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Effects of Rate of Infusion and Probenecid on Serum Levels, Renal Excretion, and Tolerance of Intravenous Doses of Cefoxitin in Humans: Comparison with Cephalothin

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Using a randomized crossover design, 1-g intravenous doses of cephalothin and cefoxitin, a cephalosporinase-resistant cephamycin, were infused into 12 normal adult males over periods of 120, 30, and 3 min, the last with and without prior intravenous infusions of probenecid (1 g). Mean peak serum concentrations of antibiotic activity after cephalothin infusions were 23, 56, 103, and 102 μg/ml, respectively, and after cefoxitin infusions they were 27, 74, 115, and 125 μg/ml, respectively. Probenecid treatment prolonged the terminal serum half-life of cephalothin-like activity from 0.52 to 1.0 h, and of cefoxitin from 0.68 to 1.4 h. In contrast to cephalothin, which was found to be metabolized about 25% to the less active desacetyl form, cefoxitin was metabolized less than 2% to the virtually inactive descarbamyl form, as judged from urinary recoveries. Neither antibiotic displayed detectable organ toxicity. Of 300 recent clinical isolates of gram-negative bacilli other than *Pseudomonas* spp., 83% were susceptible to cephalothin but 95% were susceptible to cefoxitin. Organisms resistant to cephalothin but susceptible to cefoxitin included strains of *Escherichia coli*, *Proteus vulgaris*, *Klebsiella* spp., *Serratia marcescens*, *Enterobacter* spp., and *Bacteroides* spp.

Cephalosporin antibiotics are being used increasingly as gram-negative bacilli progressively develop resistance to ampicillin (2, 15) and cotrimoxazole (9, 11). However, currently available cephalosporins have certain deficiencies, most notably that cephalosporinase-producing bacteria are resistant to them (20). Cephaloridine can cause renal toxicity (5, 12), occurring especially easily in postoperative azotaemia. Moreover, cephalothin is rapidly metabolized in man up to 35% to the less active desacetyl derivative (7, 8).

The cephamycin antibiotics (16) are significantly resistant to cephalosporinase (1). Cephamycin C is active against bacterial species resistant to cephalothin and cephaloridine, such as *Proteus vulgaris* (13). In animals, cephamycin C is therapeutically effective against systemic infections; high doses failed to reveal gross evidence of nephrotoxicity (12). Cefoxitin is an analogue of cephamycin C, with considerably heightened antibacterial potency (18) and greater resistance to cephalosporinase inactivation (14). Its structure closely resembles that of cephalothin, with two significant differences: a methoxy group (rather than a hydrogen atom) in the 7-α position, and a carbamyloxy (rather than acetoxy) substituent at the 3-methyl position.

The tolerance of volunteers to intravenous cefoxitin, and the effects of different rates of infusion and prior probenecid treatment on serum levels and renal excretion were the subjects of the present study. Other volunteers also received cephalothin under the same conditions, and all samples were assayed in one batch to allow direct comparison with a well-known antibiotic. The sensitivities of currently isolated hospital strains of pathogenic gram-negative bacilli other than *Pseudomonas* to cefoxitin and cephalothin are reported.

MATERIALS AND METHODS

Study drugs. Sodium cefoxitin for injection was supplied in vials containing the equivalent of 1 g of cefoxitin. Immediately before injection, the drug was reconstituted with 10 ml of sterile distilled water. Vials of cephalothin sodium (Keflin), containing the equivalent of 1 g of cephalothin, were similarly reconstituted. Probenecid sodium (intravenous) was used in the form of ampoules of 10% solution containing 1 g of probenecid.

Volunteers. Twelve normal adult males, junior

medical staff of this hospital, without clinical or laboratory evidence of renal, hepatic, cardiac, pulmonary, hematologic, or infectious disease, and who had not received drugs during the previous 30 days, participated in the trials. In addition, the senior author received 1 g of cefoxitin intravenously over 3 min without clinical or laboratory evidence of toxicity. The 12 volunteers were listed in order of weight and, using a system of random permutation in sets of two, were assigned to receive either cefoxitin or cephalothin. The mean weight of those receiving cefoxitin was 69.6 kg, and of those receiving cephalothin, 68.8 kg.

The members of each group received their assigned antibiotic intravenously in 1-g doses at weekly intervals for 4 weeks. The reconstituted antibiotic was diluted in saline and the infusion was given over 120 or 30 min, or it was undiluted and given over 3 min; this last rate of infusion was with or without prior intravenous injections of probenecid (1 g). The order of infusion regimens was randomized and balanced. The antibiotic was infused at 0800 h, the subject having fasted for at least 8 h. Oral probenecid is well absorbed and produces high serum concentrations (3), but to achieve standardized conditions, 1 g of probenecid sodium was diluted in 100 ml of saline and was infused intravenously over 30 min; 30 min later, either cefoxitin or cephalothin was infused over 3 min. Immediately before each infusion of antibiotic, and 2 days after the infusion, blood and urine samples were taken for safety studies in England and the U.S.A. Urine specimens were cultured for bacteria, examined for the presence of leucocytes, erythrocytes, casts, protein, and glucose, and their pH and osmolality were determined. Throat swabs were taken for culture. The following hematologic and biochemical parameters were ascertained: hematocrit, hemoglobin, erythrocyte morphology, platelets, the concentrations and distribution of blood leucocytes, serum creatinine, blood urea nitrogen, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total bilirubin, lactic dehydrogenase, and antistreptolysin titer.

Collection of specimens for antibiotic assay. A sterile indwelling intravenous catheter, approximately 8 inches (20.32 cm) in length, was inserted into the cubital vein of the forearm opposite to that used for the infusions; from this catheter, blood samples were withdrawn before each infusion and at varying times after, depending on the rate of infusion (see Tables 1 to 6, 13, 14). Urine output was measured, samples were taken hourly up to 4 or 6 h, and then the sample passed up to 12 h after the infusion was collected. The blood was allowed to clot at room temperature; the serum was removed and, with portions of the urine samples, was stored at −20 C until just before assay. Antibiotic assays were performed at the Merck Sharp and Dohme Research Laboratories, West Point, Pa. All serum samples for safety studies were tested at one time.

Antibiotic assay. Cefoxitin activity was measured by the cup-plate diffusion technique using *Staphylococcus aureus* MB 2876 as the test organism. Nutrient agar (Difco) supplemented with 0.2% yeast extract (General Biochemicals) was used for both the 15-ml base and 4-ml seed layers. The reference standard was a concentration of 5 μg/ml. In the assays of serum, pooled human serum was used to dilute both standards and samples. In urine assays, standards and samples were diluted with pH 6.0 phosphate buffer. A modified Shaw cup dispenser was used to drop six evenly spaced cylinders on each assay plate. Seeded, cupped plates were refrigerated until the samples were introduced into cups. Three cups on duplicate plates were filled alternately with each sample dilution and reference standard. Plates were incubated at 37 C for 18 h, cups were removed, and the plates were kept refrigerated until measurement of the diameter of the zones of inhibition was made by using a Fisher-Lilly antibiotic zone reader. Activity of the samples was calculated in terms of standard activity.

Cephalothin samples were assayed in a similar manner except that the test organism was *S. aureus* ATCC 6538P. The reference standard for serum was 2 μg/ml and for urine, 1 μg/ml.

Assay of urinary metabolites. Selected specimens of urine were assayed for cefoxitin, cephalothin, and their respective deacylated analogues by an anion-exchange liquid chromatography technique (unpublished data) at pH 5 to 6 on SAX resin (DuPont) by using a UV monitor under high performance conditions. Quantitation was achieved by reference to a curve prepared with the use of appropriate standard solutions. The method reliably detects concentrations of cefoxitin, cephalothin, and desacetyl-cephalothin between 20 and 500 μg/ml. The lower limit of susceptibility for detection of descarbamyl cefoxitin is either 20 μg/ml or 0.15% of the concentration of concurrently present cefoxitin, whichever is higher. Serum levels of descarbamyl cefoxitin could not be detected by this method. (This assay was kindly performed by F. J. Wolf and co-workers, Merck Sharp & Dohme Research Laboratories, Rahway, N.J.)

RESULTS

Serum concentrations. After an infusion of cetoxitin (1 g) over 3 min (Fig. 1), the mean (and range) of peak concentrations was 124 μg/ml (72 to 272 μg/ml; Table 1), and with 1 g of cephalothin it was 102 μg/ml (72 to 177 μg/ml) (Table 2). After 1 h, the mean cefoxitin concentration was 12 μg/ml, whereas that of cephalothin was 6 μg/ml. With an infusion of 1 g over 30 min (Fig. 2), the mean (and range) of peak concentrations of cefoxitin was 74 μg/ml (44 to 110 μg/ml; Table 3) and with cephalothin it was 56 μg/ml (41 to 68 μg/ml; Table 4). In all volunteers receiving cefoxitin, the concentration of antibiotic was >14 μg/ml after 1 h. With an infusion of 1 g over 120 min (Fig. 3), the mean (and range) of peak concentrations of cefoxitin was 27 μg/ml (21 to 34 μg/ml; Table 5) and with cephalothin it was 23 μg/ml (19 to 31 μg/ml; Table 6).

Terminal serum half-lives of cefoxitin and of

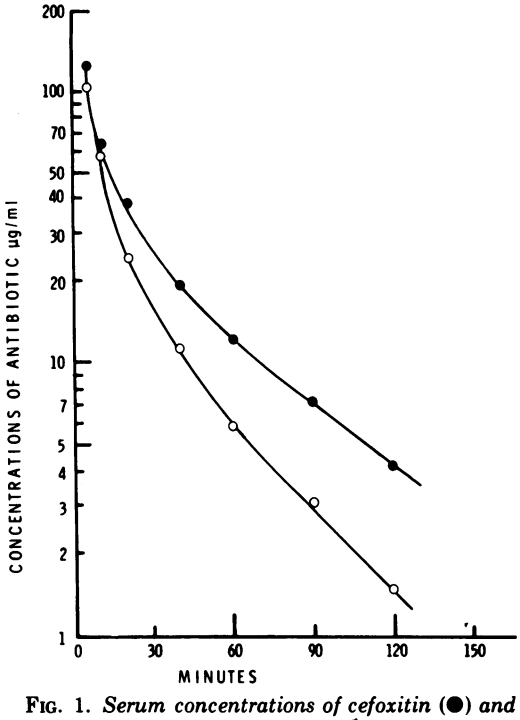


FIG. 1. *Serum concentrations of cefoxitin (●) and cephalothin (○) (mean of six volunteers) after 1 g of each over 3 min.*

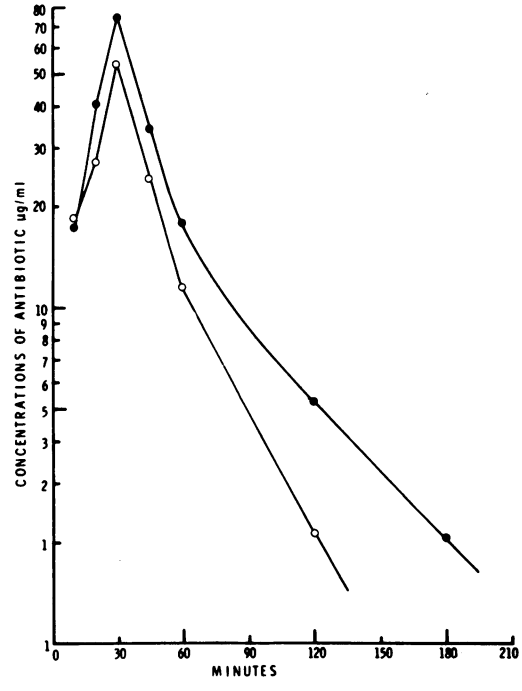


FIG. 2. *Serum concentrations of cefoxitin (●) and cephalothin (○) (mean of six volunteers) with 1 g of each over 30 min.*

TABLE 1. *Serum concentrations of cefoxitin after 1-g intravenous infusions over 3 min*

Volunteer	Dose (mg/kg)	Serum concn (µg/ml)									
		5[a]	10	20	40	60	90	120	180	240	360
1	17.5	272.00	82.80	53.90	32.10	19.76	11.20	5.19	2.23	<1.0	<1.0
4	15.9	93.60	75.00	54.60	21.90	16.40	8.90	5.30	3.25	<1.0	<1.0
6	14.7	72.40	41.40	24.92	12.60	8.60	4.00	3.08	<1.0	<1.0	<1.0
8	13.9	78.00	49.92	31.36	15.54	9.70	6.10	3.92	<1.0	<1.0	<1.0
9	13.3	86.20	58.44	35.70	18.90	10.40	7.65	4.45	2.48	<1.0	<1.0
12	12.1	146.40	69.36	31.50	13.89	7.68	5.50	3.30	<1.0	<1.0	<1.0
Mean	14.6	124.77	62.82	38.66	19.16	12.09	7.23	4.21	<1.83	<1.0	<1.0

[a] Minutes.

TABLE 2. *Serum concentrations of cephalothin-like antibacterial activity after 1-g intravenous infusions over 3 min*

Volunteer	Dose (mg/kg)	Serum concn (µg/ml)									
		5[a]	10	20	40	60	90	120	180	240	360
2	16.7	177.00	49.05	20.00	10.92	5.00	2.22	1.35	<1.0	<1.0	<1.0
3	15.9	68.40	50.70	27.80	13.14	5.56	3.90	1.57	<1.0	<1.0	<1.0
5	15.4	113.10	70.50	25.50	10.44	6.06	2.92	1.28	<1.0	<1.0	<1.0
7	14.3	96.00	72.15	26.80	10.23	5.22	3.10	1.46	<1.0	<1.0	<1.0
10	13.0	84.30	58.95	22.00	11.25	7.88	3.90	2.02	<1.0	<1.0	<1.0
11	12.8	72.00	48.45	25.30	11.70	5.62	2.63	1.33	<1.0	<1.0	<1.0
Mean	14.7	101.80	58.30	24.57	11.28	5.89	3.11	1.50	<1.0	<1.0	<1.0

[a] Minutes.

TABLE 3. *Serum concentrations of cefoxitin after 1-g intravenous infusions over 30 min*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)								
		10[a]	20	30	45	60	120	180	240	360
1	17.5	21.50	60.50	90.00	29.10	17.80	3.71	<1.0	<1.0	<1.0
4	15.9	22.00	55.50	85.00	42.00	16.40	7.90	3.25	1.55	<1.0
6	14.7	18.10	38.50	56.50	31.20	19.30	5.35	2.04	<1.0	<1.0
8	13.9	19.00	26.25	61.00	28.35	15.90	4.05	1.80	<1.0	<1.0
9	13.3	16.80	19.00	32.00	44.40	22.40	5.88	2.98	1.57	<1.0
12	12.1	5.85	39.50	109.50	27.90	14.40	4.50	1.78	<1.0	<1.0
Mean	14.6	17.21	39.88	72.33	33.83	17.70	5.23	<2.14	<1.19	<1.0

[a] Minutes.

TABLE 4. *Serum concentrations of cephalothin-like antibacterial activity after 1-g intravenous infusions over 30 min*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)								
		10[a]	20	30	45	60	120	180	240	360
2	16.7	34.00	25.00	68.00	28.80	13.70	2.35	<1.0	<1.0	<1.0
3	15.9	27.50	37.40	53.20	28.08	14.55	2.34	<1.0	<1.0	<1.0
5	15.4		41.00	31.00	15.20	8.60	1.05	<1.0	<1.0	<1.0
7	14.3	9.35	30.50	51.60	25.20	11.25	1.84	<1.0	<1.0	<1.0
10	13.0	18.00	24.70	57.60	28.08	17.80	3.24	<1.0	<1.0	<1.0
11	12.8	<1.00	4.92	62.00	36.00	3.92	1.88	<1.0	<1.0	<1.0
Mean	14.7	<17.97	27.25	53.90	26.89	11.64	2.12	<1.0	<1.0	<1.0

[a] Minutes.

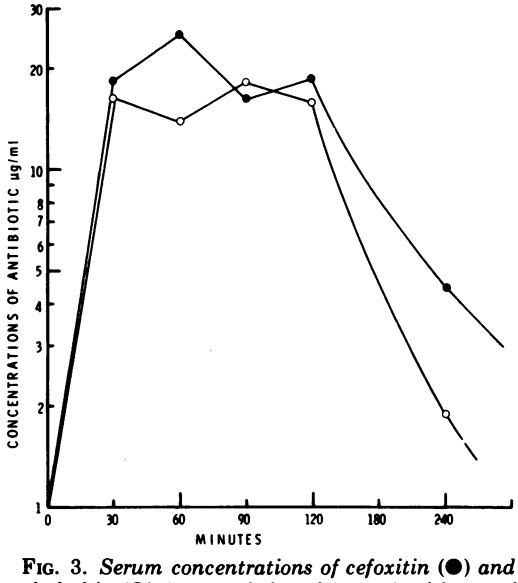


FIG. 3. *Serum concentrations of cefoxitin (●) and cephalothin (○) (mean of six volunteers) with 1 g of each intravenously over 120 min.*

cephalothin-like activity were obtained for the 3-min infusion. The mean serum half-life of cefoxitin was 41 min, with a range of 38 to 55 min; and of cephalothin-like activity, 31 min, with a range of 26 to 42 min (Table 7).

Serum concentrations of cefoxitin were best fitted by a two-compartment open model. Pharmacokinetic parameters were obtained graphically and were found to predict adequately the time course of urinary excretion. The mean rate constants for distribution (k_{12}, k_{21}) and elimination (k_{13}), and the apparent volume of distribution, are shown in Table 8.

Because it was not known which fraction of the cephalothin-like activity, observed in specimens of serum and urine obtained after cephalothin administration, represented unchanged drug and which fraction represented metabolite, pharmacokinetic modeling of cephalothin was not attempted.

Urinary excretion. Renal clearance of cefoxitin under the four infusion conditions is shown in Table 9. Urinary recoveries of cefoxitin were 74, 80, and 76%, respectively, for the 3-, 30-, and 120-min infusions. Urinary recoveries of cephalothin-like activity were 50, 49, and 45%, respectively, for the 3-, 30-, and 120-min infusions (Table 10).

Semilogarithmic plots of the amount to be excreted in the urine versus time for the 3-min

TABLE 5. *Serum concentrations of cefoxitin after 1-g intravenous infusions over 120 min*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)							
		30[a]	60	90	120	180	240	300	360
1	17.5	33.60	24.00	17.70	12.00	3.12	<1.0	<1.0	<1.0
4	15.9	32.40	28.20	25.05	19.20	5.35	2.28	<1.0	<1.0
6	14.7	5.85	28.50	18.06	28.05	4.31	1.73	<1.0	<1.0
8	13.9	18.90	23.70	9.30	18.30	4.05	1.80	<1.0	<1.0
9	13.3	2.52	24.75	14.49	18.75	7.10	3.41	1.92	<1.0
12	12.1	16.74	21.00	11.94	14.88	3.06	<1.0	<1.0	<1.0
Mean	14.6	18.34	25.03	16.09	18.53	4.50	<1.87	<1.15	<1.0

[a] Minutes.

TABLE 6. *Serum concentrations of cephalothin-like antibacterial activity after 1-g intravenous infusions over 120 min*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)							
		30[a]	60	90	120	180	240	300	360
2	16.7	14.00	15.50	18.60	10.00	1.55	<1.0	<1.0	<1.0
3	15.9	20.00	16.50	14.35	13.20	2.37	<1.0	<1.0	<1.0
5	15.4	17.95	18.25	22.20	17.00	1.28	<1.0	<1.0	<1.0
7	14.3	5.75	9.70	6.70	20.75	1.80	<1.0	<1.0	<1.0
10	13.0	30.75	12.00	23.75	18.00	1.85	<1.0	<1.0	<1.0
11	12.8	9.55	11.55	23.75	15.00	2.70	<1.0	<1.0	<1.0
Mean	14.7	16.33	13.92	18.23	15.66	1.93	<1.0	<1.0	<1.0

[a] Minutes.

TABLE 7. *Terminal serum half-lives of antimicrobial activity after 3-min intravenous infusions of cefoxitin and cephalothin with and without prior probenecid treatment*

Cefoxitin[a]			Cephalothin[a]		
Subject	No probenecid	Probenecid	Subject	No probenecid	Probenecid
1	38[b]	78	2	42	64
4	42	85	3	34	64
6	38	75	5	26	48
8	38	82	7	28	60
9	55	117	10	30	60
12	40	72	11	30	60
Harmonic mean	41	83	Harmonic mean	31	59

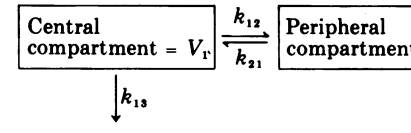
[a] 1 g.
[b] Terminal serum half-life (minutes).

infusion were prepared for each subject. Half-times for excretion were taken from the log-linear portion (0 to 2 h) of the curve. The mean half-time for urinary excretion of cefoxitin was 40 min, and for cephalothin-like activity, 32 min (Table 11). These half-times are in agreement with the terminal serum half-lives found for the 3-min infusion (Table 7).

TABLE 8. *Mean pharmacokinetic parameters for cefoxitin 3-min intravenous infusion*[a]

Tissue distribution rate constants (per min)		Elimination rate constant k_{13} (per min)	Volume of distribution V_1 (liters)
k_{12}	k_{21}		
0.0414	0.0405	0.0471	8.12

[a] Two-compartment model:



Urinary metabolites. Studies of selected urine samples suggested that cefoxitin was deacylated to detectable amounts of descarbamyl-cefoxitin only in some subjects; the metabolite was found only in the later hours, to the extent of less than 2% of the dose. In contrast, cephalothin was deacylated rapidly to desacetyl cephalothin, even during the first

TABLE 9. *Renal clearance of antimicrobial activity after cefoxitin administration*

Subject	Treatment[a]	Clearance (ml per min per 1.73 m²)			
		0 to 1[b]	0 to 2	0 to 3	0 to 4
1	A	144.5	163.9	165.5	
	B	78.4	76.3	81.6	81.3
	C	262.2	281.5		
	D	206.2	246.9	267.4	
4	A	268.4	267.1	259.1	
	B	64.1	42.1	56.4	58.8
	C	264.1	206.2	250.0	250.0
	D	216.5	225.1	204.8	206.3
6	A	279.6	304.2		
	B	107.4	98.1	97.1	96.2
	C	272.5	260.5	260.2	
	D	136.1	260.0	237.5	238.0
8	A	417.9	391.9		
	B	101.0	96.2	91.8	93.2
	C	325.4	315.0	308.1	
	D	230.3	295.4	295.1	290.5
9	A	256.8	253.8	252.1	
	B	82.9	64.5	68.0	68.6
	C	267.3	294.7	283.6	279.1
	D	122.7	343.8	315.5	304.7
12	A	302.0	305.6		
	B	73.6	80.3	84.4	85.2
	C	253.2	252.4	251.8	
	D	275.0	338.7	315.5	
Mean	A	278.2	281.1	225.6	
	B	84.6	76.2	79.9	80.6
	C	274.1	268.4	270.7	264.6
	D	197.8	285.0	272.6	259.9

[a] A, 3-min infusion; B, 3-min infusion with prior probenecid; C, 30-min infusion; D, 120-min infusion.
[b] Hours after start of infusion.

hour after the dose, to the extent of about 20 to 25% of the dose (Table 12).

Effect of probenecid. Prior probenecid treatment had a marked effect (Fig. 4), maintaining the mean serum concentration of cefoxitin after 3 h to 17.2 μg/ml (Table 13), but for cephalothin it was maintained to only 5.6 μg/ml (Table 14). This effect of probenecid can be most useful because the minimum inhibiting concentration for most strains of susceptible bacteria is ≦12 μg of cefoxitin per ml.

The mean terminal serum half-life of cefoxitin without prior probenecid treatment was 41 min, and after probenecid treatment it was 83 min. Probenecid prolonged the mean terminal serum half-life of cephalothin-like activity (31 min) to 59 min (Table 7).

Urinary excretion after probenecid treatment averaged 68% for cefoxitin, with concentrations in the urine remaining high for 4 h. Urinary excretion of cephalothin-like activity averaged 50% after procenecid treatment (Table 10).

Prior administration of probenecid appeared to increase the deacylation of cephalothin moderately in two subjects; the effect of prior probenecid treatment on the deacylation of cefoxitin in three subjects was not determined (Table 12).

Volunteer tolerance. Of all the biochemical safety studies, the only abnormally high value observed was in one volunteer receiving cephalothin, 2 days after his third dose, when his blood urea nitrogen was 40 mg per 100 ml (normal range is 5 to 25 mg per 100 ml). The same volunteer had a blood leucocyte count of

TABLE 10. *Mean urinary recovery of cefoxitin and cephalothin-like activity after intravenous infusions under various conditions*

Drug (1 g)	Treatment[a]	Mean urinary recovery					
		0 to 1[b]	1 to 2	2 to 3	3 to 4	4 to 12	Total
Cefoxitin	A	546	127	38	15	16	741
	B	305	135	103	65	77	685
	C	542	174	45	19	20	800
	D	185	364	137	44	33	763
Cephalothin	A	445	38	9	3	3	498
	B	328	98	40	19	13	498
	C	420	53	13	4	3	493
	D	162	233	39	7	5	447

[a] A, 3-min infusion; B, 3-min infusion with probenecid; C, 30-min infusion; and D, 120-min infusion.
[b] Hours after start of infusion.

TABLE 11. *Half-times for urinary excretion of antimicrobial activity after 3-min intravenous infusions of cefoxitin and cephalothin*

Cefoxitin (1 g)		Cephalothin (1 g)	
Subject	Half-time (min)	Subject	Half-time (min)
1	30	2	30
4	40	3	35
6	36	5	35
8	45	7	32
9	50	10	30
12	42	11	32
Harmonic mean	40	Harmonic mean	32

TABLE 12. *Liquid chromatographic analysis of cefoxitin, cephalothin, and their deacylated metabolites in the urine specimens of five subjects*

Subject	Treatment[a]	Compound (1 g)[b]	Percentage of dose[c]					Total recovered	
			0 to 1[d]	1 to 2	2 to 3	3 to 4	4 to 12	0 to 4	0 to 12
4	A	CFX	64	15	3.6	2.5	ND	85.1	
		DCFX	<1.0	<0.3	<0.1	<0.1	ND	<1.4	
	B	CFX	28	NS	19	12.3	16.5	59.3	75.8
		DCFX	<0.4	NS	<0.3	<0.2	4.1	<0.9	4.1 to <5.1
6	A	CFX	51	NS	3.3	2.2	ND	56.5	
		DCFX	<0.8	NS	<0.1	0.6	ND	0.6 to <1.5	
	B	CFX	37	15.8	12.5	4.7	8.5	70.0	78.5
		DCFX	<0.6	<0.3	<0.2	<0.1	4.6	<1.2	4.6 to <5.8
9	A	CFX	59	12.8	4.4	2.4	ND	78.6	
		DCFX	<0.9	<0.2	<0.1	<0.1	ND	<1.2	
	B	CFX	32	15.6	12.8	6.0	13.8	76.4	80.2
		DCFX	<0.5	<0.3	<0.2	<0.1	2.5	<1.1	2.5 to <3.6
3	A	CEPH	39.5	2.3	0.9	3.8	ND	46.5	
		DCEPH	13.8	3.5	1.0	4.0	ND	22.3	
	B	CEPH	30.6	8.2	1.7	0.9	ND	41.4	
		DCEPH	13.5	9.2	2.6	1.6	ND	26.9	
5	A	CEPH	48.2	2.8	0.3	0.3	ND	51.6	
		DCEPH	17.3	4.5	0.7	0.5	ND	23.0	
	B	CEPH	31.9	8.1	3.3	1.0	ND	44.3	
		DCEPH	13.5	9.4	5.2	2.5	ND	30.6	

[a] A, 3-min infusion; B, 3-min infusion with probenecid (1 g).
[b] CFX, Cefoxitin; DCFX, descarbamyl cefoxitin; CEPH, cephalothin; and DCEPH, desacetyl cephalothin.
[c] ND, Not done; NS, no specimen.
[d] Hours after infusion.

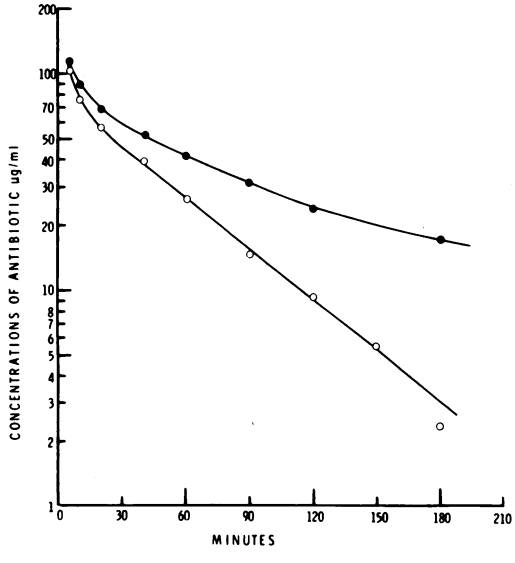


FIG. 4. *Serum concentrations of cefoxitin (●) and cephalothin (○) (mean of six volunteers) after 1 g of each over 3 min preceded by 1 g of probenecid intravenously.*

3,700 per µliter 2 days after his third dose, and on three occasions he had leucocytes in the urine, but the urine was sterile. One volunteer receiving cefoxitin had a very small number of leucocytes in his urine before receiving his first dose of cefoxitin. A severe headache lasting for 8 h was experienced on two occasions by one volunteer receiving cephalothin. Intravenous probenecid treatment was not associated with any abnormal values. All volunteers were carefully observed for systemic symptoms of hypotension and any feeling of weakness, but none were observed during the infusions. The veins used for the infusions did not show signs of phlebitis.

In vitro susceptibility tests. Three hundred strains of gram-negative bacilli, other than *Pseudomonas* spp., isolated from clinical specimens at Northwick Park Hospital during 1973 were tested for susceptibility to cephalosporins and cefoxitin by disk diffusion. The comparative method with a test organism on a separate plate, and a standardized inoculum producing semiconfluent growth (17), was used with disks of cephalothin (30 µg) and cefoxitin (30 µg). Of

TABLE 13. *Serum concentrations of cefoxitin after 1-g intravenous infusion (3 min) with prior probenecid (1 g) treatment*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)									
		5[a]	10	20	40	60	90	120	180	240	360
1	17.5	155.25	121.80	97.60	61.00	48.00	37.08	29.97	21.00	10.80	3.90
4	15.9	121.25	96.88	81.60	68.80	47.78	36.72	31.68	26.00	15.80	5.02
6	14.7	110.50	81.90	56.50	41.00	34.50	32.50	23.60	13.70	6.60	2.09
8	13.9	102.50	79.80	58.56	49.60	40.20	33.20	24.80	15.50	9.60	3.30
9	13.3	102.50	73.08	58.40	46.80	34.95	30.45	25.40	15.90	9.75	4.10
12	12.1	100.00	81.90	60.80	49.20	36.90	28.30	19.50	11.00	5.30	1.87
Mean	14.6	115.33	89.23	68.91	52.73	40.39	33.04	25.83	17.18	9.64	3.38

[a] Minutes.

TABLE 14. *Serum concentrations of cephalothin-like antibacterial activity after 1-g intravenous infusion (3 min) with prior probenecid (1-g) treatment*

Volunteer	Dose (mg/kg)	Serum concn (μg/ml)									
		5[a]	10	20	40	60	90	120	180	240	360
2	16.7	89.10	60.50	56.20	37.50	26.28	13.94	8.47	5.80	2.20	<1.0
3	15.9	119.70	83.25	54.00	38.70	28.20	16.65	11.48	4.48	2.54	<1.0
5	15.4	145.20	97.50	76.60	46.65	33.48	18.54	10.29	6.35	2.02	<1.0
7	14.3	105.60	86.50	54.80	37.50	21.12	11.61	8.61	5.95	2.44	<1.0
10	13.0	70.80	58.25	48.80	39.45	25.68	13.14	9.80	4.52	2.15	<1.0
11	12.8	87.90	69.50	49.00	36.75	21.72	14.63	8.40	6.24	2.55	<1.0
Mean	14.7	103.05	75.92	56.60	39.43	26.08	14.75	9.51	5.56	2.32	<1.0

[a] Minutes.

the isolates, 83% were found to be susceptible to cephalothin and 95% susceptible to cefoxitin; isolates resistant to cephalothin and susceptible to cefoxitin included strains of *Escherichia coli*, *P. vulgaris*, *Klebsiella* spp., *Serratia marcescens*, *Enterobacter* spp., and *Bacteroides* spp. (Table 15).

TABLE 15. *Disk-diffusion susceptibility of gram-negative hospital pathogens to cephalothin and cefoxitin*

Organism	No. studied	Cephalothin susceptibility		Cefoxitin susceptibility	
		No.	%	No.	%
Escherichia coli	153	133	86.9	149	97.4
Klebsiella spp.	66	55	83.3	57	86.4
Proteus mirabilis	54	54	100	54	100
Proteus vulgaris	11	4	36.4	11	100
Proteus morganii	4	0	0	4	100
Enterobacter spp.	2	0		2	
Alcaligenes spp.	3	1		1	
Serratia marcescens	2	0		2	
Alkalescens-dispar	1	1		1	
Bacteroides spp.	4	1	25	4	100
Total	300	249	83	285	95

DISCUSSION

The data in this study show that intravenous doses of cefoxitin produce higher and more prolonged blood concentrations than do equal doses of cephalothin. In view of evidence (unpublished data) that cefoxitin and cephalothin bind equally to human plasma proteins, this difference in serum levels is probably due primarily to the rapid metabolism of cephalothin to the desacetyl form with its lower antimicrobial activity (19), compared to the much lesser degree of metabolism of cefoxitin to the virtually inactive descarbamyl form.

Because the large majority of strains of gram-positive and gram-negative bacteria susceptible to cefoxitin possess minimum inhibitory concentrations of ≤ 12 μg/ml, and because the three speeds of infusion produced blood levels of cefoxitin in excess of this concentration, it is evident that there probably exists a wide latitude in the way in which cefoxitin may be administered intravenously in the treatment of

infections. Whether or not any particular speed of infusion will demonstrate superior efficacy or tolerance remains to be determined. Clinical experience with cephalothin has largely borne out the observation that, within a given dose range, one method of multiple-dose intravenous administration has not proved clinically superior to any other (6).

Intravenous probenecid treatment produced no ill effects, confirming other studies (3, 10), and it greatly delayed the excretion of both antibiotics.

In this study, cefoxitin appeared to be completely nontoxic, but clinical studies with frequent doses will be required to evaluate this aspect further.

A significantly higher proportion of hospital isolates of gram-negative bacilli, including *Bacteroides* spp., appeared to be more susceptible to cefoxitin than to cephalothin. Initial, presumptive treatment of septicemia, before the susceptibilities of possible pathogens are known, would thus be much more reliably undertaken with cefoxitin than with cephalothin. Cefoxitin is the first clinically available bactericidal antibiotic active against both aerobic gram-negative bacteria and *Bacteroides*. Thus, the need to add lincomycin or clindamycin to standard anti-gram-negative therapy (2) may be avoided. Cefoxitin could become an antibiotic of exceptional value in septicemia, in postoperative infection in general surgery and gynecology, and in bacteremic and septicemic babies.

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