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Pharmacokinetics of Intraperitoneal and Intravenous Fosfomycin in Automated Peritoneal Dialysis Patients without Peritonitis

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Blood and dialysate concentrations of fosfomycin were determined after intravenous and intraperitoneal application of 4 mg/liter in patients undergoing automated peritoneal dialysis. Maximum serum concentrations after intravenous (287.75 ± 86.34 mg/liter) and intraperitoneal (205.78 ± 66.78 mg/liter) administration were comparable. Ratios of intraperitoneal to systemic exposure were 1.12 (intraperitoneal administration) and 0.22 (intravenous administration), indicating good systemic exposure after intraperitoneal application but limited penetration of fosfomycin into the peritoneal fluid after the intravenous dose.

Since the introduction of volumetric cyclers, automated peritoneal dialysis (APD) has been increasingly used in many parts of the world (8). It has been reported that long-term outcomes in patients treated with APD are at least as good as those seen in patients treated with continuous ambulatory peritoneal dialysis (CAPD) (9). However, several reports have demonstrated that due to various dwell times and higher dialysate treatment volumes during cycler therapy, peritoneal clearance of antibiotics differs between CAPD and APD (1, 2, 6, 7). Fosfomycin is a bactericidal broad-spectrum antibiotic with high *in vitro* activity against most common isolates of peritoneal dialysis-associated peritonitis and may be of great interest for the treatment of PD patients (3, 11). Pharmacokinetics (PK) of fosfomycin in CAPD patients receiving both intravenous (i.v.) and intraperitoneal (i.p.) doses of 1,000 mg have been published by Bouchet et al. (1). However, no data concerning the elimination of fosfomycin from dialysate or blood during APD are available. Thus, in the present study, dialysate and blood concentrations of fosfomycin after intravenous and intraperitoneal application were measured and compared. This was a prospective, open-labeled PK study (EUDRACT 2009-011505-16) conducted at the Department of Clinical Pharmacology at the General Hospital of Vienna and performed in accordance with the actual International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines and the Declaration of Helsinki. The clinical study was approved by the Ethics Committee of the Medical University of Vienna (EK no. 767/209) and was authorized by the Austrian Agency for Health and Food Safety (AGES).

Patients on PD receiving care at the Department of Internal Medicine III, Division of Nephrology and Dialysis, Medical University Vienna, were eligible to participate if aged between 18 and 65 years and on a stable APD regimen for at least 2 months. Patients were excluded if they had any systemic infection, peritonitis, or catheter-related infection within 2 months prior to the start of the study or hypersensitivity against fosfomycin. Eight APD patients without peritonitis were randomized for the study. Intravenous and intraperitoneal single doses of 4 g fosfomycin disodium salt (Sandoz GmbH, Kundl, Austria) were given, with a 1-week washout between the two doses. On the day of the study, the dialysate of each patient was drained completely. Thereafter, patients received 4 g fosfomycin either intravenously (i.v.) or intraperitoneally (i.p.) via 2 liters of icodextrin-containing dialysis solution (Extraneal; Baxter Healthcare Corp), which was instilled into the peritoneal cavity over 10 to 15 min. Following a long dwell of 15 h, patients underwent an automated peritoneal dialysis treatment (using a Home Choice Pro Cycler; Baxter Healthcare Corp) consisting of 6 exchanges (fill volume per cycle, 2.5 liters; Dianeal PD 4; Baxter Healthcare Corp). Cycler treatment time was 9 h. One milliliter each of blood and dialysate were collected immediately after administration of fosfomycin ($t = 0$) and at 1, 2, 3, 4, 5, 6, 9, 12, 15, 17.25, 19, 21.25, and 24 h (Fig. 1). Concentrations of fosfomycin in collected samples were determined by liquid chromatography and mass spectrometry using a Dionex UltiMate 3000 system (Dionex Corp., Sunnyvale, CA) connected with an API

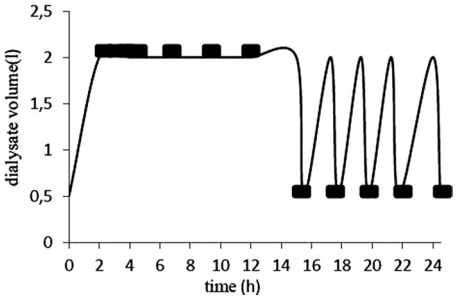

FIG 1 Schematic diagram of sampling of dialysate fluids and venous blood, performed at baseline (before application of antibiotics), at the end of intravenous/intraperitoneal administration, and 1, 2, 3, 4, 6, 9, 12, 15, 17.25, 19.5, 21.75, and 24 h after the administration, in correlation with cycling procedures.

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TABLE 1 Patient demographics[a]

Patient no.	Age (yr)	Sex	Cause of ESRD	GFR (ml/min/1.73 m^2)	Urine vol (ml/24 h) for visit 1 and visit 2	Time on APD (mo)	ABW (kg)
1	52	Female	Polycystic kidney disease	4.39	1,000, 1,000	20	72
2	65	Male	Shrunken kidneys of unknown origin	0	Anuric	19	102
3	68	Female	Shrunken kidneys of unknown origin	3.69	950, 1,110	59	57
4	50	Male	Vascular nephropathy	2.33	200	39	73
5	42	Male	Chronic glomerulonephritis	0	Anuric	2	73
6	63	Male	Diabetic nephropathy	9.68	1,880, 1,550	4	81
7	55	Female	Polycystic kidney disease	0	Anuric	44	64
8	47	Male	Vascular nephropathy	11.44	2,150, 2,100	12	75

[a] ESRD, end-stage renal disease; GFR, glomerular filtration rate; ABW, adjusted body weight.

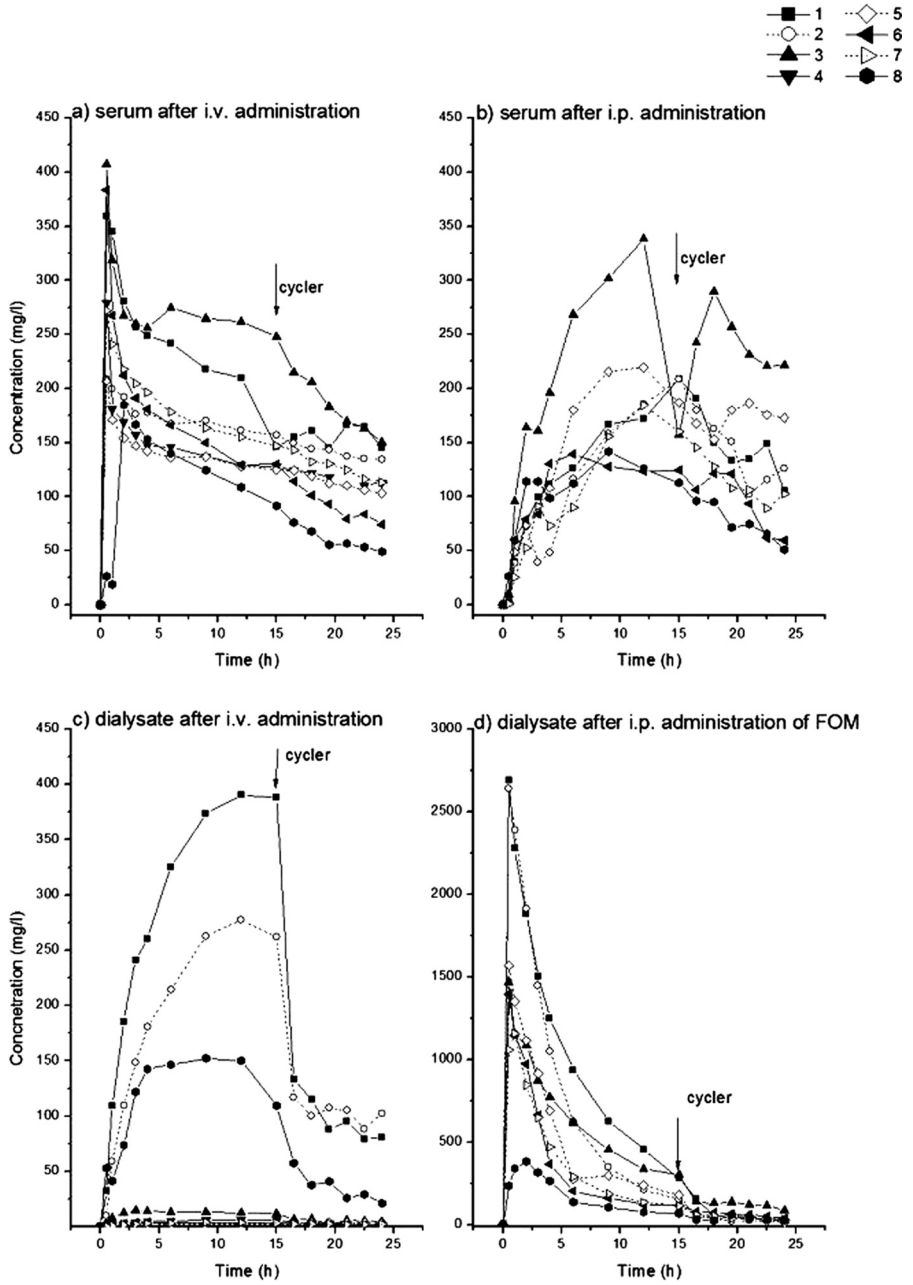

FIG 2 Pharmacokinetics of fosfomycin in serum and dialysate after i.v. and i.p. administration, illustrated for individual patients. The solid lines shows values of nonanuric patients, and the broken lines shows values of anuric patients.

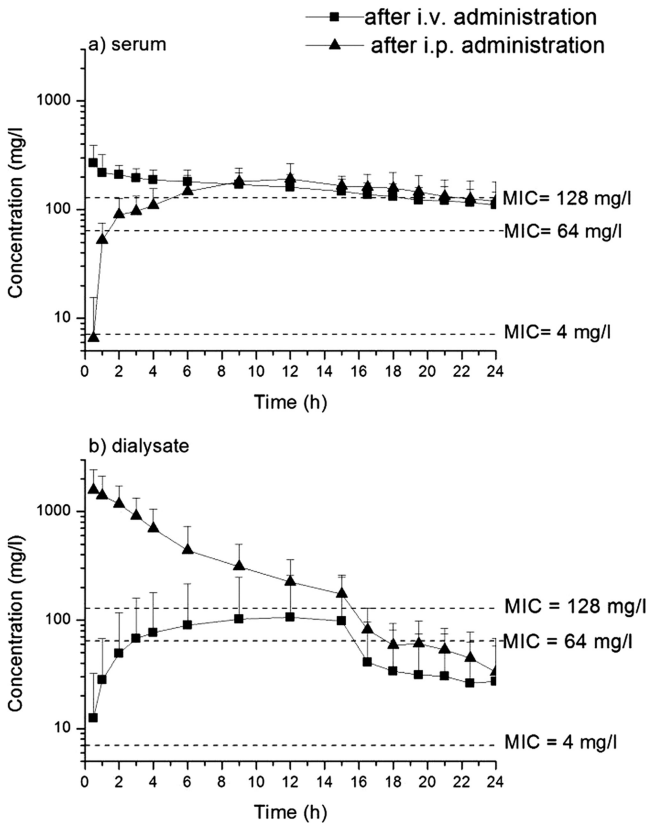

FIG 3 Relation between mean (± standard deviation [SD]) serum/dialysate concentrations of fosfomycin after intravenous (i.v.) and intraperitoneal (i.p.) administration.

4000 triple-quadrupole mass spectrometer (Applied Biosystems, Concord, Ontario, Canada). The limit of quantification for fosfomycin in serum and dialysate was 0.005 μg/ml. Intraday variability for fosfomycin ranged from 4.5 to 8.2% and interday variability ranged from 5.1 to 9.4% using fosfomycin concentrations of 0.1, 1, and 10 μg/ml serum.

Pharmacokinetic parameters were calculated using a commercially available computer program (Kinetika 3.0; Innaphase). The ratio of the systemic to the intraperitoneal exposure was calculated by the area under the concentration-time curve from 0 to 24 h for i.p. administration ($AUC_{0\text{-}24i.p.}$)/the AUC from 0 to 24 h for i.v. administration ($AUC_{0\text{-}24i.v.}$). Peritoneal dialysis clearance (CL_{APD}) was calculated by the following equation: CL_{APD} = mg of fosfomycin in the dialysate/$AUC_{0\text{-}24}$. The time intervals for which the fosfomycin concentration exceeded the MICs for relevant pathogens ($T>$MIC) were determined for individual patients for MICs of 4 mg/liter, 64 mg/liter, and 128 mg/liter and are expressed as percentages of the dosing interval of 24 h. For this purpose, the time interval in hours during which each individual concentration-versus-time profile of fosfomycin exceeded the respective MIC was divided by 24 and multiplied by 100.

Demographic characteristics of patients are shown in Table 1. Mean and individual fosfomycin serum and dialysate concentration-versus-time profiles after i.v. and i.p. administration are shown in Fig. 2 (differing between nonanuric and anuric patients) and Fig. 3. The CL_{APD} was 0.78 ± 0.54 mg/liter; other calculated fosfomycin pharmacokinetic parameters are presented in Table 2. Maximum serum concentrations after i.v. administration were observed after 0.5 h and averaged 287.75 ± 86.34 mg/liter. After i.p. administration, maximum serum concentrations were measured after 11.57 h and averaged 205.78 ± 66.78 mg/liter. The maximum dialysate concentration of fosfomycin after i.v. administration was detected after 10.69 h and averaged 106.58 ± 152.07 mg/liter. Individual and mean $T>$MIC values are shown in Table 3. For fosfomycin, $T>$MIC can be used to predict antimicrobial action, which means that optimal bacterial killing is observed when its concentration is moderately higher than the MIC of the pathogen for a period of 40 to 50% of the dosing interval. Based on the $T>$MIC for 64 mg/liter, the target value of 50% or more of the dosing interval was reached in the serum of all patients after i.v. and i.p. administration and in dialysate after i.p. administration. In contrast, after i.v. administration, a $T>$MIC of ≥50% was detected only in 3 of 7 patients and for pathogens with MICs of 4 mg/liter and not in pathogens with the higher MIC values. Based on these data, it seems that i.p. fosfomycin might be also used for APD patients with systemic infection caused by pathogens susceptible to fosfomycin (up to a MIC of >64 mg/liter). In contrast, poor diffusion of fosfomycin from serum into dialysate through the peritoneal membrane limits the i.v. use of fosfomycin for APD-associated peritonitis, particularly if the MIC of the pathogen agents is higher than 4 mg/liter. Highly different ratios of intraperitoneal to systemic exposure were observed after i.p. and i.v. administration, with $AUC_{0\text{-}24i.p.}/AUC_{0\text{-}24i.v.}$ values of 1.12 and 0.22, respectively. The mechanism underlying the inequalities in bidirectional peritoneal membrane penetration after i.v. and i.p. administration is unknown, but similar results were previously obtained for cefotaxime, vancomycin, teicoplanin, and aminoglycosides (4, 10). Thus, our findings confirm previous data suggest-

TABLE 2 Pharmacokinetics of serum and dialysate fosfomycin in patients undergoing APD following single 4-g intravenous and intraperitoneal doses[a]

Fluid and type of administration	C_{max} (mg/liter)	$t_{1/2}$ (h)	T_{max} (h)	$AUC_{0\text{-}24}$ (mg · h/liter)	Clearance (liters/h)
Serum					
i.v.	287.75 ± 86.34	30.71 ± 15.50	0.50 ± 0.00	9,031.68 ± 3,754.18	0.54 ± 0.30
i.p.	205.78 ± 66.78	28.98 ± 22.87	11.57 ± 3.21	9,116.59 ± 7,568.53	
Dialysate					
i.v.	106.58 ± 152.07	15.47 ± 6.39	10.69 ± 5.16	2,037.01 ± 2,842.88	
i.p.	1,613.67 ± 816.57	5.11 ± 2.08	0.79 ± 0.57	9,149.09 ± 4,139.75	0.56 ± 0.36

[a] The values are presented as means ± standard deviations. C_{max}, maximum concentration of the drug; $t_{1/2}$, half-life; T_{max}, time to maximum concentration of the drug.

TABLE 3 Individual and mean *T*>MIC values calculated for 3 different MICs

Fluid and patient no.	*T*>MIC value (%) for indicated MIC (mg/liter)					
	After i.v. administration			After i.p. administration		
	4	64	128	4	64	128
Serum						
1	100	100	100	97.91	91.66	56.25
2	100	100	100	97.91	91.66	43.75
3	100	100	100	100	95.83	91.66
4	100	100	68.75			
5	100	100	75	95.83	91.66	75
6	100	100	68.75	97.91	79.16	20.83
7	100	100	87.5	95.83	91.66	43.75
8	100	91.6	37.5	97.91	85.41	12.5
Mean ± SD	100 ± 0	98.95 ± 2.9	79.69 ± 21.8	97.61 ± 1.4	89.58 ± 5.5	49.1 ± 28.1
Dialysate						
1	100	95.83	60.42	100	75	75
2	100	91.66	50	100	68.75	68.75
3	95.83	0	0	100	100	87.5
4	45.83	0	0			
5	6.25	0	0	100	68.75	68.75
6	0	0	0	100	68.75	50
7	0	0	0	100	68.75	68.75
8	100	54.16	33.33	100	62.5	37.4
Mean ± SD	50.3 ± 49.04	30.21 ± 43.46	17.97 ± 28.85	100 ± 0	73.21 ± 12.3	65.16 ± 16.5

ing that for treatment of PD-associated peritonitis, i.p. administration of antibiotics is superior to i.v. dosing (12).

As expected, we detected a prolonged half-life in serum compared to that in patients with intact renal function (5). However, the mean elimination half-life of 30.71 h in serum after i.v. administration that was noted in this study is similar to the value of 38.4 h noted by Bouchet et al. in CAPD patients (1). Although the previous investigators tested the pharmacokinetics of fosfomycin in CAPD patients after administration of 1 g, whereas in our study, patients received a single dose of 4 g, plasma clearances of fosfomycin after intravenous administration were similar in the two studies (9 versus 7 ml/min, respectively). In contrast to the study in CAPD patients, we did not find a significant difference in elimination half-lives between patients with residual renal function and anuric patients; however, we observed a trend pointing in the same direction, with values of 26.88 ± 17.19 h and 37.06 ± 15.5 h, respectively. One potential limitation of the present study is the absence of peritonitis in our patients, which is a limitation common to most other studies evaluating the pharmacokinetics of antibiotics in PD patients. Peritonitis might increase peritoneal permeability, resulting in both faster drug adsorption and an increase of peritoneal drug clearance during non-drug-containing dwells (7). In conclusion, based on pharmacokinetic-pharmacodynamic target attainment, the present data indicate that i.p. administration of 4 g of fosfomycin can be used for treatment of peritonitis and systemic infections. In contrast, insufficient fosfomycin concentrations were found in the peritoneal fluid after i.v. administration of 4 g of fosfomycin in APD patients. (This study was presented in part at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, 17 to 20 September 2011.)

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