ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1974, p. 290-299

Vol. 6, No. 3.
Printed in U.S.A.

Cefoxitin and Cephalothin: Antimicrobial Activity, Human Pharmacokinetics, and Toxicology

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Received for publication 12 April 1974

Cefoxitin, a semisynthetic cephamycin, has been compared with the widely used parenteral cephalosporin, cephalothin, in terms of antibacterial activity, human pharmacokinetics, and toxicity. For both compounds, minimal inhibitory concentrations were within the therapeutic range against the 156 gram-positive cocci tested (except group D streptococci), but cephalothin was 8 to 20 times more active. Regarding the 313 gram-negative organisms tested, both antibiotics were of approximately equal activity against cephalothin-susceptible strains, but cefoxitin was outstandingly superior against *Providencia* spp. and indole-producing *Proteus* spp., and markedly better against *Serratia marcescens* and *Bacteroides fragilis*. Against these organisms, cefoxitin but not cephalothin would be expected to be therapeutically valuable. Antibiotic activity levels in the serum and urine of 18 human volunteers after parenteral administration were higher and more prolonged in the case of cefoxitin, which had an average terminal serum half-life of about 45 min and a urinary recovery of about 90%. Cefoxitin was entirely nontoxic and, given intramuscularly, slightly less painful then cephalothin. These preliminary results suggest that cephamycins may prove to be a significant chemotherapeutic advance.

Recent developments in the field of the cephalosporins have included permutations of a variety of sidechains in both the 3 and 7 positions of the 7-amino-cephalosporanic acid nucleus. Examples of such new products are cefazolin, cephradine, cephacetrile, and cephanone. However, on the basis of the evidence available, it is difficult to conclude that any of these compounds represents a significant advance, although cefazolin and cephradine have been released for clinical use. In contrast to these semisynthetic cephalosporins, a radical new departure in this field has recently been reported, namely, the discovery of the cephamycin family, which, although closely related to the cephalosporins, is a distinct entity (8, 10). Cephamycins are differentiated by their possession of a 7-α-methoxy group and 3-carbamoyl moiety (1). Cephamycin C has been chemically modified to yield the semisynthetic compound cefoxitin, which is structurally analogous to cephalothin (Fig. 1). In view of the interesting properties of cephamycin C, especially its stability to a variety of β-lactamases (3), it was of obvious interest to investigate the properties of cefoxitin, both in terms of in vitro antibacterial activity and of bioavailability. Because cephalothin is the structural analogue of cefoxitin, we thought that comparison of these two compounds was most appropriate.

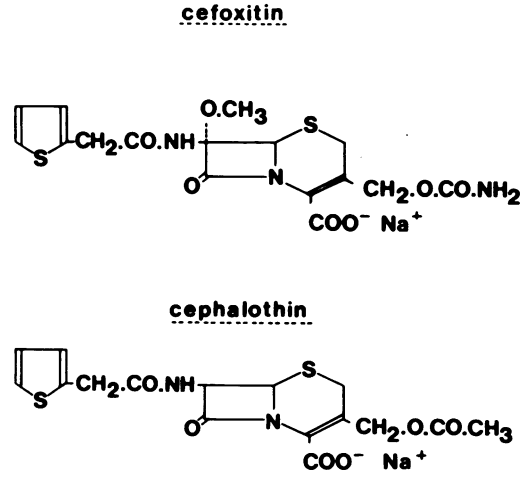

FIG. 1. *Structure of cefoxitin and cephalothin.*

This study was presented in part at the 13th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 19 to 21 September 1973.

MATERIALS AND METHODS

Bacterial strains. Apart from those mentioned below; the strains tested for susceptibility to cefoxitin and cephalothin had been isolated from clinical material sent to the routine laboratories of the Royal Free Hospital during 1973. Isolation was carried out by standard methods, and identification was based on the recommendations of Cowan and Steel (2). The Royal Free is a general hospital, and thus the bacterial isolates came from a wide range of sources, including both out- and in-patients. Fourteen indole-producing proteus and two providencia strains were isolated, and, in view of the superior activity of cefoxitin against such organisms (4), it was thought important to investigate these particular organisms more closely. Consequently, 68 further strains of indole-positive *Proteus* spp. were kindly supplied by M. T. Parker and T. L. Pitt of the Cross-Infection Reference Laboratory, Colindale, London. The histories and clinical origin of the strains were examined to exclude, as far as possible, the chance of using multiple isolates of the same strain. Three additional providencia strains, originally obtained from K. E. Price as examples of aminoglycoside-resistant organisms, were also included.

Fifteen strains of *Serratia marcescens* were sent by L. D. Sabath, who isolated them at Boston City Hospital. Twenty-six *Bacteroides fragilis* strains were obtained in all, six from B. S. Drasar, four from the National Collection of Type Cultures, four (specific substrains var. *vulgatus*, *fragilis*, *distasonis*, and *thetaiotaomicron*) from the Center for Disease Control, Atlanta, Ga., and the remainder from A. Percival.

The 126 additional strains referred to in the two previous paragraphs, thus, cannot necessarily be taken as being representative of British hospital flora.

Minimal inhibitory concentrations. Aerobic organisms were incubated overnight at 37 C in brain heart infusion broth; when streptococci were tested, 4% lysed horse blood was added. In the case of the anaerobic strains, cooked meat medium was used, and incubation was for 42 h. All cultures were diluted 1:100 in water before use.

Serial doubling dilutions of cefoxitin or cephalothin were incorporated into brain heart infusion agar (15 ml of medium per an 8.5-cm diameter plate); 4% lysed horse blood was added when streptococci or *Bacteroides* spp. were tested. Appropriate dilutions of antibiotic were used (see Table 1 and 2). Plates were inoculated by streaking radially with a 4-mm loop; a maximum of 12 strains were tested on the same plate. Plates were incubated at 37 C overnight, except the *Bacteroides* spp. strains, for which the period of incubation was extended to 48 h using the GasPak (BBL) anaerobic system. When the *Proteus* spp. strains were under investigation, to surmount the problem caused by swarming, divided dishes (10 cm square, 25 compartments) were used and inoculated with individual drops of 0.02 ml of diluted culture.

Screening of volunteers. Eighteen healthy male human subjects, aged 21 to 37 years, volunteered to take part in the pharmacokinetic study. The presence of renal, hepatic, cardiac, pulmonary, hematological, or other systemic diseases was excluded on the basis of medical history, physical examination, and the following laboratory tests: hematocrit; total and differential white blood count; platelet estimation; leukocyte and erythrocyte as well as platelet morphology; blood urea; total serum bilirubin; serum alkaline phosphatase, aspartate aminotransferase, and urine microscopy; specific gravity; pH; protein; and glucose. Volunteers with a history of allergy to any of the penicillins or cephalosporins were excluded. No medication was taken during the 3 days prior to and throughout the study.

Bioavailability study design. The trial was an open balanced study. The subjects were divided into two groups in a random way, and each received three injections of either cephalothin or cefoxitin under identical circumstances. The injections were given at 7-day intervals, and the three dosages received by each volunteer were 0.5 and 1.0 g given intramuscularly and 2.0 g given intravenously as a bolus injection over a 3-min period. Each individual received the dosages in a random order. Blood was collected before and at 10, 20, 30, 45, 60, 120, 180, 240, and 360 min after each intramuscular dose, and before and at 5, 10, 20, 40, 60, 90, 120, 180, 240, and 360 min after the intravenous dose. Urine was collected from 1 h before injection up to injection time and then 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 6, and 6 to 12 h after each intramuscular injection, and 0 to 1, 1 to 2, 2 to 3, 3 to 4, and 4 to 12 h after the intravenous injection. Crossover studies were avoided so that any toxicity to the individual drug could be assessed.

Antibiotic assay. The concentrations of cefoxitin and cephalothin in blood and urine samples were estimated by bioassay using a disk-plate method. Brain heart infusion agar, in 98-ml amounts seeded with 2 ml of a static 37 C overnight brain heart infusion broth culture of *Staphylococcus aureus* MB-2786 (kindly supplied by C. M. Martin), were poured into 23-cm square assay plates (Nunc-Bio, Copenhagen). A maximum of 42 filter paper antibiotic assay disks (Whatman; 6 mm in diameter) were placed on each plate. Appropriate dilutions of standards or samples to be assayed were imbibed into each disk by capillarity. Each disk was found, by weighing, to take up an average of 20 μliters. Plates were incubated overnight, and zones of inhibition were measured to the nearest 0.1 cm with the help of calipers or an overhead projection device. Serum samples were diluted with, and standards for serum assays made up in, pooled reconstituted citrated human plasma, whereas for urine samples and standards for urine assays the diluent was phosphate buffer, pH 6.0 (88 ml of 66.7 mM KH_2PO_4 + 12 ml of 66.7 mM Na_2HPO_4);, in each case the concentrations of standards were 50, 25, 12.5 and 6.3 μg/ml. Preliminary experiments showed that the plots were linear down to 3 μg/ml and that the lower limit of detection of either antibiotic was in the region of 2 μg/ml.

Serum samples from each profile were assayed using one entire plate; another plate was used to assay the urine samples from the same profile. Each plate

carried three sets of standards; serum and urine samples were diluted and assayed in triplicate.

Pharmacokinetic analysis. The area under the serum concentration curve was calculated by cutting off the piece of graph paper included between the curve and the x axis, by weighing it, and by comparing it with the weight of an appropriate calibration area.

Terminal serum half-life, which can be defined as the time required for the amount of unchanged drug in the serum to be reduced to one-half its value after equilibrium is established, was calculated from the serum concentration curves obtained after intravenous injection.

Distribution constants for a two-compartment open model (11) were calculated: k_{12} was the first-order constant of the rate of distribution from the first to the second compartment, whereas k_{21} was the corresponding constant for the distribution from the second to the first compartment. k_{el} was the first-order rate constant for overall elimination from the first compartment, whereas V_1 was the apparent volume of this compartment. The above parameters were estimated by using the methods recommended by Wagner (11) and were refined on the basis of how well serum data predicted urinary excretion (6). For the intramuscular doses, V_1 and k_{el} were calculated by using a pharmacokinetic modification of the model-independent method of Kwan and Till (5).

Side effects. All of the volunteers were closely observed throughout the study for the occurrence of side effects. The intensity and duration of pain after each injection were recorded. A score for the intensity of pain was made as follows: 3 = severe, 2 = moderate, 1 = mild, and 0 = no pain.

Toxicity. All of the laboratory tests performed at the screening of the volunteers were repeated before and two days after each dose.

RESULTS

Antibacterial activity of cephalothin and cefoxitin. The minimal inhibitory concentrations determined in this study are shown in Tables 1 to 3. Cephalothin was clearly considerably more active against gram-positive cocci than was cefoxitin (Table 1). In terms of C_{50} (the concentration of antibiotic capable of inhibiting 50% of the strains examined), cephalothin was 8-fold more active against *S. aureus* and hemolytic streptococci of Lancefield group A, C, or G, and about 20-fold more active against group B or D streptococci. Concerning the staphylococci, the 21 strains resistant to benzylpenicillin did not differ from the 6 benzylpenicillin-susceptible strains.

Regarding the relative activities of the two compounds against gram-negative bacilli, it can be seen (Table 2) that there was little difference in *Escherichia coli* and *Proteus mirabilis*. However, cefoxitin appeared to be slightly more active against *Enterobacter cloacae*, *Klebsiella* spp., and the few *Acinetobacter* spp. strains tested. The most striking differences were observed against *Providencia stuartii* and the indole-producing strains of proteus; this activity is analysed more closely in Table 3.

It can be seen that there were no obvious differences between strains isolated clinically and those obtained from the Reference Laboratory. *Proteus vulgaris* was as susceptible to cefoxitin as was *P. mirabilis*; all *Proteus morganii* strains except one were inhibited by 40 μg of cefoxitin per ml and, even with the most resistance species, *Proteus rettgeri*, 51% of strains were inhibited by 20 μg of cefoxitin per ml. All five strains of *P. stuartii* were also susceptible to cefoxitin. The above figures are remarkable compared with the virtually total lack of activity of cephalothin against these organisms, only two of the 87 strains were susceptible to the latter. The *S. marcescens* strains were also markedly more susceptible to cefoxitin than to cephalothin.

The distribution of susceptibility to the two antibiotics among the obligately anaerobic species *B. fragilis* suggests that these strains may be rather heterogeneous; however, it is clear that cefoxitin is superior to cephalothin against this type of bacteria.

Against *Pseudomonas aeruginosa*, the activity of cefoxitin was of a very low order and, although greater than that of cephalothin, would have no therapeutic potential.

Bioavailability. Serum concentrations of antibiotic activity were higher and longer sustained after administration of cefoxitin (Fig. 2 and 3). Peak mean levels after 0.5, 1.0, and 2.0 g of cephalothin were 6.3, 20.8, and 161.4 μg/ml, respectively, and after cefoxitin, 10.9, 22.5, and 222.6 μg/ml, respectively. Differences between the two drugs were highly significant ($P < 0.001$) at 45, 60, and 120 min after the 0.5-g dose, but less so at other times and doses. Variation coefficients had an overall mean value of 0.41 (±0.17) for cephalothin and 0.35 (±0.14) for cefoxitin. This difference was not significant ($P > 0.1$). Dose proportionality of serum concentrations was observed after intramuscular doses of cefoxitin but not of cephalothin. These findings were confirmed by calculating the area under the serum concentration curve. The mean values were 15.9 ± 3.8 and 33.6 ± 8.2 μg per ml × h for 0.5 and 1.0 g of cefoxitin and 7.4 ± 2.1 and 25.2 ± 10.0 μg per ml × h for cephalothin, respectively.

Mean terminal serum half-lives of cephalothin-like activity were 27, 28, and 32 min after a

TABLE 1. *Activity of cephalothin and cefoxitin against gram-positive bacteria*

Organism	No. tested	Drug	No. of strains inhibited													
			0.04[a]	0.08	0.16	0.32	0.63	1.25	2.5	5	10	25	50	100	200	400	800
Staphylococcus aureus	27	Cephalothin			6	20	1										
		Cefoxitin						1	23	3							
Streptococcus pyogenes (group A)	16	Cephalothin	3	6	4	2	1										
		Cefoxitin				2	11		1	1	1						
Group B β-hemolytic streptococci	12	Cephalothin		1	6	3	2										
		Cefoxitin							6	6							
Group C β-hemolytic streptococci	3	Cephalothin		1	1		1										
		Cefoxitin					2				1						
Group G β-hemolytic streptococci	7	Cephalothin		3	3		1										
		Cefoxitin					5		1	1							
Streptococcus faecalis	86	Cephalothin										28	57	1			
		Cefoxitin													2	8	76
Streptococcus durans	5	Cephalothin										1	4				
		Cefoxitin														1	4

[a] Drug concentration (micrograms per milliliter).

TABLE 2. *Activity of cephalothin and cefoxitin against gram-negative bacteria*

Organism	No. tested	Drug	No. of strains inhibited								
			2.5[a]	5	10	20	40	>40	640	1,000	>1,000
Escherichia coli	41	Cephalothin	2	9	23	7	1	2			
Alkalescens spp.	3	Cefoxitin	2	24	18						
Proteus mirabilis	27	Cephalothin	2	7	11	7					
		Cefoxitin	1	3	20	3					
Enterobacter cloacae	28	Cephalothin	1		4		1	22			
		Cefoxitin	1		6	2	2	17			
Enterobacter hafnia	3	Cephalothin	1			2					
		Cefoxitin	1			2					
Enterobacter aerogenes	4	Cephalothin					1	3			
		Cefoxitin				1	1	2			
Klebsiella spp.	36	Cephalothin	8	11	7	4	1	5			
		Cefoxitin	5	24	7						
Bacteroides fragilis	26	Cephalothin	2	1	2		3	18			
		Cefoxitin	3	2	11	6	1	3			
Acinetobacter spp.	6	Cephalothin			3			3			
		Cefoxitin			4		1	1			
Providencia stuartii and indole-positive *Proteus* spp.	87	Cephalothin			1	1		85			
		Cefoxitin	7	13	14	27	6	20			
Serratia marcescens	15	Cephalothin						15			
		Cefoxitin				6	8	1			
Haemophilus influenzae	8	Cephalothin	4	1		2	1				
		Cefoxitin		4	4						
Pseudomonas aeruginosa	29	Cephalothin									29
		Cefoxitin							2	7	20

[a] Drug concentration (micrograms per milliliter).

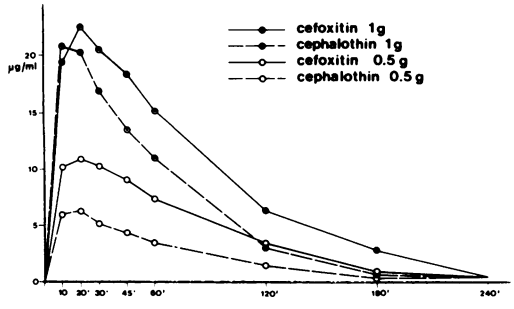

FIG. 2. *Serum concentrations of cefoxitin- and cephalothin-like activity after intramuscular administration.*

dose of 0.5, 1.0, and 2.0 g, respectively, whereas those of cefoxitin were 46, 45, and 47 min, respectively.

Antibiotic activity levels in urine were appreciably higher after injection of cefoxitin, as was the total recovery (Fig. 4). Mean values of total urinary recovery of antibiotic activity after doses of 0.5, 1.0, and 2.0 g were 47.9, 55.5, and 54.3% for cephalothin and 87.1, 90.1, and 99.0% for cefoxitin, respectively. Although, in the collections immediately after the injections, both antibiotics resulted in very high antimicrobial activity, in later collections the superiority of cefoxitin was evident, producing urine antibiotic activity of more than 5 µg/ml in all subjects throughout the 12-h collection period, whereas in 33% of the profiles obtained after cephalothin administration, no antibiotic activity was detectable in the last urine collection (6 to 12 or 4 to 12 h).

The well-known fact of the in vivo conversion of cephalothin to a less active desacetyl metabo-

TABLE 3. *Activity of cephalothin and cefoxitin against indole-producing Proteus spp. and Providencia stuartii analysed by species and by origin of strains*

Organism	No. tested	Origin	Drug	No. of strains inhibited					
				2.5[a]	5	10	20	40	>40
P. rettgeri	3	This hospital	Cephalothin						3
			Cefoxitin	1			2		
	36	Elsewhere	Cephalothin			1			35
			Cefoxitin	4	4	2	7		19
P. morganii	5	This hospital	Cephalothin						5
			Cefoxitin			1	3		1
	23	Elsewhere	Cephalothin						23
			Cefoxitin			3	15	5	
P. vulgaris	6	This hospital	Cephalothin				1		5
			Cefoxitin		4	2			
	9	Elsewhere	Cephalothin						9
			Cefoxitin		3	6			
P. stuartii	2	This hospital	Cephalothin						2
			Cefoxitin		1			1	
	3	Elsewhere	Cephalothin						3
			Cefoxitin	2	1				

[a] Drug concentration (micrograms per milliliter).

lite makes any further comparative pharmacokinetic analysis extremely difficult. The tissue distribution rate constants (k_{12}, k_{21}), elimination rate constants (k_{el}), as well as the apparent volumes of distribution, have been calculated for cefoxitin and are presented in Table 4.

Side effects. Apart from pain at the site of the intramuscular injections, there were no other side effects. Pain after injections of cephalothin was slightly stronger and more prolonged than after equal doses of cefoxitin (Table 5). Subsequently obtained levels of antibiotic activity were unrelated to intensity or duration of pain.

Toxicity. All parameters studied before and after the administration of cefoxitin gave normal results. The first and last value of each parameter for all volunteers that were included in the study are given in Table 6 and 7. None of the differences shown in these tables was significant. One further subject, a 28-year-old medical practitioner, developed a mild leukopenia after a 1.0-g dose of cephalothin: on the screening test, leukocytes were 4,100/mm³ with 2,538 polymorphs per mm³ and just before the injection these values were 4,500/mm³ and 3,285/mm³, respectively. Two days later, leukocytes were 3, 200/mm³ with 1,984 polymorphs per mm³. No

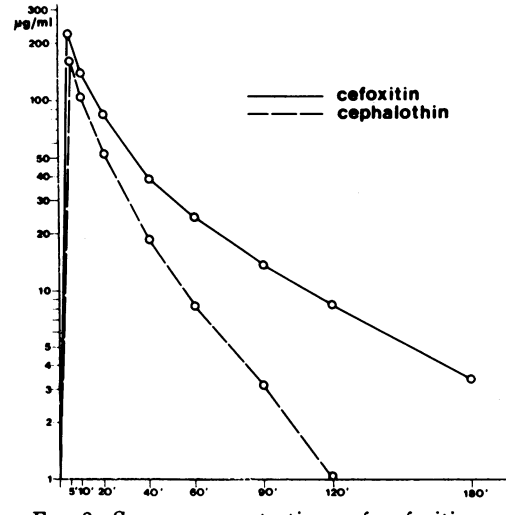

FIG. 3. *Serum concentrations of cefoxitin- and cephalothin-like activity after intravenous administration of 2 g.*

further injections were given, and 7 days after the dose, the leukocytes were 4,600/mm³ with 2,750 polymorphs per mm³. Hematology was also normal 2 weeks and 2 months later. Morphology of leukocytes and erythrocytes was normal on all occasions, as were platelets and

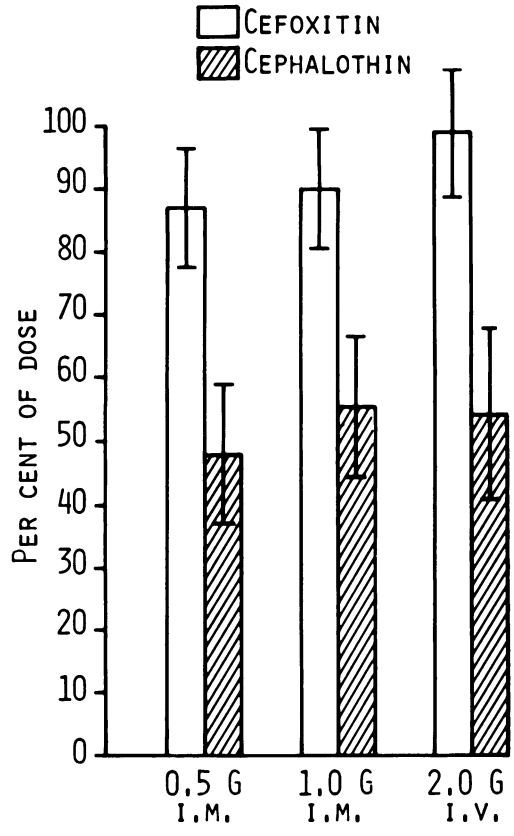

FIG. 4. *Urinary recovery of cefoxitin- and cephalothin-like activity after parenteral administration. Bars represent standard deviation*

all other laboratory parameters. The volunteer was in excellent health throughout this period, but he was not included in the bioavailability study since he only received one dose.

DISCUSSION

Regarding antibacterial activity, our results agree closely with those of Wallick and Hendlin (12), and establish cefoxitin as by far the broadest spectrum β-lactam antibiotic available at present. Besides having some quantitative advantage over cephalothin-susceptible gram-negative strains such as *E. coli* and *Klebsiella* spp., cefoxitin showed good activity against some cephalosporin-resistant organisms, such as indole-positive *Proteus* spp., *P. stuartii*, *S. marcescens*, and *B. fragilis*. It should be pointed out, however, that bacteria belonging to the first two of these classes are only rarely isolated in Britain, and *Serratia* spp. are virtually unknown.

Notwithstanding the superior activity of cephalothin against gram-positive cocci, it should be noted that 63 out of the 65 strains of staphylococci and β-hemolytic streptococci tested were inhibited by 5 μg of cefoxitin per ml, a concentration which is well within the therapeutically attainable range. With respect to the fecal-type streptococci, however, it is clear that neither antibiotic would be expected to be effective for systemic infections. However, even for these resistant organisms, eradication of a urinary infection confined to the bladder may be possible because of the very high concentrations of the two drugs in urine. In this connection, the inhibitory concentrations of cefoxitin have the advantage of being sustained for 4 to 6 h, but only for 3 to 4 h with cephalothin.

Clearly, the observed stability of cefoxitin to a variety of β-lactamases, first reported by Kosmidis et al. (4) and analysed in greater detail by Onishi et al. (9), must contribute significantly to its wider range of activity compared with that of other cephalosporins. The possibility of further chemical modification of the cephamycin C nucleus to increase intrinsic activity is obviously very real, and the resulting compound could very well equal gentamicin in the breadth of its antibacterial spectrum.

TABLE 4. *Pharmacokinetic parameters of cefoxitin in human volunteers*[a]

Dose[b]	k_{12}	k_{21}	k_{el}	V_1
0.5 g im	0.0314	0.0304	0.0553	7.94
1.0 g im	0.0314	0.0304	0.0552	7.94
2.0 g iv	0.0314	0.0304	0.0450	7.94

[a] k_{12}, Constant of distribution rate from compartment 1 to compartment 2; k_{21}, constant of distribution rate from compartment 2 to compartment 1; k_{el}, constant of overall elimination rate from compartment 1; and V_1, apparent volume of compartment 1.
[b] im, Intramuscular; iv, intravenous.

TABLE 5. *Mean intensity and duration of pain (± standard deviation) after intramuscular injections of cephalothin and cefoxitin in 18 human volunteers*

Drug	Amount (g)	Mean intensity[a]	Mean duration (min)
Cephalothin	0.5	1.8 (±0.44)	22 (±3.63)
	1.0	2.4 (±0.51)	24 (±4.63)
Cefoxitin	0.5	1.6 (±0.52)	18 (±5.00)
	1.0	2.0 (±0.5)	22 (±5.59)

[a] Pain intensity was graded after each injection: 3, severe pain; 2, moderate pain; 1, mild pain; and 0, no pain.

TABLE 6. *Toxicity studies before and after administration of cephalothin in human volunteers*[a]

Subject no.	PCV (%)		Leukocytes ($\times 10^3$/mm^3)		Neutrophils ($\times 10^3$/mm^3)		Platelets		Alkaline phosphatase (K. A. units/100 ml)		Aspartate aminotransferase (IU/liter)		Total bilirubin (mg/100 ml)		Urea (mg/100 ml)		Urinalysis	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
2	43.5	43.1	4.8	4.6	2.8	2.9	Ad	Ad	9	10	9	10	0.5	0.8	19	28	N	N
3	48.6	43.8	7.1	5.2	3.1	3.0	Ad	Ad	9	6	9	10	0.7	0.8	42	40	N	N
6	42.9	43.4	6.9	5.3	4.1	3.3	Ad	Ad	15	14	9	9	1.1	0.7	28	41	N	N
9	40.0	49.5	5.0	7.2	3.0	3.6	Ad	Ad	11	12	12	8	0.8	0.5	35	36	N	N
11	47.8	42.4	8.8	6.4	4.3	2.6	Ad	Ad	6	6	14	12	0.9	0.6	23	35	N	N
13	42.5	41.0	5.6	9.4	2.7	6.7	Ad	Ad	9	8	10	13	0.4	0.4	30	25	N	N
15	46.8	51.9	5.2	5.4	2.7	2.6	Ad	Ad	9	9	9	14	0.2	1.1	40	28	N	N
20	54.0	49.9	8.5	7.0	4.4	3.9	Ad	Ad	9	9	13	12	0.7	0.6	22	35	N	N
22	46.0	42.4	6.0	5.7	3.3	3.4	Ad	Ad	8	7	9	11	1.0	0.5	35	37	N	N
Mean	45.8	45.3	6.43	6.24	3.37	3.55			9.4	9.0	10.4	11.0	0.7	0.66	30.4	33.9		
SD	4.15	4.00	1.48	1.46	0.69	1.25			2.45	2.69	2.0	1.93	0.29	0.21	8.14	5.62		

[a] B, Before administration; A, after administration; Ad, adequate (platelets were always more than 150,000/mm^3); N, normal; and SD, standard deviation.

TABLE 7. *Toxicity studies before and after administration of cefoxitin in human volunteers*[a]

Subject no.	PCV (%)		Leukocytes ($\times 10^3$/mm^3)		Neutrophils ($\times 10^3$/mm^3)		Platelets		Alkaline phosphatase (K. A. units/100 ml)		Aspartate aminotransferase (IU/liter)		Total bilirubin (mg/100 ml)		Urea (mg/100 ml)		Urinalysis	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	44.5	42.0	7.6	4.8	4.1	2.9	Ad	Ad	8	7	8	8	0.5	0.9	38	37	N	N
5	48.3	49.7	8.1	7.7	4.2	4.2	Ad	Ad	6	7	12	13	0.7	1.0	23	33	N	N
7	41.7	47.5	8.1	7.5	4.4	4.0	Ad	Ad	12	12	7	9	0.2	0.8	40	24	N	N
10	44.4	44.7	8.9	6.8	5.5	4.2	Ad	Ad	14	11	9	10	0.2	0.5	27	20	N	N
12	48.6	43.7	5.0	7.9	3.1	4.8	Ad	Ad	8	11	9	8	0.8	0.6	31	41	N	N
14	49.4	44.6	8.1	8.7	3.9	4.9	Ad	Ad	10	9	11	16	0.8	0.8	51	41	N	N
16	47.3	40.1	6.0	5.6	3.9	2.7	Ad	Ad	7	6	11	10	0.6	0.6	28	36	N	N
17	45.8	43.3	8.0	6.7	5.4	4.8	Ad	Ad	10	10	10	10	0.7	1.0	25	25	N	N
19	41.9	40.8	8.1	7.2	4.6	4.6	Ad	Ad	8	10	9	16	1.2	0.5	33	38	N	N
Mean	45.8	44.0	7.54	6.98	4.34	4.12			9.2	9.2	9.6	11.1	0.63	0.74	32.9	32.8		
SD	2.84	3.07	1.23	1.19	0.75	0.81			2.53	2.10	1.58	3.14	0.31	0.2	8.85	7.83		

[a] B, Before administration; A, after administration; Ad, adequate (platelets were always more than 150,000/mm^3); N, normal; and SD, standard deviation.

Examination of the pharmacokinetic results shows that the two antibiotics investigated showed similar behavior after administration in man. However, cefoxitin had the following advantages. First, the peak serum level, which occurred at about 20 min after intramuscular injection, was higher and better sustained, and the terminal serum half-life was almost double that of cephalothin. Second, the urine concentrations were greater with cefoxitin and longer sustained, and the total recovery was about 90% compared with 55% in the case of cephalothin. Cefoxitin was, unlike cephalothin, excreted in fully microbiologically active form. Sonneville et al. (Prog. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 13th, Washington, D.C., Abstr. 50, 1973) have reported that it is excreted unchanged, whereas it is well known that cephalothin is excreted partially as the less microbiologically active desacetyl form. Both compounds were equally lacking in toxicity but, unfortunately, were painful on intramuscular injection.

In view of its microbiological and pharmacokinetic properties, and its efficacy in animal experiments (7), cefoxitin clearly deserves clinical trial.

ACKNOWLEDGMENTS

We thank C. M. Martin and A. Andrew of Merck Sharp and Dohme Ltd. for valuable discussion and supply of materials. D. W. Kerry gave invaluable expert technical assistance.

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