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Comparative Pharmacokinetics of Tromethamine Fosfomycin and Calcium Fosfomycin in Young and Elderly Adults

FRANÇOISE BORSA,[1] ANNIE LEROY,[1] JEAN-PAUL FILLASTRE,[2]†* MICHEL GODIN,[2] AND BRUNO MOULIN[2]

Departments of Nephrology[2] and Infectious Diseases,[1] University of Rouen, Rouen, France

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The pharmacokinetics of two oral forms of fosfomycin, tromethamine (trometamol) salt and calcium salt, were studied in five young (age, 29 ± 3 [standard deviation] years) and eight elderly (age, 72 ± 6 years) adults. The subjects received a single 40-mg/kg (body weight) (≈3-g) calcium fosfomycin dose and a 25-mg/kg (≈2-g) tromethamine fosfomycin dose in fosfomycin acid form. Blood and urine samples were collected for 24 h. Antibiotic concentrations in serum and urine were measured by microbiological assay. In all subjects, the peak levels of the calcium salt in serum were two- to fourfold lower than those of the tromethamine salt (6 to 7 and 18 to 22 μg/ml, respectively), indicating poor intestinal absorption of the calcium form. The elimination half-life of the two oral forms was about 5 h in young adults, and the half-life was only moderately longer in elderly subjects, with large individual variations: 8.28 ± 5.51 h for tromethamine fosfomycin and 11.80 ± 6.86 h for calcium fosfomycin. In elderly subjects, absorption of the tromethamine salt form was not modified, but the time to peak level was delayed for the calcium salt (2.58 ± 0.54 h versus 1.41 ± 0.67 h in young adults). Pharmacokinetic elimination of the two forms of fosfomycin was only moderately affected in elderly subjects; we observed lower urinary elimination, about 58 versus 28% of the dose in 24-h urines for the tromethamine salt and decreased renal clearance of both forms. However, the dosages of tromethamine and calcium fosfomycin need not be adjusted for elderly subjects who have endogenous creatinine clearances above 50 ml/min per 1.73 m².

The disodium salt form of fosfomycin has been used parenterally for many years in the treatment of a wide variety of infections. The disodium salt is unsuitable for oral use, since it induces gastric irritation. Two oral forms have been developed, calcium salt and tromethamine (trometamol) salt. Calcium fosfomycin has poor intestinal absorption with low concentrations in serum, while tromethamine fosfomycin produces effective antibiotic concentrations in both serum and urine and is well tolerated therapeutically; this oral form retains the antibacterial activity of the parent compound (5).

The purpose of this study was to compare the pharmacokinetics of tromethamine and calcium fosfomycin in young and elderly adults.

Subjects. Thirteen subjects with no known hypersensitivity to drugs participated in the study after giving informed written consent. They had no evidence of hepatic, renal, or hematologic disease. During the 2 weeks before drug administration, physical examinations, electrocardiograms, and biological tests were performed. All the subjects fasted overnight before the study and for 3 h after drug administration; they were sedentary during the study.

The subjects were divided into two groups. (i) The group of five young males ranged in age from 26 to 33 years (29 ± 3 years [standard deviation]) and in weight from 62 to 104 kg (77 ± 17 kg). Mean endogenous creatinine clearance was 127 ± 20 ml/min per 1.73 m² (91.7 to 140.3 ml/min per 1.73 m²). (ii) The group of eight healthy elderly subjects ranged in age from 65 to 82 years (71.8 ± 6.0 years) and in weight from 48 to 80 kg (68.8 ± 10.5 kg). Mean creatinine clearance was 77.9 ± 21.5 ml/min per 1.73 m² (53.0 to 123.5 ml/min per 1.73 m²).

All the subjects were ambulatory and were judged to be healthy on the basis of physical and biological examinations.

Dosing. The subjects received a single oral dose of tromethamine (25 mg/kg [body weight]) in one trial and of calcium fosfomycin (40 mg/kg) in a second trial. Dosages were calculated in fosfomycin acid form and were given by random distribution. The two studies were separated by a wash-out period of at least 1 week. Fosfomycin was supplied by Zambon-Farmaceutici S.p.A., Milan, Italy.

Sampling. Blood samples were collected in dry tubes without anticoagulant or preservative and were drawn before administration (time 0) and at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 h. Urine samples were collected during three periods: from 0 to 4, 4 to 8, and 8 to 24 h after administration.

Serum and urine samples were stored frozen at −80°C until assay.

Assay technique. Fosfomycin concentrations in serum and urine were measured by microbiological assay with *Proteus mirabilis* ATCC 21100 as the test strain. Tromethamine fosfomycin, with a microbiological potency of 532.5 μg/mg, and calcium fosfomycin, with a microbiological potency of 713 μg/mg, were used to prepare the standard fosfomycin concentrations. The lower limit of sensitivity for the assay was 0.8 to 1.0 μg/ml. Dilutions were made in a mixture of Tris buffer (pH 7.4) and pooled human serum for serum samples and in Tris buffer (pH 7.4) for urine samples. The intra- and interrun coefficients of variation were 6.6 and 8.8%, respectively.

Pharmacokinetic analysis. Tromethamine and calcium fosfomycin serum concentration-versus-time curves were best described by a sum of two or three exponential terms, according to the subjects. The absorption, distribution, and elimination phases were studied by using a nonlinear curve fitting.

The area under the curve was calculated by using the

* Corresponding author.
† Present address: Hôpital de Bois Guillaume, 76230 Bois Guillaume, France.

TABLE 1. Pharmacokinetic parameters of tromethamine fosfomycin and calcium fosfomycin in young adults and elderly subjects[a]

Parameter[b]	Tromethamine fosfomycin			Calcium fosfomycin		
	Young subjects	Elderly subjects	P	Young subjects	Elderly subjects	P
CL_{CR} (ml/min per 1.73 m^2)	127.0 ± 19.9	77.9 ± 21.5	0.001	127.0 ± 19.9	77.9 ± 21.5	0.001
Dose (g)	2.03 ± 0.44	1.81 ± 0.28	0.28	3.03 ± 0.66	2.69 ± 0.41	0.28
C_{max} (μg/ml)	18.48 ± 10.27	22.01 ± 8.72	0.52	7.42 ± 4.29	5.91 ± 1.69	0.38
T_{max} (h)	1.61 ± 0.23	2.16 ± 0.72	0.13	1.41 ± 0.67	2.58 ± 0.54	0.005
$AUC_{0-\infty}$ (μg · h/ml)	102.85 ± 42.10	221.36 ± 94.86	0.02	49.97 ± 20.44	116.07 ± 66.30	0.05
$t_{1/2}$ (h)	5.37 ± 2.56	8.28 ± 5.51	0.30	4.81 ± 1.90	11.80 ± 6.86	0.05
k_{el} (h^{-1})	0.156 ± 0.073	0.124 ± 0.078	0.49	0.170 ± 0.084	0.082 ± 0.047	0.03
V (liter/kg)	2.42 ± 1.68	1.47 ± 0.89	0.20	5.65 ± 1.87	5.95 ± 1.46	0.75
Urinary elimination at 24 h (%)	57.7 ± 30.2	27.5 ± 10.6	0.02	17.9 ± 21.2	9.4 ± 3.1	0.28
CL (ml/min per 1.73 m^2)	323.6 ± 139.8	161.1 ± 70.1	0.02	988.2 ± 387.7	556.6 ± 384.9	0.08
CL_R (ml/min per 1.73 m^2)	179.6 ± 25.1	48.8 ± 17.0	<0.001	83.0 ± 18.3	54.4 ± 18.7	0.03

[a] Values are means ± standard deviations.

[b] CL_{CR}, Creatinine clearance; C_{max}, peak concentration in serum; T_{max}, time to peak concentration in serum; $AUC_{0-\infty}$, area under the curve from time zero to infinity; $t_{1/2}$, terminal half-life; k_{el}, apparent elimination rate constant; V, apparent volume of distribution; CL, total body clearance; CL_R, renal clearance.

trapezoidal rule and was extrapolated to infinity ($AUC_{0-\infty}$). The apparent volume of distribution (V) and total body clearance (CL) were determined by using the following classical equations: $V = \text{dose}/AUC_{\infty} \cdot k_{el}$ and $CL/F = \text{dose}/AUC_{\infty}$, where k_{el} was the apparent elimination rate constant. The bioavailability could not be determined in our study, and the values obtained for these two kinetic parameters were found to be artificially too high.

The renal clearance (CL_R) was calculated by using the formula $CL_R = X_u^{0-24}/AUC_{0-24}$, where X_u^{0-24} was the amount of antibiotic excreted in 24-h urine and AUC_{0-24} was the area under the serum curve during the same time interval.

Statistical analysis. The pharmacokinetic parameters of the two forms of fosfomycin in young and elderly subjects were compared by using the paired and unpaired Student t tests. The acceptable level of significance was $P < 0.05$.

The pharmacokinetic parameters of the two oral forms of fosfomycin in young and elderly subjects are shown in Table 1.

Comparison of the two fosfomycin salts. After a single 2-g dose of tromethamine fosfomycin, the mean peak concentrations in serum were two- to fourfold higher than those obtained after a single 3-g dose of calcium fosfomycin. The areas under the serum curve from time zero to infinity were approximately twofold higher for the tromethamine than for the calcium salt ($P = 0.02$ for both young and elderly subjects). The times to peak level in serum were not statistically different for the two forms ($P = 0.60$ for young subjects and $P = 0.10$ for elderly subjects). The terminal half-lives were not significantly different for the two forms in young subjects ($P = 0.61$) and elderly subjects ($P = 0.28$).

The apparent volume of distribution and the total body clearance of calcium fosfomycin were about threefold higher than those of tromethamine fosfomycin.

Urinary excretion of the calcium salt was significantly lower than that of the tromethamine salt ($P < 0.001$ for young subjects and $P = 0.001$ for elderly subjects).

Tromethamine renal clearances were higher than calcium renal clearances in young subjects ($P = 0.002$). In elderly subjects, no significant difference was observed in the renal clearances of the two forms ($P = 0.58$).

After the same oral dose of the tromethamine salt as in healthy young subjects, the peak level and the time to peak level were not significantly different in elderly subjects ($P = 0.52$, $P = 0.13$) but the areas under the curves increased from 103 to 221 μg · h/ml ($P = 0.02$).

The terminal half-life and the apparent elimination rate constant of tromethamine fosfomycin were slightly modified in elderly subjects, but the difference was not significant ($P = 0.30$, $P = 0.49$) (Fig. 1).

The apparent volumes of distribution were not significantly different between elderly and young subjects ($P = 0.20$).

The total body clearance and the renal clearance of tromethamine fosfomycin decreased in elderly subjects, but the nonrenal clearances were not significantly different in

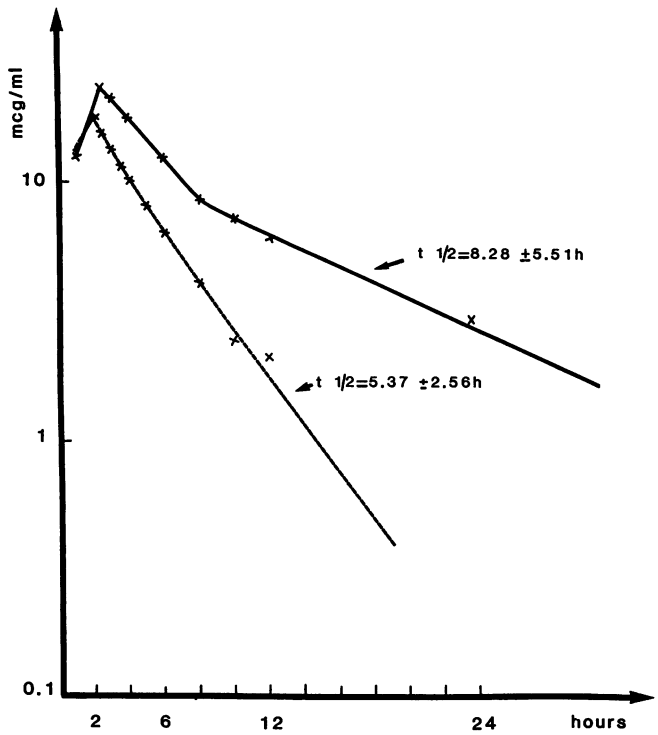

FIG. 1. Mean serum concentration-versus-time curves of tromethamine fosfomycin in healthy young (----; $n = 5$) and elderly (——; $n = 8$) subjects after a single 2-g oral dose.

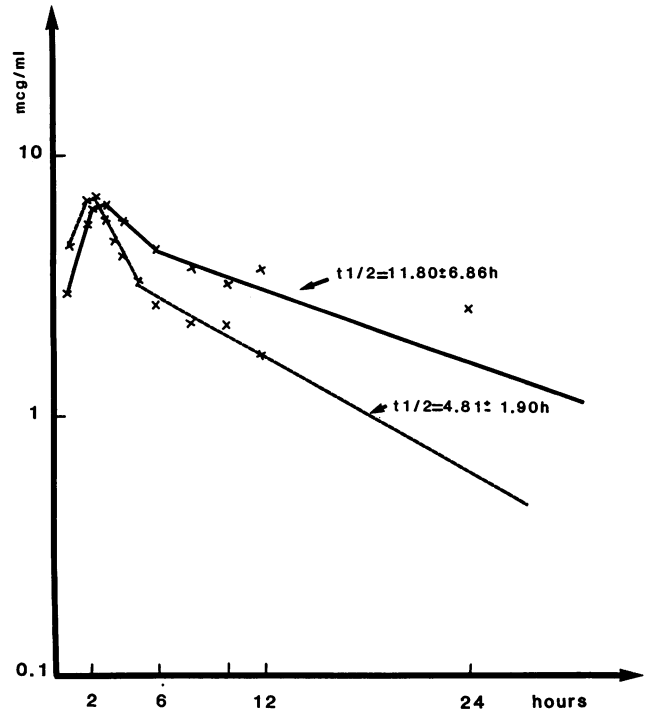

FIG. 2. Mean serum concentration-versus-time curves of calcium fosfomycin in healthy young (----; $n = 5$) and elderly (——; $n = 8$) subjects after a single 3-g oral dose.

young and elderly subjects: 183.8 ± 117.2 and 112.3 ± 68.7 ml/min per 1.73 m^2, respectively ($P = 0.21$).

Excretion of the tromethamine salt was reduced in the 24-h urines of elderly subjects ($P = 0.02$).

For the calcium salt, pharmacokinetic comparison between young and elderly subjects shows that the time to peak level was delayed in elderly subjects ($P = 0.005$). The areas under the curve were twofold higher in elderly subjects ($P = 0.06$), with large individual variations.

The terminal half-life values ranged from 3.12 to 18.39 h in elderly subjects, but no relation was found between half-life and glomerular filtration rate (Fig. 2).

The apparent volumes of distribution of calcium fosfomycin were not significantly different between young and elderly subjects ($P = 0.75$).

The mean renal clearance of the calcium salt was lower in elderly subjects ($P = 0.03$), but the nonrenal clearance remained unchanged ($P = 0.06$).

No significant difference was observed in urinary excretions in young and elderly subjects. It should be noted that urinary excretion of the calcium salt ranged from 7.8 to 55.9% of the dose in young subjects and from 5.0 to 13.8% of the dose in elderly subjects.

Discussion. Results after administration of calcium fosfomycin showed poor bioavailability and reduced intestinal absorption in all subjects studied. In healthy young adults, our results are similar to those found by others. After single oral doses of 0.5 and 1 g, Shimizu (8) obtained peak levels of 3.3 and 5.5 μg/ml respectively. After 0.5-, 1-, and 2-g doses, Kestle and Kirby (6) reported peak levels of 3.2, 5.3, and 7.1 μg/ml. In another study (4) performed with seven healthy subjects, after a single dose of 40 mg of calcium salt per kg the mean peak levels were 9.4 ± 3.6 μg/ml and 25% of the dose was recovered in 24-h urines. After a similar dose, we found a peak level of 7.4 ± 4.3 μg/ml and 18% of the dose in 24-h urines. Foltz et al. (3) found peak levels of 2.8, 5.2, and 6.9 μg/ml after 0.25-, 1-, and 2-g doses, respectively.

After the same oral dose of calcium fosfomycin in elderly subjects, we found the time to peak level to be delayed, the elimination half-life to be slightly increased ($P = 0.05$), and the renal clearance to be decreased ($P = 0.03$). The other kinetic data were similar to those obtained in healthy young adults.

The pharmacokinetics of the tromethamine salt form show antibiotic concentrations in serum and urine much higher than those of the calcium salt, in both young and elderly subjects. This oral form of fosfomycin has greater bioavailability than does the calcium salt.

Our results with healthy young adults are in good agreement with those reported in the literature. In 10 healthy subjects receiving a 50-mg/kg dose of tromethamine fosfomycin, Bergogne-Berezin et al. (1) found a mean peak level of 22.55 ± 6.03 μg/ml and a mean half-life of 7.31 ± 1.74 h.

In a comparative study of the two oral forms of fosfomycin, Ferrari et al. (2) found peak levels of 20.9 ± 7.0 and 5.7 ± 5.0 μg/ml after single 2-g doses of tromethamine and calcium fosfomycin, respectively. Segre et al. (7) studied tromethamine fosfomycin kinetics in four subjects after single doses of 2, 3, 4, and 5 g. After the 2-g dose, the peak levels, obtained at 3 h, were 14.59 ± 0.35 μg/ml; 50.7 ± 11.5% of the dose was excreted in 24-h urines (7), compared with 57.7 ± 30.2% in our study.

In elderly subjects, peak levels of tromethamine fosfomycin and times to peak levels were found to be similar to those obtained in young subjects ($P = 0.52$, $P = 0.13$). Elimination half-life did not significantly increase ($P = 0.30$). Urinary excretion and total body and renal clearances of tromethamine fosfomycin were lower in elderly subjects, but nonrenal clearances were similar in young and elderly subjects.

In conclusion, this comparative pharmacokinetic study of the two oral forms of fosfomycin in young and elderly adults showed, as in previous studies, a higher bioavailability of the tromethamine form, with antibiotic concentrations in serum two- to fourfold higher than those obtained for the calcium salt. A single 2- to 3-g dose of tromethamine fosfomycin produces effective concentrations in urine for at least 24 h.

In elderly subjects, the peak concentrations in serum, the apparent volumes of distribution, and the nonrenal clearances of both tromethamine and calcium fosfomycin were not significantly modified. The terminal half-life was moderately increased, but this increase was not significant for tromethamine fosfomycin.

Urinary excretion of the two forms of fosfomycin was slightly impaired in elderly subjects.

However, dosage adjustments should not be necessary for elderly subjects who have creatinine clearances above 50 ml/min per 1.73 m^2.

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