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Pharmacokinetics of Cephem Antibiotics in Exudate of Pelvic Retroperitoneal Space after Radical Hysterectomy and Pelvic Lymphadenectomy

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Many cephalosporin antibiotics have recently been invented and attempts have been made to use them clinically. The choice of which of these drugs should be used has been difficult in gynecology. The efficacies of these drugs depend on their antibacterial spectra, potencies, and concentrations in tissues. This study was designed to investigate the pharmacokinetics of various cephem antibiotics in the exudate of the retroperitoneal space that is formed after radical hysterectomy and pelvic lymphadenectomy. These cephem antibiotics were cefoxitin, cefotiam, cefotetan, cefpiramide, cefminox, cefotaxime, ceftizoxime, cefoperazone, cefmenoxime, cefbuperazone, ceftazidime, cefpimizole, flomoxef, and cefuzonam. The maximum concentrations after administration of a 1-g dose in the exudate of the pelvic retroperitoneal space were 37.9 μg/ml with cefminox, 30.3 μg/ml with cefpimizole, 21.6 μg/ml with flomoxef, 21.5 μg/ml with ceftazidime, and 17.6 μg/ml with cefbuperazone, which were relatively high. When selecting antibiotics for prophylactic use against infections in the retroperitoneal space after radical hysterectomy and pelvic lymphadenectomy, on the basis of drug transfer, flomoxef, cefminox, cefbuperazone, ceftazidime, and cefpimizole were considered to be the drugs of first choice at a dose of 1 g.

Many cephalosporin antibiotics have been invented recently, and attempts have been made to use them clinically. It has been difficult to determine which of these drugs should be chosen for clinical use, for example, against postoperative infections.

The efficacies of these drugs are dependent upon their half-lives ($t_{1/2}$s), antibacterial spectra, antibacterial potencies, and concentrations in tissues. Based on these parameters, this study was designed to investigate the pharmacokinetics of various cephem antibiotics in the exudates of the retroperitoneal spaces that were formed after radical hysterectomy and pelvic lymphadenectomy. Results of this study may provide some suggestions for treating infections of the retroperitoneal space.

MATERIALS AND METHODS

Drugs. Fourteen antibiotics were used in this study: cefoxitin, cefotiam, cefotetan, cefpiramide, cefminox, cefotaxime, ceftizoxime, cefoperazone, cefmenoxime, cefbuperazone, ceftazidime, cefpimizole, flomoxef, and cefuzonam.

Subjects. Seventy-two patients who underwent radical hysterectomy and pelvic lymphadenectomy for the treatment of cervical cancer at our institution were used in this study. They agreed to participate in this study and allowed venous blood samples and exudates of the retroperitoneal space after antibiotic loading to be taken. These patients showed no liver function abnormalities, including a normal serum transaminase level, and no renal function abnormalities, including normal blood urea nitrogen and creatinine levels. Each drug was administered to four to six patients. The study was designed so that four patients were the minimum necessary for analysis, since there was a limit in the number of patients undergoing radical hysterectomy.

Experimental methods. (i) Drug administration. Two grams of each of cefoxitin, cefotiam, or cefotaxime was dissolved in 200 ml of a 5% glucose solution and administered to the patients for 60 min exactly by using an automatic drip infusion pump. For the remaining 11 drugs, cefotetan, cefpiramide, cefminox, ceftizoxime, cefoperazone, cefmenoxime, cefbuperazone, ceftazidime, cefpimizole, flomoxef, and cefuzonam, 1 g of each drug was dissolved in 200 ml of a 5% glucose solution and administered to the patients as described above for the other drugs.

(ii) Sampling method. In patients who received a radical hysterectomy and pelvic lymphadenectomy, the vaginal cuff was closed and pelvic reperitonealization was done. Therefore, the pelvic retroperitoneal space was formed as an enclosed cavity. Before closure of the pelvic peritoneum, a 16F thoracic catheter (Argyle) was inserted from the retroperitoneum of the lateral abdominal wall into one side of the pelvic retroperitoneal space. Drip infusion of each drug was started immediately after surgery. As the exudate of the retroperitoneal space was left in situ, 2 ml of the exudate was sampled by aspiration with a 6F catheter through a 16F thoracic catheter at various times after the beginning of the drip infusion. After centrifugal separation (1,000 × g, 15 min), the supernatant of the exudate was frozen and stored at −80°C. At the corresponding time, 3 ml of antecubital venous blood was drawn, and after centrifugal separation (1,000 × g, 15 min), the serum was frozen and stored at −80°C.

(iii) Measurement of drug concentration. The concentrations of cefotetan and cefotaxime were measured by a high-pressure liquid chromatographic method, as follows. For cefotetan, a Nucleosil $5C_{18}$ column (4.0 by 150 mm; particle size, 5 μm) was used with UV detection at 280 nm and a transfer phase of 1/15 M phosphate-buffered saline and CH_3CN. For cefotaxime, a Lichrosorb RP-18 column (4.6 by 200 mm; particle size, 7 μm) was used with UV detection at 245 nm and a transfer phase of 1/15 M phosphate-buffered saline and CH_3OH. The concentrations of the other antibiotics were measured by a bioassay with the test organisms

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TABLE 1. Bioassay methods used to measure antibiotic concentrations with various test organisms[a]

Antibiotic Drug	Test organism	Type of bioassay
Cefoxitin	*S. aureus* MB2786	Paper disk
Cefotiam	*P. mirabilis* 2110	Agar well
Cefpiramide	*E. coli* NIHJ	Agar well
Cefminox	*E. coli* NIHJ	Paper disk
Ceftizoxime	*B. subtilis* ATCC 6633	Paper disk
Cefoperazone	*M. luteus* ATCC 9434	Paper disk
Cefmenoxime	*E. coli* NIHJ-JC-2	Agar well
Cefbuperazone	*K. pneumoniae* ATCC 10031	Cylinder cup
Ceftazidime	*P. mirabilis* ATCC 22100	Paper disk
Cefpimizole	*K. pneumoniae* IFO 3317	Paper disk
Flomoxef	*E. coli* 7437	Band culture
Cefuzonam	*E. coli* NIHJ	Cylinder cup

[a] For serum the diluent was consecutive serum samples; for exudate the diluent was 0.1 M phosphate-buffered saline (pH 7.0).

Staphylococcus aureus for cefoxitin; *Proteus mirabilis* for cefotiam and ceftazidime; *Escherichia coli* for cefpiramide, cefminox, cefmenoxime, cefuzonam, and flomoxef; *Klebsiella pneumoniae* for cefbuperazone and cefpiramide; *Micrococcus luteus* for cefoperazone; and *Bacillus subtilis* for ceftizoxime (Table 1).

(iv) Method of analysis. Since the retroperitoneal space was closed, transfer of the drug could occur both from the venous blood to the exudate and from the exudate to the venous blood. Furthermore, the successive change of the drug concentration in serum could be analyzed precisely; analysis was performed with a two-compartment model by regarding the retroperitoneal space as a small peripheral compartment (Fig. 1) (3). Each value that was measured was weighted with the reciprocal of that value. Pharmacokinetic parameters were calculated by the least-squares method. Concentration curves were drawn by using these values.

RESULTS

Findings. The mean concentrations of each drug at various times are given in Tables 2 and 3. The mean concentrations are shown graphically in Fig. 2 to 4.

(i) Concentrations of drugs in serum. The highest concentrations of drug in serum determined in 1 h of drip infusion was observed to be between 41.2 and 244.5 μg/ml. Cefpiramide, cefotetan, cefpimizole, cefoperazone, cefotiam, and cefoxitin showed relatively high concentrations. Cefoxitin and cefotiam were administered at the 2-g dose, but the other drugs were given at the 1-g dose. Cefpimizole showed a particularly high concentration. Cefmenoxime, cefuzonam, flomoxef, and ceftizoxime showed relatively low concentrations. Over time, the concentrations declined linearly, with drug concentrations in serum ranging from 121.5 to 3.8 μg/ml after 3 hours and from 70 μg/ml to the undetectable range after 6 h. Cefpiramide, cefotetan, and cefoperazone had relatively long $t_{1/2}$ values; and cefmenoxime, ceftizoxime, cefotaxime, cefoxitin and cefuzonam had relatively short $t_{1/2}$ values.

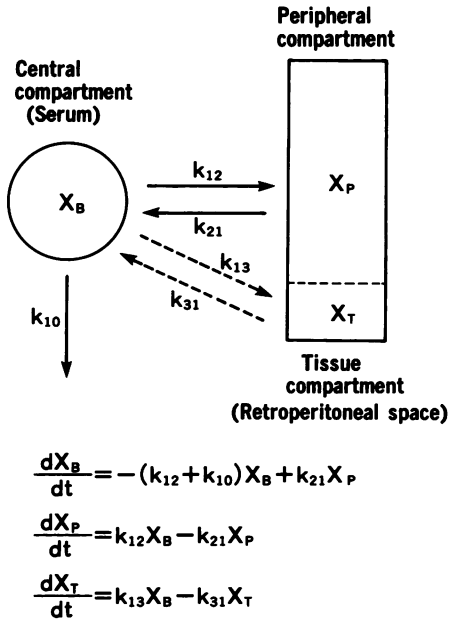

FIG. 1. Two-compartment model for analysis of the drug concentration in serum. Abbreviations: X_B, amount of drug in central compartment; k_{12}, k_{21}, k_{13}, and k_{31}, transfer rate constants; k_{10}, elimination rate constant; X_P, amount of drug in peripheral compartment; X_T, amount of drug in tissue compartment.

(ii) Drug concentrations in exudates of pelvic retroperitoneal spaces. The peaks of the mean drug concentrations in the exudates of the pelvic retroperitoneal spaces were observed between 2 and 7 h and ranged from 45.1 to 6.2 μg/ml. Cefminox, cefotiam, and cefpimizole showed relatively high

TABLE 2. Mean concentrations of 14 antibiotics in serum after intravenous drip infusion for 60 min

Antibiotic	Mean concn (μg/ml) at the following times (h) postinfusion:											
	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0
Cefoxitin		104	41.0	23.1	11.3	5.77	3.18	1.80				
Cefotiam	97.0	112	52.4	30.7	13.8	7.80		3.59				
Cefotetan	88.6	132	92.6	71.4	49.9	36.2		18.8		11.2	5.65	
Cefpiramide		245	183	157	122		94.0		71.9			
Cefminox	66.0	90.1	68.0	47.7	32.0	17.1	10.1	6.37		2.83	1.45	0.750
Cefotaxime	64.7	89.8	34.9	16.5	5.91	2.74		0.710				
Ceftizoxime		53.6	27.9	18.2	8.90		3.34		1.52			
Cefoperazone		120	72.2	57.4	38.0	25.6	16.0	14.3		8.40	5.30	2.20
Cefmenoxime	35.8	41.2	17.2	9.76	3.76	1.97						
Cefbuperazone		83.6	44.6	33.8	18.9	12.9		4.80		2.30	1.10	
Ceftazidime		76.3	41.1	27.3	12.2	8.05		3.61		1.33	0.570	0.700
Cefpimizole		128	98.4	66.4	42.0	28.3		11.8				
Flomoxef		49.5	27.4	13.4	7.20	3.62		0.960		0.410		
Cefuzonam		46.9	14.3	10.8	3.85	1.96		0.740		0.350	0.120	

TABLE 3. Mean concentrations of 14 antibiotics in exudate of pelvic retroperitoneal space after intravenous drip infusion for 60 min

Antibiotic	Mean concn (μg/ml) at the following times (h) postinfusion:											
	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0
Cefoxitin		14.5		24.1	21.5	17.4	12.8	9.73		5.00	3.10	1.90
Cefotiam	5.44	19.1	33.7	34.5	23.4	19.6		13.4		8.00	4.73	
Cefotetan			9.18	7.41	9.54	10.0		9.82		8.99	6.72	3.64
Cefpiramide		0.880	1.90	3.25	5.15		5.85		6.25			
Cefminox		19.9		35.2	45.1	41.5	31.0	23.2		16.4	11.1	7.94
Cefotaxime	1.50	6.03	12.0	13.9	13.0	10.5		7.19		4.60	2.93	
Ceftizoxime		10.0	14.5	16.0	15.6		9.67		4.87			
Cefoperazone		5.20		15.1	16.4	13.3	11.3	15.2	13.3	13.3	6.80	5.20
Cefmenoxime	1.11	3.26	9.48	12.5	11.5	9.72		6.41		3.38	1.70	1.85
Cefbuperazone		9.10	16.9	19.4	16.0	16.0		12.6		6.00	3.60	2.10
Ceftazidime		13.4	22.6	23.0	21.6	18.7		13.5		8.87	5.25	2.80
Cefpimizole		12.7		25.0	29.2	27.8		18.9		13.0	4.93	5.43
Flomoxef		11.8		19.9	20.4	19.4		7.85		4.50		
Cefuzonam		7.13		9.91	9.75	10.1		7.42		5.74	1.75	

concentrations, whereas cefpiramide, cefotetan, and cefuzonam showed relatively low concentrations. Cefotetan, cefpiramide, and cefoperazone had relatively long $t_{1/2}$ values, whereas cefoxitin, cefbuperazone, and flomoxef had relatively short ones.

Simulation curve of drug concentrations. The parameters of the formulas analyzed by the two-compartment model were determined by the least-squares method, and a simulation curve was made.

The parameters for each drug are shown in Table 4 for drug concentration in serum and in Table 5 for drug concentration in the exudates of the pelvic retroperitoneal spaces.

The simulation curves that were made for each drug are shown in Fig. 2 to 4.

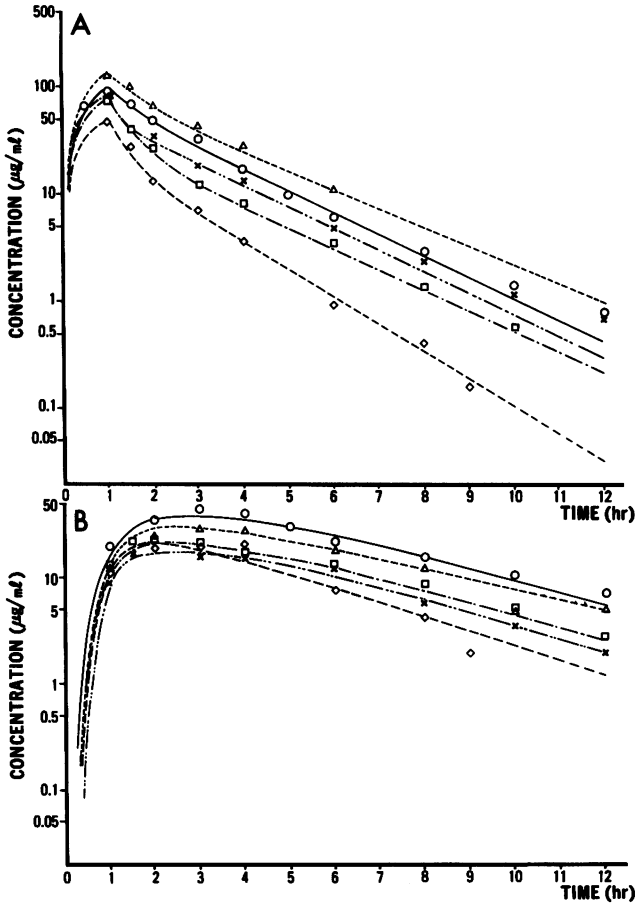

FIG. 2. Concentrations of drugs in sera (A) and exudates (B) of retroperitoneal spaces. Symbols: ○, cefminox; △, cefpimizole; ◇, flomoxef; □, ceftazidime; ×, cefbuperazone.

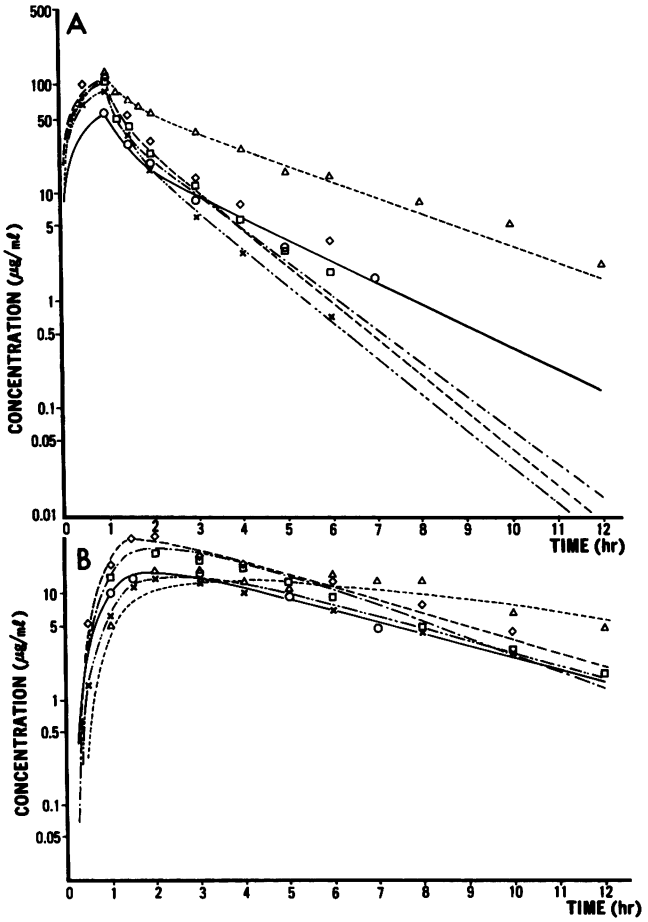

FIG. 3. Concentrations of drugs in sera (A) and exudates (B) of retroperitoneal spaces. Symbols: ○, ceftizoxime; △, cefoperazone; ◇, cefotiam; □, cefoxitin; ×, cefotaxime.

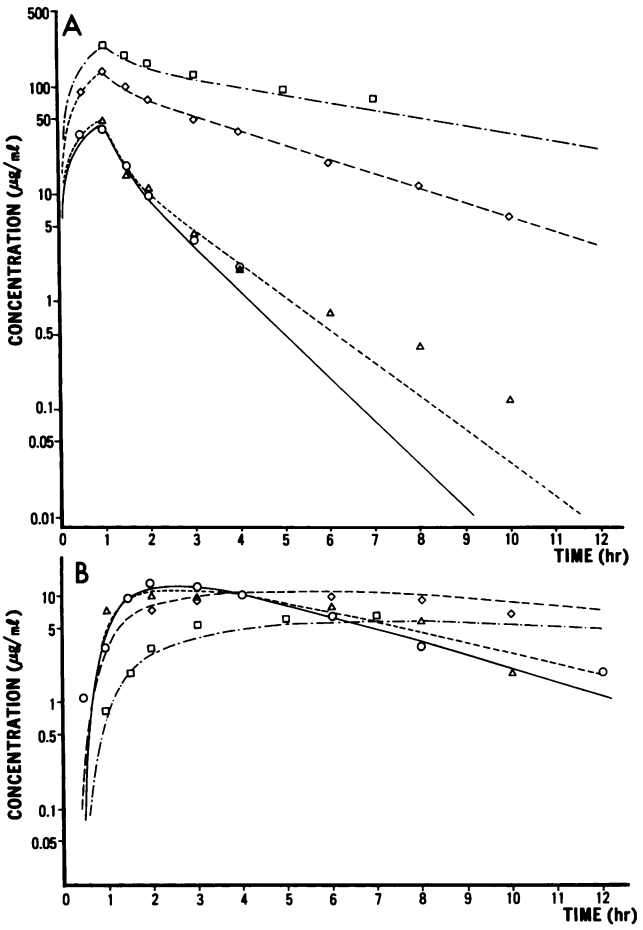

FIG. 4. Concentrations of drugs in sera (A) and exudates (B) of retroperitoneal spaces. Symbols: ○, cefmenoxime; △, cefuzonam; ◇, cefotetan; □, cefpiramide.

(i) Drug concentrations in serum. The maximum drug concentrations (c_{max}; i.e., the maximal drug concentration at the end of drip infusion) were 237.4 μg/ml for cefpiramide, 137.0 μg/ml for cefotetan, 129.1 μg/ml for cefpimizole, 115.3 μg/ml for cefoperazone, 110.9 μg/ml for cefotiam, and 101.4 μg/ml for cefoxitin, which were relatively high levels of drug in serum; 98.8 μg/ml for cefminox, 88.9 μg/ml for cefotaxime, 88.5 μg/ml for cefbuperazone, and 75.4 μg/ml for ceftazidime, which were intermediate levels of drug in serum; and 53.6 μg/ml for ceftizoxime, 49.4 μg/ml for flomoxef, 47.0 μg/ml for cefuzonam, and 43.1 μg/ml for cefmenoxime, which were relatively low levels of drug in serum.

The $t_{1/2}$ was relatively long for cefpiramide (4.1 h), cefotetan (2.2 h), and cefoperazone (2.0 h), and was relatively short for cefmenoxime (0.8 h), cefotiam (0.9 h), cefotaxime (0.9 h), cefoxitin (1.0 h), and cefuzonam (1.0 h). Among the drugs tested, cefminox, ceftizoxime, cefbuperazone, ceftazidime, and flomoxef, which had intermediate concentrations in serum, $t_{1/2}$ values were between 1 and 2 h.

The value of the area under the time-serum concentration curve ($AUC_{0-\infty}$) tended to be relatively larger in the drugs with high C_{max} values and long $t_{1/2}$ values. Among the drugs tested the value of $AUC_{0-\infty}$ was 1,110.2 μg · h/ml for cefpiramide, 400.7 μg · h/ml for cefotetan, 341.9 μg · h/ml for cefoperazone, and 308.3 μg · h/ml for cefpimizole, which were relatively high, and 57.0 μg · h/ml for cefmenoxime, 65.6 μg · h/ml for cefuzonam, 78.0 μg · h/ml for flomoxef, and 95.8 μg · h/ml for ceftizomine, which were relatively low. The $AUC_{0-\infty}$ values for the remaining drugs, cefoxitin, cefminox, cefotaxime, cefbuperazone, and ceftazidime, were between 100 and 300 μg · h/ml.

(ii) Drug concentrations in exudates of the pelvic retroperitoneal spaces. The C_{max} values in the exudates of the pelvic retroperitoneal spaces were 37.9 μg/ml for cefminox, 33.4 μg/ml for cefotiam, 30.3 μg/ml for cefpimizole, and 26.6 μg/ml for cefoxitin, which were relatively high; 21.6 μg/ml for flomoxef, 21.5 μg/ml for ceftazidime, 17.6 μg/ml for cefbuperazone, 16.2 μg/ml for ceftizoxime, 14.5 μg/ml for cefotaxime, and 13.4 μg/ml for cefoperazone, which were intermediate; and 12.1 μg/ml for cefmenoxime, 11.3 μg/ml for cefuzonam, 10.8 μg/ml for cefotetan, and 5.5 μg/ml for cefpiramide, which were relatively low.

The times to reach the maximum concentration of drug (T_{max}) in the exudates of the retroperitoneal spaces were 7.2 h for cefpiramide, 5.0 h for cefotetan, and 4.1 h for cefoperazone, which were relatively long, and 1.6 h for cefotiam, 1.8 h for ceftizoxime, and 1.9 h for flomoxef, which were relatively short. For cefoxitin, cefminox, cefotaxime, cefmenoxime, cefbuperazone, ceftazidime, and cefuzonam, the T_{max} values were between 2 and 3 h.

The duration of the $t_{1/2}$ tended to be similar to that of the

TABLE 4. Pharmacokinetic parameters for drugs in serum[a]

Antibiotic	α	β	A^*	B^*	A	B	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)
Cefoxitin	4.882	0.719	60.65	80.41	60.19	41.23	1.00	101.42	0.96	141.06
Cefotiam	4.816	0.792	58.44	96.75	57.97	52.92	1.00	110.90	0.88	155.19
Cefotetan	2.868	0.313	43.52	357.14	41.05	95.98	1.00	137.03	2.21	400.66
Cefpiramide	1.716	0.169	97.46	1,012.73	79.94	157.47	1.00	237.41	4.10	1,110.19
Cefminox	1.821	0.462	36.77	183.80	30.80	68.00	1.00	98.82	1.50	220.57
Cefotaxime	3.132	0.772	60.36	57.96	57.73	31.17	1.00	88.90	0.90	118.31
Ceftizoxime	2.600	0.452	33.30	62.51	30.82	22.73	1.00	53.55	1.53	95.81
Cefoperazome	2.671	0.346	45.70	250.47	42.54	73.26	1.00	115.80	2.00	341.87
Cefmenoxime	3.102	0.919	24.93	32.08	23.81	19.28	1.00	43.09	0.75	57.01
Cefbuperazone	6.077	0.466	32.23	132.43	32.16	49.33	1.00	81.49	1.49	164.66
Ceftazidime	1.913	0.436	56.89	76.06	48.49	26.88	1.00	75.37	1.59	132.95
Cefpimizole	1.432	0.400	63.65	244.60	48.45	80.44	1.00	129.09	1.73	308.25
Flomoxef	2.410	0.589	31.63	46.32	28.79	20.62	1.00	49.41	1.18	77.95
Cefuzonam	3.632	0.707	29.34	36.24	28.56	18.39	1.00	46.95	0.98	65.63

[a] For $0 < t < 1.0$, $C = A^*(1 - e^{-\alpha t}) + B^*(1 - e^{-\beta t})$, and for $t \geq 1.0$, $C = Ae^{-\alpha(t - 1.0)} + Be^{-\beta(t - 1.0)}$, where α is a rate constant in the distribution, β is a rate constant in the elimination, A^* is $A/(1 - e^{-\alpha})$, B^* is $B/(1 - e^{-\beta})$, A is the intercept for α phase at $t = 1$, and B is the intercept for β phase at $t = 1$.

TABLE 5. Pharmacokinetic parameters for drugs in exudate of pelvic retroperitoneal space[a]

Antibiotic	α	β	k_{31}	A^*	B^*	C^*	A	B	C	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg · h/ml)
Cefoxitin	4.882	0.719	0.371	−5.77	−120.64	265.07	−5.73	−61.86	82.16	2.11	26.55	1.87	138.66
Cefotiam	4.816	0.792	0.285	−16.44	−24.81	204.17	−16.31	−13.57	50.63	1.56	33.35	2.43	162.92
Cefotetan	2.868	0.313	0.113	−2.31	−79.40	247.83	−2.18	−21.34	26.48	5.02	10.75	6.13	166.12
Cefpiramide	1.716	0.169	0.123	−0.87	−270.76	376.11	−0.71	−42.10	43.53	7.18	5.54	5.64	104.48
Cefminox	1.821	0.462	0.300	−13.67	−412.78	693.76	−11.46	−152.72	179.81	2.81	37.86	2.31	267.31
Cefotaxime	3.132	0.772	0.269	−2.38	−45.19	140.38	−2.28	−24.31	33.11	2.50	14.46	2.58	92.31
Ceftizoxime	2.600	0.452	0.277	−10.46	−43.42	146.23	−9.68	−15.79	35.38	1.83	16.14	2.50	92.35
Cefoperazone	2.671	0.346	0.166	−3.35	−123.56	281.98	−3.12	−36.14	43.13	4.10	13.42	4.18	155.07
Cefmenoxime	3.102	0.919	0.291	−1.43	−36.27	107.97	−1.37	−21.80	27.26	2.49	12.11	2.38	70.27
Cefbuperazone	6.077	0.466	0.337	−6.24	−247.58	367.61	−6.23	−92.22	105.17	2.50	17.60	2.06	113.79
Ceftazidime	1.913	0.436	0.296	−16.03	−167.24	321.80	−13.66	−59.10	82.45	2.33	21.45	2.34	138.53
Cefpimizole	1.432	0.400	0.247	−35.38	−138.71	387.56	−26.93	−45.73	84.82	2.51	30.32	2.81	213.47
Flomoxef	2.410	0.589	0.331	−18.62	−47.29	171.69	−16.95	−21.05	48.38	1.91	21.59	2.09	105.78
Cefuzonam	3.632	0.707	0.236	−4.44	−29.99	112.31	−4.32	−15.20	23.61	2.44	11.29	2.94	77.88

[a] For $0 < t < 1.0$, $C = A^*(1 - e^{-\alpha t}) + B^*(1 - e^{-\beta t}) + C^*(1 - e^{-k_{31}t})$, and for $t \geq 1.0$, $C = Ae^{-\alpha(t-1.0)} + Be^{-\beta(t-1.0)} + Ce^{-k_{31}(t-1.0)}$, where α is the distribution phase, β is the elimination phase, k_{31} is the transfer rate constant, A^* is $A/(1 - e^{-\alpha})$, B^* is $B/(1 - e^{-\beta})$, C^* is $C/(1 - e^{-k_{31}})$, A is the intercept for α phase at $t = 1$, B is the intercept for β phase at $t = 1$, and C is the intercept for an elimination phase at $t = 1$.

T_{max}. They were long for cefotetan (6.1 h), cefpiramide (5.6 h), and cefoperazone (4.2 h) and short for cefoxitin (1.4 h). The values were between 2 and 3 h for cefminox, cefotaxime, ceftizoxime, cefmenoxime, cefbuperazone, ceftazidime, cefpimizole, flomoxef, and cefuzonam.

The $AUC_{0-\infty}$ values for cefminox and cefpimizole were 267.3 and 213.5 μg · h/ml, respectively, which were relatively high. The $AUC_{0-\infty}$ values were 166.1 μg · h/ml for cefotetan, 162.9 μg · h/ml for cefotiam, 155.1 μg · h/ml for cefoperazone, 138.7 μg · h/ml for cefoxitin, 133.5 μg · h/ml for ceftazidime, 105.7 μg · h/ml for flomoxef, 104.5 μg · h/ml for cefpiramide, 91.8 μg · h/ml for cefotaxime, 91.4 μg · h/ml for ceftizoxime, 77.9 μg · h/ml for cefuzonam, and 70.3 μg · h/ml for cefmenoxime.

DISCUSSION

In serum, cefpiramide, cefotetan, and cefoperazone showed high concentrations and long $t_{1/2}$ values; but the C_{max} values of these drugs in the exudates of the pelvic retroperitoneal spaces were relatively low, and the $t_{1/2}$ values were relatively long. These three drugs bind to serum protein with a high affinity (cefpiramide, 96.3% [2]; cefotetan, 91.0% [1], cefoperazone, 86.8% [4]), but their transfer into tissues is considered to be poor.

Cefminox, cefotiam, cefpimizole, and cefoxitin, which had C_{max} values over 25 μg/ml in the exudates of the pelvic retroperitoneal spaces, had relatively low C_{max} values in serum. Therefore, these drugs seem to be capable of transferring easily to the pelvic retroperitoneal space. In this study, cefmenoxime and cefuzonam showed relatively low concentrations in the exudates of the pelvic retroperitoneal spaces but showed particularly low concentrations in sera. Therefore, transfer of these drugs into the pelvic retroperitoneal space is considered to be relatively good because of the drug concentration in the serum. Increases in the doses of these two drugs is expected to bring higher concentrations of the drugs in the exudates of the pelvic retroperitoneal space.

Cephalosporin antibiotics have their own antibacterial potencies and spectra, but to demonstrate efficacy, their concentrations must be at least over 12.5 μg/ml in the target tissue. Among the drugs that we studied, cefminox, cefotiam, cefpimizole, cefoxitin, flomoxef, ceftazidime, cefbuperazone, ceftizoxime, cefotaxime, and cefoperazone provided clinically efficacious concentrations in tissues. Cefmenoxime and cefuzonam may provide clinically efficacious concentrations if their doses were increased to 2 g.

At 1-g doses, cefminox, cefpimizole, flomoxef, ceftazidime, and cefbuperazone can be easily transferred to the pelvic retroperitoneal space; and the MICs of cefminox against *S. aureus* and *E. coli* were 12.5 and 0.78 μg/ml, respectively. They were 12.5 and 12.5 μg/ml for cefpimizole, 1.56 and 0.2 μg/ml for flomoxef, 12.5 and 0.2 μg/ml for ceftazidime, and 12.5 and 0.2 μg/ml for cefbuperazone, respectively. Therefore, these drugs can be considered as prophylactic drugs of first choice against retroperitoneal space infections after radical hysterectomy and pelvic lymphadenectomy. At 2-g doses, ceftizoxime, cefotiam, cefoxitin, cefotaxime, cefmenoxime, and cefuzonam might be indicated for use as prophylactic drugs of first choice.

From the results of this study, it is suggested that drugs with a short $t_{1/2}$ in serum can transfer smoothly to tissues, while those with long $t_{1/2}$ values in serum transfer to the tissues poorly. Drugs with long $t_{1/2}$ values in serum can be ruled out as being efficacious.

LITERATURE CITED

1. **Komiya, K., Y. Kikuchi, and A. Tachibana.** 1982. Absorption, distribution, metabolism and excretion of cefotetan (YM 09330), a new broad spectrum cephamycin, in experimental animals. Chemotherapy **30**:(Suppl. 1):106–118.
2. **Matsui, H., Y. Noshiro, and K. Yano.** 1983. Pharmacokinetics of cefpiramide (SM-1652), new broad-spectrum and long-acting cephalosporin, parenterally administered to laboratory animals. Chemotherapy **31**(Suppl. 1):114–123.
3. **Mizuta, E., and A. Tsubotani.** 1985. A pharmacokinetic model for simulating drug concentrations in the tissue or fluids and its application to antibiotics. Chem. Pharm. Bull. **33**:2974–2982.
4. **Saikawa, I., T. Yasuda, and Y. Watanabe.** 1980. Studies on the protein binding of cefoperazone (T-1551). Chemotherapy **28**(Suppl 6):173–178.