ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1997, p. 1783–1787 Vol. 41, No. 8
0066-4804/97/$04.00+0

Pharmacokinetics of Intravenously and Intramuscularly Administered Cefepime in Infants and Children

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Received 23 December 1996/Returned for modification 26 April 1997/Accepted 8 June 1997

The pharmacokinetic characteristics of cefepime were determined after first dose ($n = 35$) and again under steady-state conditions ($n = 31$) with a group of 37 infants and children. In eight subjects, a cefepime dose given by intramuscular injection was substituted for an intravenous dose, and disposition characteristics were studied again. Study subjects ranged in age from 2.1 months to 16.4 years, and all had normal renal function. Each patient received 50 mg of cefepime/kg of body weight intravenously every 8 h, up to a total maximum individual dose of 2 g. With the exception of one study patient who received a single cefepime dose for surgical prophylaxis, the patients received cefepime for 2 to 13 days. Elimination half-life ($t_{1/2}$), steady-state volume of distribution, total body clearance, and renal clearance after first dose administration averaged 1.7 h, 0.35 liter/kg, and 3.1 and 1.9 ml/min/kg, respectively. Although cefepime $t_{1/2}$ and mean residence time (MRT) were slightly longer for subjects <6 months of age than for older subjects, no differences in cefepime disposition characteristics between first dose and steady-state evaluations were observed. $t_{1/2}$ (1.8 versus 1.9 h) and MRT (2.3 versus 3.2 h) were slightly prolonged after intramuscular administration, reflecting the influence of absorption from the intramuscular injection site on cefepime elimination. Bioavailability after intramuscular administration averaged 82% (range, 61 to 124%). Fifty-seven percent of the first dose and 88.9% of the last dose were recovered as unchanged drug in urine over the 8- and 24-h sampling periods, respectively. These pharmacokinetic data support a single cefepime dosing strategy for patients ≥2 months of age. The integration of the cefepime pharmacokinetic data generated in our study with the MICs for important pathogens responsible for infections in infants and children supports the administration of a dose of 50 mg of cefepime/kg every 12 h for patients ≥2 months of age to treat infections caused by pathogens for which cefepime MICs are ≤8 mg/liter.

Cephalosporins remain one of the most common classes of antibiotics used to treat bacterial infections in both pediatric and adult patients. Over the past 2 decades, these drugs have proven to be very safe, clinically effective, and easy to use (17, 27). Their immense popularity has fostered the discovery and continual development of numerous analogs, resulting in the availability of >30 different cephalosporin antibiotics worldwide for clinical use. The expanded-spectrum cephalosporins (e.g., cefotaxime, ceftriaxone, ceftazidime), either alone or in combination with other agents, are the most common antibiotics used as initial empiric therapy for the treatment of serious infections (16). Unfortunately, their extensive use has been accompanied by the development of antibiotic resistance in some bacterial pathogens (16, 25, 26), underscoring the importance not only of rational clinical use but also of the need for newer agents. Preliminary data assessing the in vitro antibacterial activity, clinical pharmacology, safety, and efficacy of a new class of zwitterionic, 7-methoxyimino cephalosporins are most encouraging. These therapeutic agents are effective against a wide range of bacterial pathogens, including many gram-negative organisms resistant to currently available cephalosporins (6, 19, 23, 24).

Cefepime, one of the new 7-methoxyimino "fourth-generation" cephalosporins, possesses a broad spectrum of antibacterial activity including most gram-positive and gram-negative pathogens responsible for infections in pediatric patients (6, 10, 19, 22–24). In addition, the drug's antibacterial activity encompasses many pathogens resistant to expanded-spectrum cephalosporins (10, 19, 24). The pharmacokinetics of cefepime have been studied extensively in adult subjects with normal (1, 3–5, 13) and impaired renal function (3, 4). These data reveal disposition characteristics for cefepime which are similar to those reported for many of the expanded-spectrum cephalosporins, including linearity over a broad dose range (250 to 2,000 mg) (1), limited metabolism, and clearance primarily by the kidney through glomerular filtration (1, 3–5, 13). In adult subjects with normal renal function, the elimination half-life of cefepime ranges from 2 to 2.3 h, and ~80% of the administered dose is recovered unchanged in the urine (1, 3). Despite these reports, data describing the pharmacokinetics of cefepime in pediatric patients are limited. The purpose of the present investigation was to assess the safety and pharmacokinetics of cefepime after intravenous (i.v.) and intramuscular (i.m.) administration in hospitalized pediatric patients.

(Portions of this work appeared in abstract form at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Fla., October 1994, and the 17th Annual Meeting of the American College of Clinical Pharmacy, 1996.)

MATERIALS AND METHODS

Patient inclusion and exclusion criteria. Infants and children between the ages of 2 months and 18 years admitted to Rainbow Babies and Childrens Hospital with a presumed or documented bacterial infection were eligible to receive cefepime. Patients enrolled in this study represent a subgroup of patients enrolled in an open, clinical evaluation of the efficacy and safety of cefepime

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monotherapy for hospitalized pediatric patients. Patients were excluded from the study if there was (i) a history or documentation of allergy to beta-lactam antibiotics; (ii) evidence of involvement of the central nervous system; (iii) human immunodeficiency virus infection, cystic fibrosis, endocarditis, lung abscess, osteomyelitis, severe burns (20% or more full thickness), or an infected prosthesis; or (iv) granulocytopenia (an absolute granulocyte count of <500/mm^3) or compromised renal function (serum creatinine was >2 mg/dl). The performance of this study was approved by the Institutional Review Board for Human Subjects Investigation of The University Hospitals of Cleveland, and written consent for study participation was obtained from a parent or legal guardian for each patient.

Prior to enrollment and drug administration, each patient provided a complete medical history and underwent a complete physical examination. Blood was obtained for the determination of serum electrolytes, creatinine, urea nitrogen, calcium, phosphorus, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase (AST), total and direct bilirubin, total protein, albumin, and a complete blood count. Urine was sent for urinalysis. These laboratory evaluations were repeated during and on completion of cefepime therapy and were performed by the clinical laboratories of the University Hospitals of Cleveland.

Drug administration and sample collection. Cefepime was provided as a sterile crystalline powder equivalent to 1 g of cefepime per vial (Bristol-Myers Squibb Co., Wallingford, Conn.). The drug was reconstituted with sterile water just prior to administration and further diluted in 20 to 50 ml of normal saline. Each patient received an i.v. infusion of 50 mg of cefepime/kg of body weight, up to a maximum total single dose of 2 g, infused over 30 min and administered every 8 h. Patients were enrolled in the pharmacokinetic segment of the study in an attempt to obtain a fair representation of study subjects in five specific age groups: 2 to <6 months, 6 to <24 months, 2 to <6 years, 6 to <12 years, and >12 years. A subgroup of patients ($n = 8$) received a single cefepime dose by i.m. injection in place of a scheduled i.v. dose, permitting an assessment of cefepime disposition after i.m. administration.

Blood (~1.5 ml) for the determination of cefepime in serum was obtained at 0, 30, and 45 min and at 1, 2, 4, 6, and 8 h after the beginning of the i.v. infusion. This sampling strategy was performed after the first dose and again under steady-state conditions (a minimum of 48 h of uninterrupted therapy). In a subgroup of patients at anticipated steady state, an i.m. injection of an identical dose was substituted for a scheduled i.v. dose, and multiple blood samples were obtained as described above. Blood was collected in sterile glass tubes, allowed to clot, and centrifuged, and the serum was harvested. Similarly, urine was collected before administration of the first dose and as timed aliquots 0 to 4 and 4 to 8 h after the first dose and when possible, 0 to 4, 4 to 8, 8 to 16, and 16 to 24 h after the last dose. All specimens were stored at −70°C and shipped on dry ice to Bristol-Myers Squibb Pharmaceuticals within 4 weeks of collection for cefepime analysis. The quantitation of cefepime in serum and urine was performed by high-performance liquid chromatography as described previously (2).

Pharmacokinetic analysis. The disposition of cefepime was characterized by using standard noncompartmental pharmacokinetic techniques (12). Serum cefepime concentrations were plotted against time on a semilogarithmic scale. The area under the serum concentration-time curve (AUC) was obtained by using the linear trapezoidal rule up to the final measured concentration and was extrapolated to infinity after the first dose and to the end of the dosing interval under steady-state conditions. The terminal elimination rate constant (k_d) and elimination half-life ($t_{1/2}$) were determined by linear regression analysis of the postdistributive terminal portion of the serum concentration-time curve. Total body clearance (CL) was determined by using the formula (dose) (F)/$AUC_{0-\infty}$ after the first dose and (dose) (F)/$AUC_{0-\tau}$ under steady-state conditions, where F is drug bioavailability. Cefepime bioavailability (F) after i.m. administration was determined from the ratio AUC i.m./AUC i.v. for individual patients with paired studies. The apparent steady-state volume of distribution (V_{SS}) was determined by the equation $V_{SS} = [(\text{dose})\ (F)\ (\text{AUMC})/\text{AUC}^2] - [(\text{dose})\ (F)\ (T)/(\text{AUC} \times 2)]$, where AUMC is the area under the first moment of the concentration time curve, and T is the infusion duration. The determination of V_{SS} after multiple dosing was calculated by the method of Yamashita et al. (28). The V was calculated as CL/k, where k is the elimination rate constant. Mean residence time (MRT) was calculated as AUMC/AUC. The renal clearance (CL_R) of cefepime was calculated as $CL_R = A_{0-\tau}/AUC_{0-\tau}$, where A is the cumulative amount of drug excreted within the sampling interval, t, and AUC is the drug AUC in serum during the same time period.

Statistical analysis. Statistical analysis was performed by using analysis of variance, multiple analysis of covariance, paired and unpaired Student's t tests, Pearson correlation, and linear regression analysis. All statistical analyses were performed by using standard methods, with an acceptable level of significance of P of <0.05. Data are presented as means, standard deviations (±SD), and ranges.

RESULTS

A total of 37 patients participated in the pharmacokinetic portion of this study. The clinical and demographic data for these patients are shown in Table 1. Study patients ranged in age from 2.1 months to 16.4 years; 16 were female, and 16 were Caucasian. All subjects had normal renal function for their ages, according to serum creatinine determinations. With the exception of one patient who received one i.v. dose of cefepime for surgical prophylaxis, the duration of cefepime therapy averaged 6.5 (±6) days and ranged from 2 to 13 days. Fifty percent of the study subjects received cefepime for ≤5 days.

TABLE 1. Patient characteristics[a]

Characteristic	Mean (±SD)	Range
Body weight (kg)	16 (16)	3.7–75
Body surface area (m^2)	0.61 (0.44)	
Serum creatinine (mg/dl)	0.4 (0.2)	0.1–0.8
Serum AST (IU/liter)	35 (52)	2–296
Serum total bilirubin (g/dl)	0.4 (0.4)	0–1.7
Subject age for study group		
2–6 mo ($n = 8$)	3.6 (1.3)	2.1–5.9
6–24 mo ($n = 13$)	11.4 (4.1)	6.1–19.1
2–6 yr ($n = 6$)	3.1 (0.8)	2.3–4.4
6–12 yr ($n = 6$)	8.5 (1.7)	6.9–11.2
>12 yr ($n = 4$)	14.1 (2)	12.1–16.4
Cefepime dose (mg/kg)[b]	49 (5)	27–54

[a] $n = 37$.
[b] Individual dose administered was 50 mg/kg with a maximum single dose of 2 g i.v. every 8 h.

The drug was well tolerated by all study subjects. Elevated serum AST determined in two patients at the start of therapy fell during 2 days of cefepime treatment, whereas AST values in two other patients increased during therapy. None of these four patients exhibited any clinical or additional laboratory abnormalities consistent with liver dysfunction. One additional patient had an elevated total serum bilirubin concentration (1.7 mg/dl) after 5 days of cefepime, just before he succumbed to a serious underlying respiratory disease. Three patients developed diarrhea, and two developed nausea and vomiting that usually lasted 1 day, required no therapy, and resolved during cefepime therapy. One patient developed candidal pharyngitis 4 days after cefepime was stopped.

Clinical pharmacokinetics. Thirty-one of the thirty-five study patients with complete serum cefepime concentration-time data received the study target dose of 50 mg/kg. Due to their body weight (>40 kg), four additional patients received the ceiling dose of 2 g (range, 27 to 46 mg/kg); sampling data were incomplete for two patients. The overall mean (±SD) serum cefepime concentration-time curve after the first i.v. dose and after i.m. administration for those patients who received the 50-mg/kg target dose is shown in Fig. 1. Peak serum cefepime concentrations obtained immediately upon completion of the 30-min i.v. infusion averaged 174 (±28) mg/liter, declining linearly to 4.4 (±3.6) mg/liter at 8 h after drug administration. Identical disposition characteristics were observed under steady-state conditions (data not shown), with slight accumulation observed. With repeated dosing, average 0.5-h peak and 8-h trough concentrations were 184.2 (±38) and, excluding troughs from two outliers, 6 (±7) mg/liter, respectively. In contrast, peak serum cefepime concentrations obtained after i.m. administration were much lower, averaging 76 (±41) mg/liter at 0.5 h and falling slightly to 75.2 (±37) mg/liter at 0.75 h and 64 (±33) mg/liter 1 h after injection.

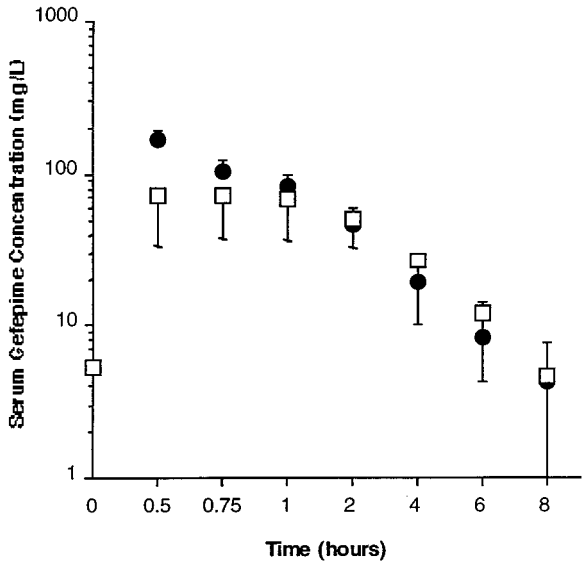

FIG. 1. Overall mean (±SD) cefepime serum concentration-time curve after first dose i.v. administration (●) and intramuscular injection (□). The i.m. injection was administered while patients were receiving multiple doses of cefepime (see text for details).

Eight-hour trough concentrations after i.m. administration averaged 4.8 (±4) mg/liter (Fig. 1).

The cefepime pharmacokinetic parameter estimates obtained after the first dose, subdivided by age, are shown in Table 2. As expected for infants <6 months of age, the cefepime $t_{1/2}$ and MRT were slightly longer than those observed for other age groups. Nevertheless, no statistically significant differences were observed for any of these pharmacokinetic parameter estimates between any age groups (Table 2). Similarly, no differences were observed between the pharmacokinetic data obtained after first-dose administration, under steady-state conditions, and after i.m. administration (individual age group data not shown). Thus, for further presentation and analysis, the data were pooled (Table 3).

Pooled cefepime pharmacokinetic parameter estimates obtained after first dose and again under steady-state conditions and after i.v. and i.m. administration are shown in Table 3. Complete pharmacokinetic analysis was possible for 35 patients after first dose, 31 under steady-state conditions, and 8 patients after i.m. administration (Table 3). Complete urine collections were obtained for 29 and 23 patients after i.v. administration of the first dose and at steady state respectively, and for 7 of 8 patients after an i.m. dose (Table 3). The cefepime $t_{1/2}$ ranged from 1.7 to 1.8 h after i.v. administration and was slightly longer, 1.9 h, after i.m. administration. A similar, apparent prolongation of the cefepime MRT was observed between i.v. and i.m. administration (2.3 versus 3.2 h) (Table 3). Statistical analysis of paired cefepime pharmacokinetic data for the eight patients studied after i.v. and i.m. administration (data not shown) revealed a slight difference for MRT (2.5 versus 3.2 h, $P < 0.05$) and CL (2.9 versus 3.2 ml/min/kg, $P < 0.02$). To further investigate these apparent differences, we analyzed the disposition data obtained after i.m. administration under the conditions of the "flip-flop" phenomenon (8). This analysis confirmed no inherent differences in cefepime MRT, V, or CL between i.m. or i.v. routes of drug administration, indicating the influence of drug absorption from the i.m. injection site on the determination of these pharmacokinetic parameter estimates. The bioavailability of cefepime after i.m. injection averaged 82% (Table 3).

Urinary recovery evaluations revealed approximately 57 to 68% of the administered cefepime dose as unchanged compound in the subjects' urine during the first 8-h sampling period (Table 3 and Fig. 2). CL_R accounted for 60 to 70% of the total body CL, though substantial variation was observed in the total amount excreted during the collection interval. The urinary recovery of cefepime presented as a percentage of the dose administered after the first dose (0- to 8-h sampling period) and the last dose, under steady-state conditions (0- to 24-h sampling period), is shown in Fig. 2. Most of the drug in the urine was excreted over the first 4 h. The total amount of cefepime recovered in the urine after the first dose was 57%, with ~88% recovered after the last dose over the longer 24-h collection period (Fig. 2).

DISCUSSION

Resistance of important bacterial pathogens to commonly used extended-spectrum cephalosporins is increasing with alarming frequency (18, 19, 23–26). Cefepime is a new 7-methoxyimino cephalosporin which possesses a relatively low affinity for and a very high resistance to hydrolysis by Class 1 beta-lactamases (19). Like all 7-methoxyimino cephalosporins, cefepime is a zwitterion maintaining a net neutral charge at pH ranges encountered in vivo. The presence of a positively charged region in the structure of these antibiotics may enhance their penetration through the OmpF porins, which appear to be selective for cations (19). Overall, cefepime and other fourth-generation cephalosporins possess potent in vitro antibacterial activity against a broad spectrum of gram-positive and gram-negative pathogens (6). These drugs possess much greater activity than did earlier cephalosporin analogs against bacterial strains which elaborate Class 1 chromosomally mediated beta-lactamases, pathogens (e.g., *Enterobacteriaceae*) which are increasingly responsible for nosocomial infections in both pediatric and adult patients.

The pharmacokinetic characteristics of cefepime in healthy adult volunteers and subjects with impaired renal function have been adequately described (1, 3–5, 13). In this report, we

TABLE 2. First dose pharmacokinetics of cefepime relative to patient age[a]

Age group and no. of subjects	$t_{1/2}$ (h)	MRT (h)	V (liter/kg)	V_{SS} (liter/kg)	CL (ml/min/kg)	CL_R (ml/min/kg)	CL:CL_R
2–<6 mo (n = 9)	1.9 (0.5)	2.6 (0.7)	0.43 (0.1)	0.37 (0.1)	2.7 (0.7)	1.6 (0.9)	0.58 (0.3)
6–<24 mo (n = 10)	1.6 (0.5)	2.1 (0.7)	0.44 (0.1)	0.35 (0.1)	3.4 (1.3)	1.9 (1.6)	0.52 (0.3)
2–<6 yr (n = 6)	1.5 (0.2)	1.9 (0.4)	0.45 (0.1)	0.33 (0.1)	3.4 (0.5)	2.3 (0.9)	0.64 (0.2)
6–<12 yr (n = 6)	1.5 (0.2)	2.1 (0.4)	0.39 (0.1)	0.32 (0.1)	3.0 (0.6)	2.3 (0.6)	0.81 (0.3)
12–<16 yr (n = 4)[b]	1.7 (0.4)	2.5 (0.6)	0.42 (0.1)	0.38 (0.1)	3.0 (1.2)		

[a] Values are presented as means (±SDs).
[b] Inadequate urine collections prevented determination of CL_R for this group.

TABLE 3. Cefepime pharmacokinetic parameter estimates determined after first dose and again under steady-state conditions[a]

Drug administration (no. of subjects)	$t_{1/2}$ (h)	MRT (h)	V (liter/kg)	V_{SS} (liter/kg)	CL (ml/min/kg)	CL_R (ml/min/kg)	CL:CL_R	Fe (% dose)[b]	F (%)
First dose (n = 35)	1.7 (0.4)	2.3 (0.6)	0.43 (0.1)	0.35 (0.1)	3.1 (0.9)	1.9 (1.1)[c]	0.6 (0.3)[c]	57 (28)[c]	
Steady state (n = 31)	1.8 (0.6)	2.4 (0.9)	0.41 (0.2)	0.33 (0.1)	2.8 (1.4)	2.0 (1.4)[d]	0.62 (0.3)[d]	62.6 (30)	
i.m. (n = 8)	1.9 (0.4)	3.2 (0.7)	0.58 (0.2)	0.55 (0.2)	3.7 (1.5)	2.5 (1.3)[e]	0.74 (0.2)[e]	68.5 (20)[e]	82 (21)

[a] Data are presented as means (±SDs). First-dose and steady-state assessments were determined after i.v. administration; evaluation with i.m. administration was performed under steady-state conditions (see text for details).
[b] Fe, amount of cefepime excreted unchanged in urine over 8-h dosing interval.
[c] n = 29.
[d] n = 23.
[e] n = 7.

describe the disposition characteristics of cefepime in a group of pediatric patients who received the drug as a component of their treatment for presumed or documented infection. A total of 37 infants and children were studied (Table 1). Study subjects ranged in age from 2.1 months to 16.4 years, and 36 patients received repeated doses administered every 8 h from between 2 to 13 days (Table 1). The drug was well tolerated by all study patients. Two patients experienced mild elevations in AST. Three patients developed mild diarrhea, and two developed nausea and vomiting that usually lasted for 1 day and resolved during continued cefepime therapy. One child developed candidal pharyngitis 4 days after stopping cefepime treatment.

Important cefepime pharmacokinetic parameter estimates determined after first dose administration and subdivided by age are shown in Table 2. For the infants <6 months of age, the cefepime $t_{1/2}$ and MRT were slightly longer than those for the older infants and children. Given the dependence of cefepime CL on renal function, this difference is most likely reflective of the active maturation in the infant's renal function, which normally occurs during this period of growth (20). Nevertheless, the pharmacokinetic parameter estimates for the youngest group of patients were similar to and not statistically different from the parameter estimates obtained for older patients (Table 2), underscoring the recommendation of a single dose of cefepime for patients ≥2 months of age. Optimal dosing of cefepime for premature or full-term infants <2 months of age, a period of highly variable and dynamic changes in renal maturation (20), requires specific study and cannot be extrapolated from our data.

The pooled cefepime pharmacokinetic data generated in our study after first dose and under steady-state conditions and after i.v. and i.m. administration are shown in Table 3. No clinically important differences in cefepime disposition were observed between first-dose and steady-state evaluations or between i.v. and i.m. administration. Unlike data reported for healthy adult volunteers, where cefepime bioavailability was found to be 100% (5), cefepime bioavailability after i.m. administration was variable, ranging from 61 to 124%. Overall cefepime bioavailability averaged 82% in the eight subjects studied after i.m. administration (Table 3). The reasons for this difference in cefepime bioavailability between healthy adult volunteers and our pediatric patients are unclear but may reflect differences in drug absorption from i.m. injection sites that could be due to hemodynamic differences accompanying periods of illness. Despite this difference, the cefepime serum concentration-time curve after i.m. administration (Fig. 1) appears to result in cefepime concentrations effective against many target pathogens over an 8- or 12-h dosing interval (Table 4). Nevertheless, the use of the i.m. route for drug administration should be cautiously considered for very sick patients,

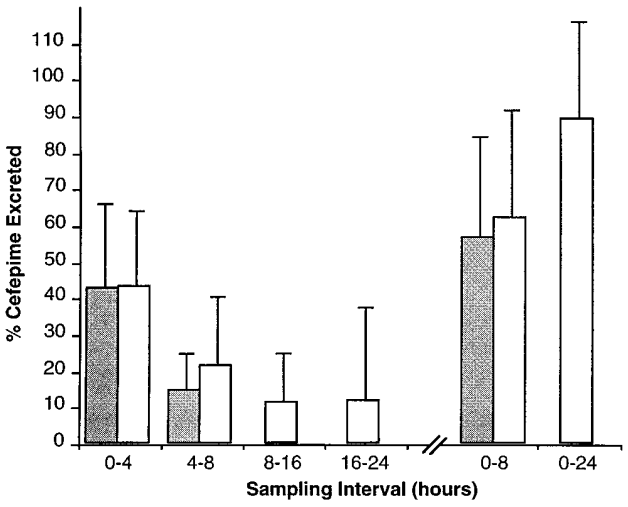

FIG. 2. Urinary recovery of cefepime after the first dose (0 to 8 h, n = 29, [▨]) and after the last dose under steady-state conditions (0 to 24 h, n = 23, [□]). Each bar represents the mean (±SD) of the percentage of the cefepime dose excreted in the aliquots during the intervals shown.

TABLE 4. Predicted pharmacodynamic relationships for cefepime

MIC_{90} (mg/liter)[a]	$T > MIC$ (h)[b]		Representative pathogen(s)
	Total	Free	
≤0.5	14.6	11.4	*Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Escherichia coli*, *Proteus* spp., *Morganella morganii*, *Klebsiella oxytoca*, *Enterobacter aerogenes*, *Citrobacter freundii*, *Serratia marcescens*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*
1	12.9	10.4	*Enterobacter cloacae*, *Enterobacter* spp.
2	11.3	9.2	*Klebsiella pneumoniae*
4	9.6	7.8	
8	7.9	6.4	*Pseudomonas aeruginosa*, *Staphylococcus aureus*

[a] MIC_{90}s, MICs at which 90% of the isolates are inhibited, were obtained from reference 10.
[b] $T > MIC$, the time serum cefepime concentrations exceeded the corresponding MIC. Total, total drug concentration (plasma protein bound plus free protein). Free, analysis performed correcting total serum cefepime concentrations for an expected average 19% binding to plasma protein.

particularly for patients who are hemodynamically unstable. Although statistically significant differences were observed for cefepime MRT ($P < 0.05$) and CL ($P < 0.02$) between i.v. and i.m. administration (Table 3), these differences appear to be of minimal clinical significance and artifactual, merely reflecting the influence of cefepime absorption from the i.m. injection site on the determination of the elimination rate constant, k_d. Similar differences have been described for adults (5).

Compared to published cefepime pharmacokinetic data for adults (6), the disposition characteristics of cefepime for infants and children (Table 3) appear to reflect a slightly shorter overall $t_{1/2}$ (1.7 versus 2.2 h), larger V_{SS} (0.35 versus 0.21 liter/kg), and a more rapid CL (3.1 versus 1.5 ml/min/kg). These differences in cefepime disposition between children and adults are consistent with data describing increased rates of elimination and relatively larger Vs for other beta-lactam and cephalosporin antibiotics in pediatric patients (14), including moxalactam (21), cefotaxime (15), and ceftazidime (7). Despite these differences in disposition characteristics between children and adults, the maintenance of cefepime serum concentrations (Fig. 1) in pediatric patients above the MICs for important pathogens (Table 4) supports similar cefepime dosing intervals for pediatric and adult patients.

The clinical pharmacokinetic data generated in the present study provide a foundation for the design of rational dosing regimens for cefepime for the treatment of bacterial infections occurring outside the central nervous system in infants and children. For beta-lactam antibiotics, most authorities have advocated the time the serum drug concentration exceeds the MIC for the pathogen as a primary determinant of antibacterial efficacy (9, 11). Integration of the pooled cefepime pharmacokinetic data generated from our pediatric patients (Table 3) with the MICs for important pathogens responsible for infections in infants and children is shown in Table 4. The time cefepime serum concentrations exceed the MICs for these important pathogens (Table 4) supports the administration of a dose of 50 mg of cefepime/kg every 12 h for patients $\geq$2 months of age for the treatment of infections caused by pathogens for which cefepime MICs were $\leq$8 mg/liter. This target MIC range of $\leq$8 mg/liter encompasses the vast majority of pathogens for which cefepime would be used in pediatric patients and is reflective of the drug's potent in vitro antibacterial activity.

ACKNOWLEDGMENTS

Support for this work was provided, in part, by Bristol-Myers Squibb Co., The Children's Research Foundation of Cleveland, and the Pediatric Pharmacology Research Unit grant HD 31323-02.

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