25, 0.5, 1, 2, 4, 6, and 8 h after intravenous administration and at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after oral administration. Samples were always withdrawn from the arm contralateral to that used for injection. Serum was separated as soon as clotting had occurred. Urine specimens were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 24 h after dosage. Both serum and urine samples were stored at −20°C until assayed.

Microbiological assay. The concentrations of fosfomycin in serum were determined by an agar (Difco Laboratories, Detroit, Mich.; nutrient agar) diffusion test method (cup plate) previously described (5), using *Proteus* sp. MB-838 as the test organism. Urine concentrations were measured by the same procedure. A standard solution series was prepared with 0.05 M tris(hydroxymethyl)aminomethane buffer (pH 7.0). Urine samples were also diluted with this buffer. Concentrations of fosfomycin of 0.1 μg/ml or greater could be determined.

Calculation of pharmacokinetic constants. Unweighted serum concentration data (C_t) after single intravenous doses of fosfomycin were fitted to the following biexponential equation (3, 6):

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \quad (1)$$

where A, B, α (h^{-1}), and β (h^{-1}) denote the hybrid

constants. The apparent steady state volume of distribution, Vdss (liters), the distribution rate constants k_{12}, k_{21} and k_{10} (h^{-1}), the elimination rate constant from the central compartment, and the area under the curve (AUC_0^∞) were calculated by the usual procedure with equation 1 (3, 6). The area-derived volume of distribution was also calculated by the usual procedure (6).

The C_t, after single oral administration, were fitted to a one-compartment open model by using the following equation (14).

$$C_t = \frac{F \cdot D \cdot k_a}{\mathrm{Vd}\,(K_a - k_{el})} \cdot [e^{-k_{el}(t - t_0)} - e^{-k_a(t - t_0)}] \quad (2)$$

where k_a is the apparent first-order absorption rate constant (h^{-1}), k_{el} is the apparent first-order elimination rate constant (h^{-1}), Vd is the apparent volume of distribution (liters), F is the apparent fraction of the dose available, and t_0 is the lag time preceding initiation of absorption (hours).

Both fosfomycin disodium salt and fosfomycin calcium salt are present in the blood in ionized form, and with fosfomycin there is no first-pass effect (9). Therefore, F was determined by equation 3 (16), and subsequent calculation of the other pharmacokinetic parameters was performed.

$$F = \frac{AUC_{0_{po}}^{\infty}}{AUC_{0_{iv}}^{\infty}} \quad (3)$$

The predicted time of the peak serum level after oral administration (t_{max}) was calculated as the time when dC_t/dt equals 0.

$$t_{max} = \{\ln[(k_a \cdot e^{k_{el} \cdot t_0})/(k_{el} \cdot e^{k_a \cdot t_0})]\}/(k_a - k_{el}) \quad (4)$$

Total serum clearance (Cl_{tot}) and renal clearance (Cl_r) after intravenous administration were estimated from dose/$AUC_{0_{iv}}^{\infty}$ and $Xu_{0_{iv}}^{8}/AUC_{0_{iv}}^{8}$, respectively. $Xu_{0_{iv}}^{8}$ means the amount of the drug excreted in the urine during the period 0 to 8 h after intravenous administration. The Cl_{tot} after oral administration was also estimated from the $F \cdot \mathrm{dose}/AUC_{0_{po}}^{\infty}$.

The best values of various pharmacokinetic parameters were calculated by the least-squares method in conjunction with a Toshiba model TOSBAC 40 computer (Tokyo Shibaura Electric Co., Ltd., Tokyo, Japan) (5).

RESULTS

The mean serum levels of fosfomycin after intravenous administration of 20 and 40 mg/kg are shown in Fig. 1. The mean peak levels at 0 h were 132.1 and 259.3 μg/ml at the respective doses. At 8 h, levels were respectively 4.4 and 6.8 μg/ml.

The kinetic parameters are listed in Table 1. Vdss for fosfomycin administered intravenously was 0.34 ± 0.08 liter/kg, ranging from 23 to 48% of body weight. $AUC_{0_{iv}}^{\infty}$ was linearly related to dose. The other kinetic parameters were similar and independent of dose in the same individual. For instance, despite the fact that the k_{10} in different individuals varied between 0.54 and 1.46 h^{-1}, it was fairly reproducible ($r = 0.769$; $P < 0.05$) in the same subject.

The average C_t values of fosfomycin after oral administration at doses of 20 and 40 mg/kg are shown in Fig. 2. The observed maximum concentration (C_{max}) ranged from 4.4 to 8.6 μg/ml and from 6.9 to 13.4 μg/ml after administration of the respective doses. The mean t_{max} calculated by using equation 4 were 2.3 ± 0.3 and 2.7 ± 0.2 h, respectively. There was an increase in serum concentration with the high doses, but this was not proportional to the dosage increment.

The pharmacokinetic data analyzed by using equation 2 are summarized in Table 2. At doses of 20 and 40 mg/kg, the mean value of k_{el} was 0.24 and 0.14 h^{-1} and that of Vd was 0.52 and 1.04 liters/kg, respectively. Although these data appear to show dose-dependent kinetics, the Cl_{tot} were similar in spite of the difference in dosage, indicating linear kinetics. The Cl_{tot} values after oral administration were also identical with those after intravenous administration. Mean bioavailability of fosfomycin calcium salt, calculated by using equation 3, was 0.28 at both the high and the low dose.

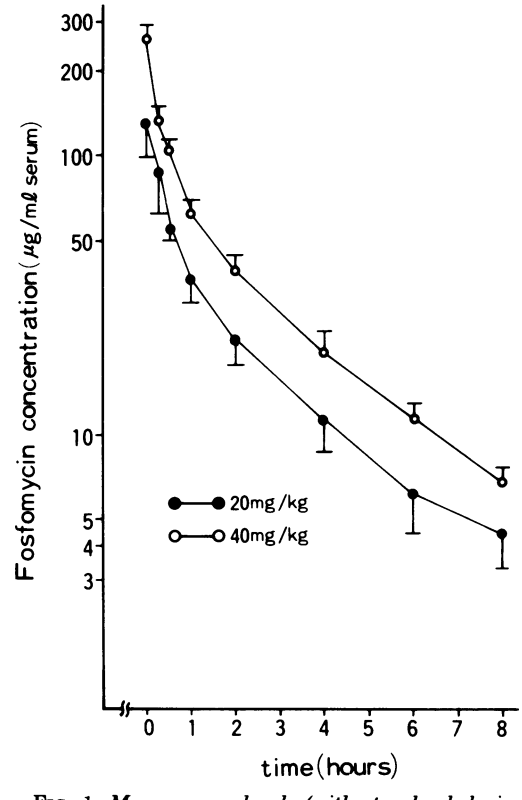

FIG. 1. *Mean serum levels (with standard deviation) of fosfomycin after intravenous administration as bolus over 5 min.*

TABLE 1. *Pharmacokinetic parameters of fosfomycin after intravenous administration at dose of 20 or 40 mg/kg in seven volunteers*[a]

Dose (mg/kg)	Parameter													
	α (h^{-1})	β (h^{-1})	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	$t_{1/2}$ β (h)[b]	V_1 (liters/kg)[c]	V_2 (liters/kg)[d]	V_{dss} (liters/kg)	$V_d\beta$ (liters/kg)	C_{max} (μg/ml)[e]	C_{min} (μg/ml)[f]	AUC_0^∞ (μg.h/ml)	Cl_{tot} (ml/min per kg)	Cl_r (ml/min per kg)
20	3.64 ± 1.49	0.34 ± 0.12	1.62 ± 0.76	1.45 ± 0.75	0.92 ± 0.31	2.25 ± 0.74	0.15 ± 0.05	0.17 ± 0.03	0.32 ± 0.08	0.38 ± 0.11	132.1 ± 31.8	4.1 ± 1.0	167.9 ± 26.4	2.08 ± 0.45	1.74 ± 0.63
40	3.74 ± 1.34	0.32 ± 0.06	1.84 ± 0.85	1.30 ± 0.49	0.99 ± 0.22	2.22 ± 0.46	0.15 ± 0.05	0.22 ± 0.05	0.36 ± 0.06	0.44 ± 0.08	259.3 ± 32.5	6.8 ± 0.6	290.8 ± 25.3	2.31 ± 0.22	1.91 ± 0.26

[a] Data are given as mean ± standard deviation.
[b] Calculated as $t_{1/2}\beta = 0.693/\beta$.
[c] Volume of distribution in the central compartment.
[d] Volume of distribution in the peripheral compartment.
[e] Serum fosfomycin concentration at 0 h (1 min) after completion of injection.
[f] Serum fosfomycin concentration at 8 h (the last recorded level) after completion of injection.

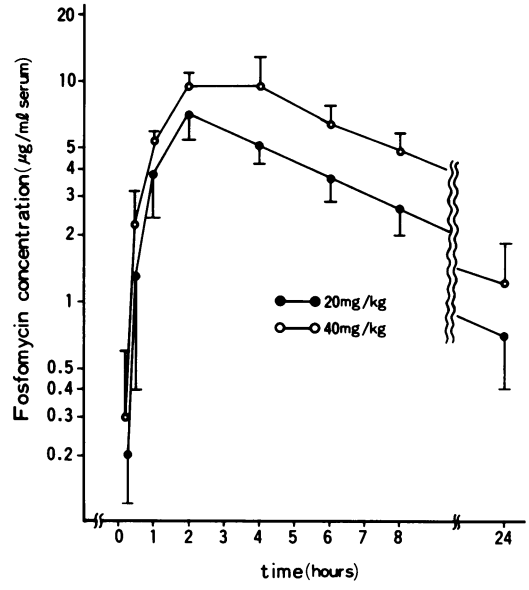

FIG. 2. *Mean serum levels (with standard deviation) of fosfomycin after oral administration.*

Cumulative excretion of fosfomycin after intravenous and oral administration is shown in Fig. 3. Of the total dose administered intravenously, 70% or more was excreted during the first 6 h, and only 10% was excreted during the following 18 h, whereas after oral administration, only half of the $Xu_{0_{po}}^{24}$ was recovered within the first 6 h, and the urinary recovery rate during 24 h was approximately 25%. Because of the low recovery in the two aged volunteers (less than 70%), the mean values of recovery for fosfomycin are slightly lower than those reported previously (12).

DISCUSSION

The previous study with a 500-mg dose administered intravenously showed that fosfomycin is eliminated biexponentially from serum with a mean $t_{1/2}$ β of 2.04 h and a Vdss of approximately 0.32 liter/kg (1). These kinetic parameters and those of this study are in good agreement, suggesting that the pharmacokinetic properties of fosfomycin are relatively independent of dosage.

When β of the intravenous study was compared with the k_{el} of the oral study, the values of β were seen to be greater than those of the k_{el}; this trend was statistically significant in the high-dose study. This might be due to continuous absorption of fosfomycin for 8 h after oral administration (1). The fact that the values of k_{el} at high dosages were smaller than those at low dosages is consistent with slow, steady ab-

TABLE 2. *Pharmacokinetic parameters of fosfomycin after oral administration at dose of 20 or 40 mg/kg in seven volunteers*[a]

Dose (mg/kg)	Parameter									
	k_a (h^{-1})	k_{el} (h^{-1})	$t_{1/2}$ (h)[b]	F[c]	Vd (liters/kg)	C_{max} (μg/ml)	C_{min} (μg/ml)[d]	T_{max} (h)		AUC_0^∞ (μg·h/ml)	Cl_{tot} (ml/min per kg)
								Predicted[e]	Observed		
20	1.03 ± 0.38	0.24 ± 0.05	3.01 ± 0.67	0.28 ± 0.07	0.52 ± 0.08	7.1 ± 1.6	0.7 ± 0.3	2.3 ± 0.3	2.3 ± 0.7	45.2 ± 10.8	2.05 ± 0.42
40	0.92 ± 0.40	0.14 ± 0.02	5.05 ± 0.81	0.28 ± 0.08	1.04 ± 0.30	9.4 ± 1.6	1.2 ± 0.6	2.7 ± 0.2	2.9 ± 1.0	79.1 ± 15.9	2.59 ± 0.48

[a] Data are given as mean ± standard deviation.
[b] Calculated as $t_{1/2} = 0.693/k_{el}$.
[c] Calculated by using equation 3.
[d] Serum fosfomycin concentration at 24 h (the last recorded level) after oral administration.
[e] Calculated by using equation 4.

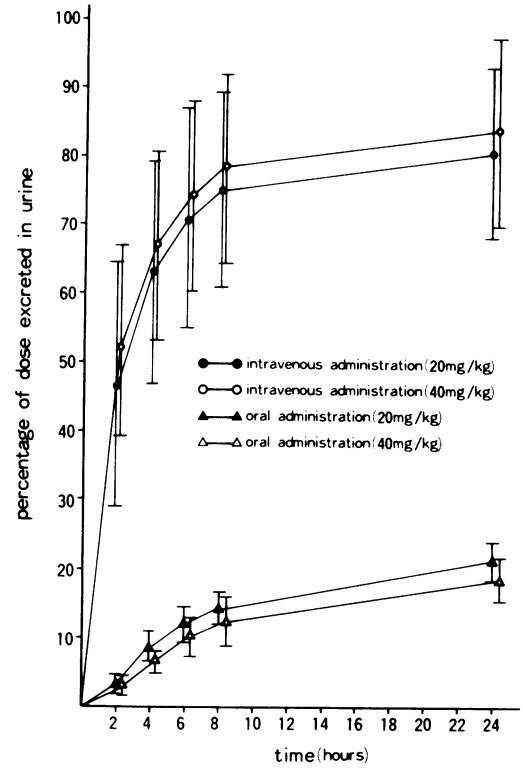

FIG. 3. *Mean cumulative urinary recovery (with standard deviation) of fosfomycin after oral and intravenous administration at doses of 20 and 40 mg/kg.*

sorption and elimination. The fact that the mean value of Vd was greater than that of Vdss may also be due to the phenomenon mentioned above. Therefore, the pharmacokinetic model used in the oral study might be too simple for analyzing the C_t after oral administration.

There are three components of the temporal blood concentration profile that may influence the effectiveness of the antibiotic dosage regimen (7, 11, 13): (i) the magnitude of peak blood level compared with the minimal inhibitory concentration (MIC); (ii) the duration of the blood level above the MIC during each dosage interval; and (iii) the product of (i) and (ii) (the intensity factor = C_{max}/MIC × hours supra-MIC/dosing interval).

In consideration of these pharmacokinetic indices and parameters of fosfomycin, dosage schedules for clinical success have been developed. The MICs of fosfomycin range from 6.25 to 12.5 μg/ml for many strains of *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (4). The highest blood level should exceed 100 μg as free drug per ml to obtain the high ratio of peak blood level to MIC, that is,

achievement of a serum inhibitory level of ≧1:8, which indicates intravenous administration of 20 mg/kg or more because of the absence of protein binding (10). Secondly, to achieve a supra-MIC duration for one-half or more of the dosage interval, this antibiotic should be administered at 8- to 12-h intervals. Provided fosfomycin is administered intravenously according to such a schedule, an intensity factor value of 4, which is considered a high value, could be accomplished.

It is difficult to attain a high value of C_{max}/MIC by the oral route, because of poor absorption (2, 10). However, fosfomycin is largely excreted by glomerular filtration without biotransformation (9). Accordingly, urinary levels exceed 100 μg/ml during 24 h with oral doses of 20 or 40 mg/kg once a day, doses adequate to inhibit a wide range of bacteria (4).

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