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Comparison of the Pharmacokinetics of Ceftazidime and Moxalactam and Their Microbiological Correlates in Volunteers

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We compared ceftazidime with moxalactam, a commonly utilized, currently available drug. The microbiological activities of ceftazidime and moxalactam were studied. In addition, single-dose pharmacokinetics and serum bactericidal activity 1 and 6 h after a 2.0-g, 30-min infusion of each drug were determined in a crossover study in human volunteers. In vitro, both drugs had MICs for 90% of the isolates of <1.0 μg/ml against the common members of the family *Enterobacteriaceae* and of 8.0 μg/ml against *Staphylococcus aureus*. Against *Pseudomonas aeruginosa* ceftazidime was more active than moxalactam, the respective MICs for 90% of the isolates being 8 and 128 μg/ml. Mean half-lives were 1.75 (± 0.21) h for ceftazidime and 2.5 (± 0.38) h for moxalactam. The serum bactericidal titers for both compounds against *Escherichia coli* and *Klebsiella pneumoniae* were high. Titers against *S. aureus* 6 h after infusion were negative. The mean (geometric) serum bactericidal titer of ceftazidime against 31 strains of *P. aeruginosa* (1:44) was higher than that of moxalactam (1:3.4).

Ceftazidime is a new aminothiazolyl cephalosporin that is active against facultative or aerobic gram-negative bacilli (21) and is beta-lactamase stable (13, 16). Most interestingly, the MICs of ceftazidime against *Pseudomonas aeruginosa* are low (MIC for 90% of the isolates [MIC_{90}], 8.0 μg/ml) (21). Preliminary investigations have indicated favorable pharmacokinetic properties (7). Moxalactam, the first drug of the class of oxa-beta-lactams, also possesses good activity against facultative or aerobic gram-negative bacilli (10) and has a favorable pharmacokinetic profile (19). Clinical experience suggests that moxalactam provides effective single-agent therapy for serious infections (15, 17). Consequently, we felt that moxalactam furnishes an excellent standard against which to judge ceftazidime. We performed an in vitro microbiological comparison of these compounds, coupled with a crossover design evaluation of their pharmacokinetic profiles in normal volunteers. We further evaluated these compounds by a computer integration of their pharmacological and microbiological characteristics and also by determining the serum bactericidal activity both compounds generated in six volunteers against *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*.

MATERIALS AND METHODS

Volunteer studies. Volunteers were normal males, varying from 18 to 35 years in age, and 59 to 86.4 kg in weight. They were fully informed before the study and granted consent in accordance with institutional guidelines. They received both moxalactam and ceftazidime in a crossover manner, with at least 6 days elapsing between each administration. Two grams of moxalactam or ceftazidime diluted to 23 ml with 5% dextrose and water was infused by a Harvard pump (Harvard Apparatus, Inc., South Natick, Mass.) over a period of 30 min. Blood was obtained before infusion, immediately after infusion, and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, and 12 h postinfusion; urine was collected from 0 to 2, 2 to 4, 4 to 6, 6 to 12, and 12 to 24 h. The serum was promptly separated and frozen at −70°C until assayed. Urine collections were measured, and samples were frozen at −70°C until assayed.

Antibiotic assay. The concentrations of antibiotic in serum and urine were determined by high-pressure liquid chromatography. The moxalactam assay was a variant of the method of Miner et al. (12) and utilized for serum a reverse-phase C18 column in a radial compression module. Ceftazidime assays were performed by a variation of the method of Ayrton (1). The percent coefficient of variation for both assays did not exceed 6% over the concentration range tested.

Protein binding. Free drug levels were calculated by utilizing the total drug level and multiplying by 100% minus the percent bound. Protein-binding values were obtained by Amicon Cone Ultrafiltration (Amicon Corp., Lexington, Mass.). Pooled human serum was used for the determination. Cones were checked for their ability to bind both moxalactam and ceftazidime. For each drug, >95% was recovered after filtration when suspended in phosphate-buffered saline.

Microbiological methods. (i) Isolates. A total of 571 isolates acquired from the clinical services of the University of Maryland Cancer Center were used in the microbiological studies, 45 *S. aureus* strains and 526 gram-negative rods. Stock cultures were prepared from primary isolation plates and maintained in semisolid agar at room temperature for at most 3 months.

(ii) MIC determinations. MICs of ceftazidime and moxalactam were determined by a microtiter dilution method (14) by using Mueller-Hinton broth with Ca^{2+} and Mg^{2+} supplementation as the growth medium and diluent. An

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overnight broth culture was adjusted to a turbidity corresponding to a 0.5 McFarland standard (10^7 to 10^8 CFU/ml). A pin inoculator transferred 0.0015 ml of this inoculum to microtiter wells to produce concentrations of organisms of ca. 5×10^5 CFU/ml. The MIC was defined as the lowest concentration that prevented visible growth after 18 h of incubation at 37°C. The MIC_{50}s and MIC_{90}s of each drug were calculated.

Serum bactericidal activity. The bactericidal activity of serum samples was determined by a microtiter dilution method utilizing equal quantities of pooled human serum and supplemented Mueller-Hinton broth as the diluent (18). Each sample from each volunteer was serially diluted with heat-inactivated, normal human serum. Equal quantities of cation-supplemented Mueller-Hinton broth were added to provide serial dilutions of 1:2 to 1:256. The inoculum, consisting of 0.0015 ml of a 1:50 dilution of an overnight culture, was added to the dilutions by the microinoculator, making the final concentration of bacteria ca. 5×10^5 bacteria per ml in a total volume of 0.1 ml. The endpoint for the serum inhibitory activity was the last well in which there was no turbidity. The endpoint for the serum bactericidal concentration was determined as the lowest concentration which allowed no growth after subculturing 0.0015 ml of each nonturbid well onto agar plates, a 99.8% kill.

Pharmacokinetic analysis. Serum concentrations following the 2.0-g, 30 min intravenous infusion were fitted to a two-compartment, open model, with elimination only from the central compartment. This was accomplished by an iterative, nonlinear, least-squares-regression technique, a variant of the NON-LIN program of C. M. Metzler, G. K. Elfring, and A. J. McEwen (Biometrics **30**:562–563, 1974). Pharmacokinetic parameters were calculated by standard methods (5). Clearance values were expressed in liters per hour and normalized by multiplying by 1.73 m^2/BSA, where BSA equals the body surface area of the volunteer. All rate constants were assumed to be first order and with units of reciprocal time (per hour). Volume terms were expressed as liters per kilogram. The pharmacokinetic parameters were transformed for infusion times where indicated by the method of Loo and Reigelman (11).

The serum concentration-time curve for each volunteer was constructed according to the equation:

$$C = \frac{K_0 (K_{21} - \alpha)(1 - e^{\alpha T})}{V_c \alpha(\alpha - \beta)} e^{-\alpha t} + \frac{K_0(\beta - K_{21})(1 - e^{\beta T})}{V_c \beta(\alpha - \beta)} e^{-\beta t}$$

where K_0 is the infusion rate, V_c is the volume of the central compartment, K_{21} is the transfer rate constant from the peripheral to the central compartment, α and β are complex functions of the intercompartmental transfer constants and elimination rate constant and are related to the distribution and elimination half-lives, and t is the elapsed time since the start of the infusion. During the infusion, T equals t and varies with time. After the end of the infusion, T is a constant, equal to the time the infusion was stopped.

To calculate the time that the serum concentration remains above the MIC_{90} of common pathogens and to calculate the area under the curve, serum concentration-time curves were constructed for each volunteer for each drug from his pharmacokinetic parameters. Concentrations were calculated at 0.1-h intervals for the 24 h beginning with the initiation of the infusion of the single 2.0-g dose. The duration of time the drug level was in excess of the MIC_{90} for each species of organism was determined from the calculated values of the free serum level. The area under the curve was calculated for both the total and free drug values by the trapezoidal rule.

Statistical analysis. The geometric mean serum bactericidal activity calculated for each species of microorganism was tested by Student's t test for significant differences between regimens. The cumulative percentage of the serum bactericidal activity at each level of dilution was calculated for each species of microorganism for each drug.

RESULTS

Pharmacokinetic parameters. The serum levels obtained after the 30-min infusion of 2.0 g of each of the antibiotics are shown in Table 1. The levels immediately after the infusion were higher for moxalactam than for ceftazidime, 220 and 159 μg/ml, respectively. By 1 h, the moxalactam and ceftazidime levels had declined to 100 and 65.2 μg/ml, respectively. At 4 and 8 h the respective values were 39.7 and 13.4 μg/ml for moxalactam an 16.7 and 3.7 μg/ml for ceftazidime.

The pharmacokinetic parameters are displayed in Table 2. The terminal half-life ($t_{1/2\beta}$) after this method of administration was 2.5 h for moxalactam, compared with 1.75 h for ceftazidime. The volumes of distribution are consistently smaller for moxalactam. The serum clearance averaged 6.4 liters/h per 1.73 m^2 for ceftazidime, as compared with 3.4 liters/h per 1.73 m^2 for moxalactam. Both drugs were eliminated primarily by renal excretion, with >70% of the administered dose being recovered in the urine for both drugs within the first 6 h. The renal clearance in both instances accounted for ca. 80% of the corresponding serum clearance (Table 2).

The fractional urinary concentrations of these compounds are shown in Table 3. Overall, 80% of the administered dose of ceftazidime was recovered in the urine in 24 h and 79% of the administered dose of moxalactam was recovered in the urine in 24 h, most of which was recovered in the first 6 h.

Protein binding. The protein binding of moxalactam at 50 μg/ml was 65%; that of ceftazidime at 50 μg/ml was 16%. The percent coefficient of variation for each drug was 13.1 and 3.8%, respectively, at 50 μg/ml. Protein binding at other concentrations from 10 to 200 μg/ml was not significantly different for either drug.

Computer comparison. The calculated time that the free serum level for each drug remained above the MIC_{50} and MIC_{90} for each species of microorganism is displayed in Table 4. For moxalactam, the MIC_{90}s ranged from 0.125 μg/ml for *E. coli* to 128 μg/ml for *P. aeruginosa*. For ceftazidime, they ranged from 0.06 μg/ml for *Proteus mirabilis* to 8 μg/ml for *P. aeruginosa*. These values are in close agreement with other MIC_{90}s for large collections of organisms reported in the literature (6, 10, 16, 21). When free drug levels were examined, the area under the concentration-time curve was 268 μg · h/ml for moxalactam and 238 μg · h/ml for ceftazidime. For the *Enterobacteriaceae*, both drugs had free drug levels exceeding the MIC_{90}s for 5.8 to 21.0 h after drug administration, with the single exception of moxalactam against *Enterobacter hafniae*. However, for *P. aeruginosa*, the time that serum levels were above the MIC_{90} decreased to <0.5 h for moxalactam; this is in contrast to 5.8 h for ceftazidime. The MIC_{90} *S. aureus* was exceeded for 6.4 h by moxalactam and 5.8 h by ceftazidime.

TABLE 1. Mean serum concentrations of the study drugs at various times after dosage

Infusion and patient no.	Serum concn (μg/ml) at h:										
	0	0.25	0.50	0.75	1.0	2.0	3.0	4.0	6.0	8.0	12.0
Ceftazidime (2.0 g, 30 min)											
1	87.6	84.2	69.9	57.0	53.6	32.1	22.6	15.3	7.9	3.6	0.8
2	138.0	97.7	79.1	66.2	57.5	36.3	24.6	15.7	7.7	4.4	1.2
3	149.0	102.0	82.1	68.7	58.9	36.4	23.3	16.6	8.5	4.0	1.1
4	218.0	119.0	108.0	90.4	78.3	44.0	30.9	20.4	9.5	4.6	1.0
5	232.0	134.0	104.0	87.8	79.1	47.6	29.9	19.8	7.0	3.0	<0.5 (0.3)[a]
6	131.0	103.0	84.0	70.0	63.8	35.7	22.1	12.3	5.4	2.8	0.6
Mean ± SD	159.3 ± 55.2	106.7 ± 17.4	87.9 ± 14.9	73.4 ± 13.0	65.2 ± 11.0	38.7 ± 5.8	25.6 ± 3.9	16.7 ± 3.0	7.7 ± 1.4	3.7 ± 0.7	0.8 ± 0.4
Moxalactam (2.0 g, 30 min)											
1	199.1	151.8	118.9	103.7	97.1	65.4	45.7	39.0	21.8	11.3	4.4
2	196.9	141.4	123.4	107.1	91.1	67.1	49.1	35.6	19.3	12.8	6.7
3	230.5	160.1	134.0	120.1	108.6	74.1	57.2	48.3	33.1	19.3	10.2
4	229.6	166.2	151.2	125.3	110.3	75.8	55.0	46.3	29.6	13.4	5.2
5	239.0	163.5	139.8	117.7	95.4	68.4	43.7	31.4	20.7	15.5	2.7
6	223.6	159.8	130.7	106.9	96.8	69.4	48.5	37.6	20.0	7.8	5.2
Mean ± SD	219.8 ± 17.6	157.1 ± 9.1	133.0 ± 11.6	113.5 ± 8.7	99.9 ± 7.7	70.0 ± 4.1	49.9 ± 5.3	39.7 ± 6.5	24.1 ± 5.8	13.4 ± 3.9	5.7 ± 2.5

[a] Number in parentheses was less than the lowest measured standard.

Serum bactericidal activity. Serum was obtained at 1 and 6 h postinfusion for the determination of serum bactericidal activities against a battery of 31 strains of *P. aeruginosa* and 7 strains each of *E. coli*, *K. pneumoniae*, and *S. aureus*. For *E. coli* and *K. pneumoniae*, none of the strains had an MBC to either drug of >1 μg/ml. Two strains of *S. aureus* were methicillin resistant, and the MBCs to both agents were high. The other five organisms had an MBC to both drugs of ≤16 μg/ml. All 31 *P. aeruginosa* strains had MBCs to moxalactam of ≥4 μg/ml; 12 of these were >16 μg/ml. By contrast, only 1 of the 31 strains had an MBC to ceftazidime of >16 μg/ml, and 26 had an MBC of ≤4 μg/ml. Table 5

TABLE 2. Pharmacokinetic parameters of ceftazidime and moxalactam after a 2.0-g, 30-min infusion to six normal volunteers[a]

Drug and patient no.	V_c (liters/kg)	V_{area} (liters/kg)	V_{ss} (liters/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	AUC (μg · h/ml)	Serum clearance (liters/h per 1.73 m²)	Renal clearance (liters/h per 1.73 m²)	Nonrenal clearance (liters/h per 1.73 m²)	Creatinine clearance (liters/h per 1.73 m²)	Renal/serum clearance ratio	Renal/creatinine clearance ratio
Ceftazidime												
1	0.24	0.32	0.28	0.63	2.00	226	7.4	4.8	2.6	4.4	0.65	1.07
2	0.13	0.26	0.23	0.26	1.91	267	6.7	5.9	0.8	5.8	0.88	1.02
3	0.11	0.24	0.20	0.26	1.87	272	6.1	4.2	1.9	4.5	0.69	0.92
4	0.06	0.22	0.19	0.09	1.66	360	5.7	4.7	1.0	5.3	0.84	0.90
5	0.07	0.19	0.16	0.11	1.47	353	5.8	4.9	0.9	7.8	0.85	0.63
6	0.15	0.22	0.19	0.41	1.57	246	6.8	5.9	0.9	6.8	0.87	0.87
Mean ± SD	0.13 ± 0.07	0.24 ± 0.05	0.21 ± 0.04	0.29 ± 0.20	1.75 ± 0.21	287 ± 56	6.4 ± 0.7	5.1 ± 0.7	1.3 ± 0.7	5.8 ± 1.3	0.80 ± 0.10	0.90 ± 0.15
Moxalactam												
1	0.09	0.18	0.16	0.28	2.48	495	3.4	3.4	0.0	4.8	1.00	0.70
2	0.09	0.17	0.16	0.20	2.25	481	3.7	3.3	0.4	6.8	0.88	0.48
3	0.08	0.17	0.16	0.28	3.25	644	2.6	1.3	1.3	4.2	0.51	0.32
4	0.11	0.21	0.19	0.31	2.58	588	3.5	2.3	1.2	6.0	0.65	0.38
5	0.09	0.21	0.18	0.28	2.34	509	4.0	3.5	0.5	6.6	0.87	0.53
6	0.07	0.15	0.14	0.22	2.22	499	3.4	2.8	0.6	8.4	0.82	0.33
Mean ± SD	0.09 ± 0.01	0.18 ± 0.02	0.17 ± 0.02	0.26 ± 0.04	2.52 ± 0.38	536 ± 65	3.4 ± 0.5	2.8 ± 0.8	0.7 ± 0.5	6.1 ± 1.5	0.79 ± 0.18	0.46 ± 0.15

[a] V_c, Volume of distribution of the central compartment; V_{area}, volume of distribution of drug in the body; V_{ss}, volume at steady state; $t_{1/2\alpha}$ and $t_{1/2\beta}$, distribution and elimination half-lives, respectively; AUC, area under the concentration-time curve.

TABLE 3. Fractional urinary concentrations of ceftazidime and moxalactam at various times after dosage

Drug	Mean (range) concn in urine (μg/ml) at h:				
	0 to 2	>2 to 4	>4 to 6	>6 to 12	>12 to 24
Ceftazidime	5,810 (1,510–9,230)	1,459 (539–3,760)	556 (150–1,520)	82 (<15–269)	20 (<15–59)
Moxalactam	6,202 (1,975–17,549)	2,368 (435–5,642)	1,032 (155–2,990)	315 (105–601)	60 (<20–95)

TABLE 4. Integration of the pharmacological and microbiological properties of ceftazidime and moxalactam

Microorganism (no. of strains)	Cumulative MIC (μg/ml) of:				Time (h) that free drug concn was >MIC_{50} and >MIC_{90} of:			
	Ceftazidime		Moxalactam		Ceftazidime		Moxalactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	>MIC_{50}	>MIC_{90}	>MIC_{50}	>MIC_{90}
Escherichia coli (52)	0.125	0.125	0.06	0.125	>12	>12	>12	>12
Klebsiella pneumoniae (55)	0.125	0.25	0.125	0.125	>12	>12	>12	>12
Klebsiella oxytoca (28)	0.06	0.125	0.125	0.25	>12	>12	>12	>12
Pseudomonas aeruginosa (118)	2.0	8.0	16.0	128.0	9.3	5.8	3.9	0.0
Enterobacter cloacae (30)	0.125	1.0	0.06	2.0	>12	11.0	>12	11.5
Enterobacter aerogenes (44)	0.125	0.5	0.125	0.25	>12	>12	>12	>12
Enterobacter hafnia (18)	0.5	8.0	0.125	32.0	>12	5.8	>12	1.5
Serratia marcescens (37)	0.125	0.25	0.25	0.5	>12	>12	>12	>12
Proteus mirabilis (25)	0.03	0.06	0.125	0.125	>12	>12	>12	>12
Proteus vulgaris (24)	0.03	0.125	0.125	0.25	>12	>12	>12	>12
Morganella morganii (31)	0.125	0.25	0.125	0.25	>12	>12	>12	>12
Citrobacter freundii (40)	0.125	0.5	0.125	0.25	>12	>12	>12	>12
Citrobacter amaloniticus (24)	0.125	0.5	0.06	0.125	>12	>12	>12	>12
Staphylococcus aureus (45)	4.0	8.0	4.0	8.0	7.5	5.8	8.9	6.4

presents the geometric mean bactericidal activity generated by each drug at 1 and 6 h for each species of microorganism. Figure 1 presents the cumulative frequency of the serum bactericidal activity for each organism at each dilution tested for the 1- and 6-h time points for moxalactam and ceftazidime. Both drugs were active against *E. coli* and *K. pneumoniae*, and consistently high serum bactericidal activities were generated at 1 and 6 h. Both drugs produced serum bactericidal activity at 1 h postinfusion for *S. aureus* but failed to produce any serum bactericidal activity at 6 h. It should be noted, however, that two of our randomly selected strains were methicillin resistant, adversely affecting the performance of both drugs. When the methicillin-resistant strains are removed from consideration, the geometric mean bactericidal titer at 1 h was 1:5.5 for ceftazidime and 1:4.6 for moxalactam. At 6 h neither drug produced significant activity (<1:2). There were no statistically significant differences between the bactericidal activities generated by these two drugs for these three species of microorganisms. However, the difference in geometric mean bactericidal activity for the 31 strains of *P. aeruginosa* was statistically significant ($P < 10^{-6}$) at 1 and 6 h.

DISCUSSION

With the rapid proliferation of new beta-lactam antibiotics, the place of a new drug in the armamentarium of the physician is frequently unclear. Consequently, we undertook this study, in which a promising new compound, ceftazidime, was compared microbiologically and pharmacologically with a well-studied compound, moxalactam.

From the MIC_{50}s and MIC_{90}s alone, it was apparent that both drugs were active against the *Enterobacteriaciae* and less active against *S. aureus*. However, only ceftazidime was active against *P. aeruginosa*. These in vitro activities cannot be properly interpreted without integrating pharmacokinetic and protein-binding properties.

When administered in a dose and manner likely to be used in clinical situations, both drugs produced high concentrations in the serum and had reasonably long half-lives. Both drugs were rapidly excreted into the urine, providing high urinary concentrations for long periods of time, which suggests 12-h dosing intervals for the treatment of urinary tract infections.

The data suggest that both drugs have a minor nonrenal pathway of elimination. Since both markedly decrease the aerobic or facultative gram-negative rod content of the stool (B. Kemmerich, W. Warns, H. Knothe, K. Borner, P. Koeppe, and H. Lode, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 21st, Chicago, Ill., abstr.

TABLE 5. Geometric mean serum bactericidal activities at 1 and 6 h postinfusion of six volunteers receiving 2.0-g, 30-min infusions of ceftazidime and moxalactam

Microorganism (no. of strains)	Geometric mean serum bactericidal activity with:			
	Ceftazidime		Moxalactam	
	1 h	6 h	1 h	6 h
Pseudomonas aeruginosa[a] (31)	1:44.4	1:4.7	1:3.4	1:2.0
Escherichia coli (7)	1:256	1:132.3	1:256	1:134.5
Klebsiella pneumoniae (7)	1:239.6	1:98.3	1:228.1	1:75.5
Staphylococcus aureus (7)	1:3.7	<1:2.0	1:3.0	<1:2.0

[a] Differences at 1 and 6 h highly significant ($P < 10^{-6}$).

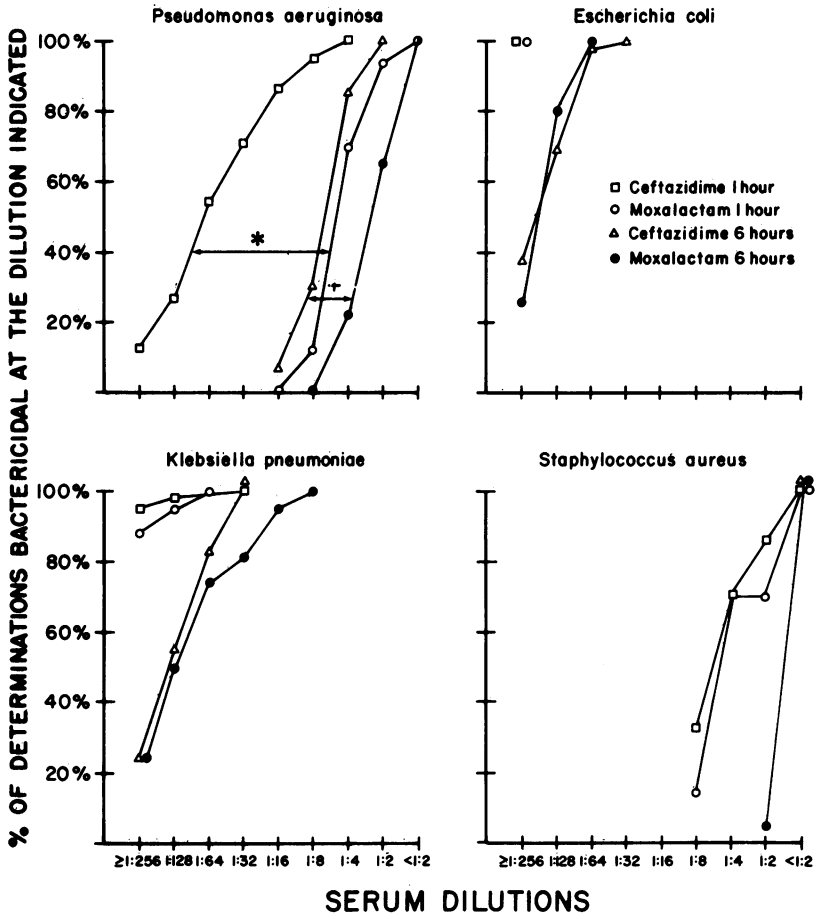

FIG. 1. Cumulative bactericidal activities in serum at 1 and 6 h after drug administration: ceftazidime versus moxalactam.

no. 173, 1981; J. H. Tenney, B. Clayman, and J. W. Warren, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, p. 98/63–98/66, 1983), biliary excretion or diffusion across the bowel wall may account for some of the nonrenal clearance. Both drugs were stable, and no metabolites were identified in either serum or urine.

Neither drug was highly protein bound. Somewhat surprising was the relative long half-life coupled with the low protein binding of ceftazidime. Although the effect of probenecid on renal excretion was not studied, renal clearances were very close to the measured creatinine clearances, suggesting that ceftazidime is excreted in the main by glomerular filtration and that tubular secretion contributes little to clearance of the drug, as is the case for moxalactam (3).

By correlating the serum concentration-time profile with the microbiological data, the length of time that serum levels were adequate to inhibit clinically important pathogens was derived. These drugs lack a post-antibiotic effect for aerobic or facultative gram-negative bacilli. The possible clinical implications of this observation with reference to the concentration-time profile of antibiotics have been reviewed elsewhere (4). Protein binding was also included in the evaluation for two reasons. First, protein binding determines the amount of free drug in the serum, and only this free drug is microbiologically active (20). Second, only the free drug diffuses to the periphery. Indeed, numerous investigators (2, 8, 22) have demonstrated a linear relationship between the area under the time curve of free drug concentration in the serum and the area under the curve of antibiotic concentration in the interstitial fluid.

Consequently, we felt it was rational to compare the relative activities of these new beta-lactams by determining the amount of time that the free drug concentration remained above the MIC_{90} of clinically important pathogens. With this comparison, both drugs had activity against most of the *Enterobacteriaciae* for the duration of the recommended 8-h dosing interval. However, only ceftazidime provided activity against a large percentage of *P. aeruginosa* strains during this dosing interval. Both drugs, although modestly active against *S. aureus*, do possess a post-antibiotic effect for this organism and should provide adequate empiric coverage of this microogranism until definitive therapy can be administered. Ceftazidime, therefore, may be appropriate to use as a single agent for seriously ill patients with suspected sepsis.

In addition, Klastersky et al. (9) working with cancer patients and Platt et al. (17) studying general hospital patients with sepsis have shown that a good outcome is significantly more likely for the patient who develops a serum bactericidal activity of ≥1:8 at 1 h postinfusion. With this yardstick, the sera from volunteers receiving these drugs had good antimicrobial activity against *E. coli* and *K. pneumoniae* but performed only modestly well against the *S. aureus* strains. Against *P. aeruginosa*, the sera of those

volunteers receiving ceftazidime were very active; over 95% of the determinations had serum bactericidal activity at least at 1:8 at 1 h postinfusion.

By all the microbiological and pharmacokinetic indices measured, we feel ceftazidime shows promise as a single agent for the empiric therapy of suspected gram-negative bacillary sepsis. This agent merits extensive evaluation in controlled clinical trials.

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LITERATURE CITED

1. **Ayrton, J.** 1981. Assay of ceftazidime in biological fluids using high-pressure liquid chromatography. J. Antimicrob. Chemother. **8**(Suppl.):227–231.
2. **Bergan, T.** 1981. Pharmacokinetics of tissue penetration of antibiotics. Rev. Infect. Dis. **3**:45–66.
3. **DeSante, K. A., K. S. Israel, G. L. Brier, J. D. Wolny, and B. L. Hatcher.** 1982. Effect of probenecid on the pharmacokinetics of moxalactam. Antimicrob. Agents Chemother. **21**:58–61.
4. **Drusano, G. L., P. A. Ryan, H. C. Standiford, M. R. Moody, and S. C. Schimpff.** 1984. Integration of selected pharmacologic and microbiologic properties of three new beta-lactam antibiotics: a hypothesis for rational comparison. Rev. Infect. Dis. **6**:357–363.
5. **Gibaldi, M., and D. Perrier.** 1975. Pharmacokinetics, p. 45–128. Marcel Dekker, Inc., New York.
6. **Hall, W. H., B. J. Opfer, and D. N. Gerding.** 1980. Comparative activities of the oxa-β-lactam LY127935, cefotaxime, cefoperazone, cefamandole, and ticarcillin against multiply resistant gram-negative bacilli. Antimicrob. Agents Chemother. **17**: 273–279.
7. **Harding, S. M., J. Ayrton, J. E. Thornton, A. J. Munro, and M. I. J. Hogg.** 1981. Pharmacokinetics of ceftazidime in normal subjects. J. Antimicrob. Chemother. **8**(Suppl. B):261.
8. **Hoffstedt, B., and M. Walder.** 1981. Influence of serum protein binding and mode of administration on penetration of five cephalosporins into subcutaneous tissue fluid in humans. Antimicrob. Agents Chemother. **20**:783–786.
9. **Klastersky, J., D. Didier, G. Swings, and D. Werts.** 1974. Antibacterial activity in serum and urine as a therapeutic guide in bacterial infections. J. Infect. Dis. **129**:187–193.
10. **Lang, S. D. R., D. J. Edwards, and D. T. Durack.** 1980. Comparison of cefoperazone, cefotaxime, and moxalactam (LY127935) against aerobic gram-negative bacilli. Antimicrob. Agents Chemother. **17**:488–493.
11. **Loo, J. C. K., and S. Riegelman.** 1970. Assessment of pharmacokinetic constants from post-infusion blood curves obtained after iv infusion. J. Pharm. Sci. **59**:53–55.
12. **Miner, D. J., D. L. Coleman, A. M. M. Shepherd, and T. C. Hardin.** 1981. Determination of moxalactam in human body fluids by liquid chromatographic and microbiological methods. Antimicrob. Agents Chemother. **20**:252–257.
13. **Mouton, R. P., G. P. A. Bongaerts, and M. H. van Gestel.** 1981. Susceptibility of ceftazidime and other cephalosporins to a range of beta-lactamases and their potential as inducing agents. J. Antimicrob. Chemother. **8**(Suppl. B):147–152.
14. **National Committee for Clinical Laboratory Standards.** 1980. Standard methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically. Proposed standard M7-P. National Committee for Clinical Laboratory Standards, Villanova, Pa.
15. **Oblinger, M. J., J. T. Bowers, M. A. Sande, and G. L. Mandell.** 1982. Moxalactam therapy vs. standard antimicrobial therapy for selected serious infections. Rev. Infect. Dis. **4**(Suppl.): S639–S649.
16. **Phillips, I., C. Warren, K. Shannon, A. King, and D. Hanslo.** 1981. Ceftazidime: *in-vitro* antibacterial activity and susceptibility to beta-lactamases compared with that of cefotaxime, moxalactam and other beta-lactam antibiotics. J. Antimicrob. Chemother. **8**(Suppl. B):23–31.
17. **Platt, R., S. L. Ehrlich, J. Afarian, T. F. O'Brien, J. E. Pennington, and E. H. Kass.** 1981. Moxalactam therapy of infections caused by cephalothin-resistant bacteria: influence of serum inhibitory activity on clinical response and acquisition of antibiotic resistance during therapy. Antimicrob. Agents Chemother. **20**:351–355.
18. **Reller, L. B., and C. W. Stratton.** 1977. Serum dilution test for bactericidal activity. II. Standardization and correlation with antimicrobial assays and susceptibility tests. J. Infect. Dis. **136**:196–204.
19. **Standiford, H. C., G. L. Drusano, W. B. McNamee, B. Tatem, P. A. Ryan, and S. C. Schimpff.** 1982. Comparative pharmacokinetics of moxalactam, cefoperazone, and cefotaxime in normal volunteers. Rev. Infect. Dis. **4**(Suppl.):S585–S594.
20. **Tompsett, R., S. Shultz, and W. McDermott.** 1947. The relation of protein binding to the pharmacology and antibacterial activity of penicillins X, G, dihydro F, and K. J. Bacteriol. **53**:581–595.
21. **Verbist, L., and J. Verhaegen.** 1981. Ceftazidime: comparative *in-vitro* study. J. Antimicrob. Chemother. **8**(Suppl. B):67–71.
22. **Wise, R., A. P. Gillett, B. Cadge, S. R. Durham, and S. Baker.** 1980. The influence of protein binding upon tissue fluid levels of six beta-lactam antiobiotics. J. Infect. Dis. **142**:77–82.