ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1995, p. 1721–1725 Vol. 39, No. 8
0066-4804/95/$04.00+0

Sequential, Single-Dose Pharmacokinetic Evaluation of Meropenem in Hospitalized Infants and Children

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Received 20 June 1994/Returned for modification 14 October 1994/Accepted 1 May 1995

Meropenem is a new carbapenem antibiotic which possesses a broad spectrum of antibacterial activity against many of the pathogens responsible for pediatric bacterial infections. In order to define meropenem dosing guidelines for children, an escalating, single-dose, pharmacokinetic study at 10, 20, and 40 mg/kg of body weight was performed. A total of 73 infants and children in four age groups were enrolled in the study: 2 to 5 months, 6 to 23 months, 2 to 5 years, and 6 to 12 years. The first patients enrolled were those in the oldest age group, who received the lowest dose. Subsequent enrollment was determined by decreasing age and increasing dose. Complete studies were performed on 63 patients. No age- or dose-dependent effects on pharmacokinetic parameter estimates were noted. Mean pharmacokinetic parameter estimates were as follows: half-life, 1.13 ± 0.15 h; volume of distribution at steady state, 0.43 ± 0.06 liters/kg; mean residence time, 1.57 ± 0.11 h; clearance, 5.63 ± 0.75 ml/min/kg; and renal clearance, 2.53 ± 0.50 ml/min/liters kg. Approximately 55% of the administered dose was recovered as unchanged drug in the urine during the 12 h after dosing. No significant side effects were reported in any patients. By using the derived pharmacokinetic parameter estimates, a dose of 20 mg/kg given every 8 h will maintain plasma meropenem concentrations above the MIC that inhibits 90% of strains tested for virtually all potentially susceptible bacterial pathogens.

Infants and children presenting with signs and symptoms of infection remain challenging clinical problems. Patients with infections thought to be mild are generally treated with oral antibiotics, while those appearing to have moderate to severe infections are frequently admitted to the hospital for parenteral antibiotic therapy (20).

Decisions concerning antibiotic selection are ideally made on the basis of pathogen identification and known susceptibility patterns (16). Unfortunately, this is seldom possible in infants and children. Children who have moderate or severe infections require the initiation of therapy before any culture or antimicrobial susceptibility data are available. Thus, therapy is generally initiated on an empiric basis. In many cases, cultures are not obtained because invasive procedures are involved in sampling the infected material. When cultures are obtained, they are usually limited to blood and urine samples collected by any one of a variety of techniques. The results of these efforts are often negative and lead to a continued reliance on empiric drug selection.

This reliance on empiric antibiotic therapy poses a particular challenge to clinicians treating pediatric patients. Children are susceptible to infections caused by a wide range of bacterial pathogens (20). The frequency with which these pathogens are seen, as well as the sites most often involved, show a marked age dependence. As a result, empiric regimens involving two and three drugs are quite common in the treatment of moderate to severe infections in these patients (14).

Recently, a number of the bacterial pathogens that commonly account for pediatric infections have developed resistance to the antibiotics most often used to treat pediatric patients (1). This has resulted in the use of more complex, more expensive multiagent regimens. There is an urgent need for a single agent possessing potent activity against a wide range of pathogens and sharing the broad margin of safety that characterizes the antibiotics currently used in the treatment of moderate to severe infections in children.

Meropenem is a novel β-lactam antibiotic belonging to the carbapenem class (17). It has an in vitro spectrum of activity that includes virtually all of the bacteria for which empiric coverage might be desired in a pediatric patient (13, 23). Unlike the only clinically available carbapenem, imipenem, meropenem is four times more stable against inactivation by human renal dehydropeptidase-I (8). In order to determine a possible role for meropenem in the treatment of infections in children, an appropriate dosing strategy must be developed. This requires a thorough understanding of the biodisposition of meropenem in this patient population. The present study was designed to evaluate the safety, tolerance, and pharmacokinetics of single doses of meropenem administered to infants and children 2 months to 12 years of age.

(Portions of this work were presented at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, Calif., 11 to 14 October 1992.)

MATERIALS AND METHODS

Study design. The study described here was a multicenter, open-label, sequential, parallel-group trial. Eligible subjects were hospitalized pediatric patients who were in generally good condition, were clinically stable, and either had completed a minimum of 2 days of conventional therapy for a specific bacterial infection or were currently receiving intravenous prophylactic antibiotics. Meropenem was substituted for one of the doses of prescribed antibiotics. The protocol was approved by the appropriate institutional review boards, and written consent was obtained from a parent or legal guardian before patient enrollment.

Study procedures. Patients were stratified into four groups by age: 2 to 5 months, 6 to 23 months, 2 to 5 years, and 6 to 12 years. Each group was to consist of six patients per dose. Meropenem (10 mg/kg of body weight) was first given to the oldest group and then to each successively younger group. Higher doses (20

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TABLE 1. Patient characteristics

Characteristic	Mean (± SD)	No.	Range
No. of patients		63	
No. of males, no. of females		38, 25	
No. of patients in meropenem dose (mg/kg) group:			
10		20	
20 mg/kg		25	
40 mg/kg		18	
Patient age (yr)	4.0 (3.5)		0.23–12.3
Body weight (kg)	16.5 (11.0)		3.7–45
Serum creatinine (mg/dl)	0.45 (0.2)		0.2–1.10
Total bilirubin (mg/dl)	0.46 (0.5)		0–2.4
Meropenem dose (mg)	369 (398)		39.4–1,000

and 40 mg/kg) were given after all age groups had reasonable exposure at the previous dose. A maximum dose of 1 g was allowed. The infusion of other solutions was temporarily discontinued, and an infusion pump was used to administer each intravenous dose of meropenem over 30 min.

Blood samples for meropenem analysis were taken immediately before infusion and at 30 (end of infusion), 60, 120, 240, 360, and 480 min after the start of dosing. Plasma samples were transferred into polypropylene tubes, rapidly frozen in dry ice, and maintained at −70°C until they were analyzed.

Urine samples were collected for determination of the concentration of meropenem and the only identified metabolite, ICI 213,689, before dosing and over four time intervals: 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after dosing. For each patient, during each collection interval the volume of urine was measured and the samples were pooled, mixed, and stored in the refrigerator. Two 5- to 10-ml aliquots were removed, frozen on dry ice, and maintained at −70°C until they were analyzed.

Safety was determined by using both clinical and laboratory parameters. Complete physical examinations were performed within 24 h before and within 24 h after dosing. Vital signs were obtained immediately before, during (15 min into the infusion), and at the end of the meropenem infusion and at 60, 120, 240, 360, 480, and 720 min after the start of the drug infusion. Clinical laboratory tests including hemoglobin, hematocrit, erythrocyte, leukocyte, and differential counts; platelet counts; prothrombin time; activated partial thromboplastin time; direct and indirect Coombs test; aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total protein, total bilirubin, blood urea nitrogen, serum albumin, serum creatine, sodium, potassium, and chloride levels; and gross and microscopic urinalyses were performed along with the physical examinations.

Determination of meropenem in concentration plasma. A validated, reverse-phase high-performance liquid chromatography (HPLC) procedure was used to determine the concentration of meropenem in plasma (11). The assay is based on a solid-phase extraction that is followed by reverse-phase chromatography with UV detection at 296 nm. Plasma samples (0.1 ml) were first adsorbed to preconditioned C_{18} Bond Elut extraction columns which were then washed with 50 mM KH_2PO_4. Meropenem was then eluted with 0.8 ml of HPLC eluent. A portion of the eluent was injected onto a 3 μM Hyperal octyldecyl silane column (4 mm [inner diameter] by 10 cm) and was eluted with methanol-tetrabutyl ammonium dihydrogen phosphate (5 mM) at a ratio of 12:88 (vol/vol). The limit of detection of this assay was 60 ng/ml, with a limit of quantitation of ~500 ng/ml. The intraday and between-day coefficients of variation were 4.3 and 6.7 overall, respectively, with values for the low and high quality control concentrations varying from 3.9 to 3.1 within days and from 7.2 to 5.6 between days, respectively.

Determination of meropenem and metabolite concentrations in urine. Urine meropenem concentrations were measured by direct injection of diluted urine (typically 1:10 [vol/vol] in distilled water) onto a similar reverse-phase column. Acetonitrile–10 mM phosphate buffer (pH 7.4; 6:100 [vol/vol]) was used as the elution solvent. The limits of detection and quantitation were 1.0 μg/ml, with intraday and between-day coefficients of variation equal to 2.4 and 6.7, respectively.

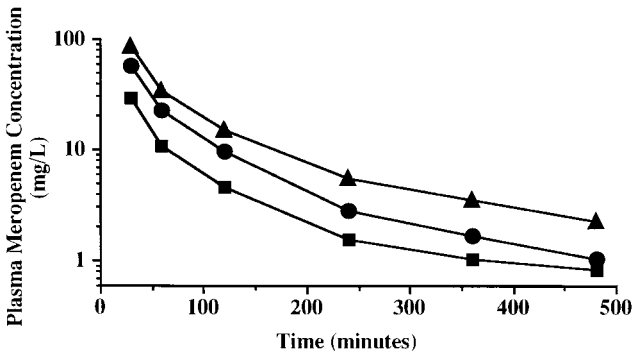

FIG. 1. Meropenem plasma concentration-time curves. Infants and children received either 10 (■), 20 (●), or 40 (△) mg of meropenem per kg of body weight as a 30-min infusion. Blood sampling was performed as described in Materials and Methods. Each point represents the mean of values from all patients receiving the indicated dose. Standard deviations did not exceed 15% of the mean at any time point for any dose.

ICI 213,689 concentrations in urine were determined by a specific validated radioimmunoassay with a limit of quantitation of 40 ng/ml. The overall within-day and between-day coefficients of variation were 7.7 and 10.9, respectively.

Pharmacokinetic analysis. The disposition of meropenem was characterized by standard noncompartmental techniques (10). Plasma meropenem concentrations for each patient were plotted against time on a semilogarithmic scale. The area under the plasma drug concentration-time curve (AUC) was obtained by the linear trapezoidal rule up to the final measured concentration and was extrapolated to infinity ($AUC_{0-\infty}$). The extrapolated portion was generally <5% of the measured area. The terminal elimination rate constant (K_d) and elimination half-life ($t_{1/2}$) were determined after nonlinear least-squares regression analysis was used to fit a line to the datum points. Then, the points in the postdistributive terminal portion of the curve were selected by visual inspection and were used to calculate K_d; $t_{1/2}$ was calculated as $0.693/K_d$. Total body clearance (CL) was determined by using the formula dose/$AUC_{0-\infty}$. The apparent steady-state volume of distribution (V_{SS}) was determined by the equation: Vss-[(dose)(AUMC)/AUC2]-[(dose)(*T*)/(AUC × 2)], where AUMC is the area under the first moment of the concentration time curve, and *T* is the infusion duration. The volume of distribution (*V*) by the area method was calculated as CL/K_d, and mean residence time (MRT) was calculated as $AUMC/AUC_{0-\tau}$, where τ is the last measured concentration. The renal clearance (CL_R) of meropenem for each patient having complete urine collections (48 of 63 patients studied) was calculated by the equation $CL_R = A/AUC$, where *A* is the cumulative amount of drug excreted within the sampling interval and AUC is the AUC of the drug in plasma extrapolated to the end of the urine collection period (26).

Statistical analysis. Two-way analysis of variance was performed to evaluate the pharmacokinetic data. The analysis of variance model included age, effect, dose effect, and interactions between age and dose. The linear dose trend and the linear age trend were also examined. The present study was designed to expose a minimum number of patients representing a clinically acceptable distribution of age and doses; thus, a priori power considerations were not made.

RESULTS

A total of 73 patients participated in the study. While the safety and tolerance of the drug were evaluated in all patients, pharmacokinetic data are reported for only 63 children (Table 1). Patients were excluded from pharmacokinetic analysis be-

TABLE 2. Effect on dose on meropenem pharmacokinetics[a]

Meropenem dose (mg/kg)	$t_{1/2}$ (h)	*V* (liters/kg)	V_{SS} (liters/kg)	MRT (h)	CL (ml/min/kg)	CL_R (ml/min/kg)	CL_R:CL	*F′* from 0–12 h (% dose)[b]
10 (n = 28)	1.0 (0.4)	0.4 (0.1)	0.4 (0.1)	1.5 (0.4)	5.2 (1.3)	2.6 (1.0)	0.53 (0.19)	0.61 (0.08)
20 (n = 25)	1.1 (0.5)	0.4 (0.1)	0.4 (0.1)	1.5 (0.5)	5.2 (1.6)	2.0 (1.3)	0.39 (0.21)	0.52 (0.14)
40 (n = 18)	1.3 (0.6)	0.6 (0.2)	0.5 (0.1)	1.7 (0.7)	6.5 (2.0)	3.0 (2.1)	0.46 (0.28)	0.48 (0.26)

[a] Values are expressed as means (± standard deviations).
[b] *F′* is bioavailability (complete data only).

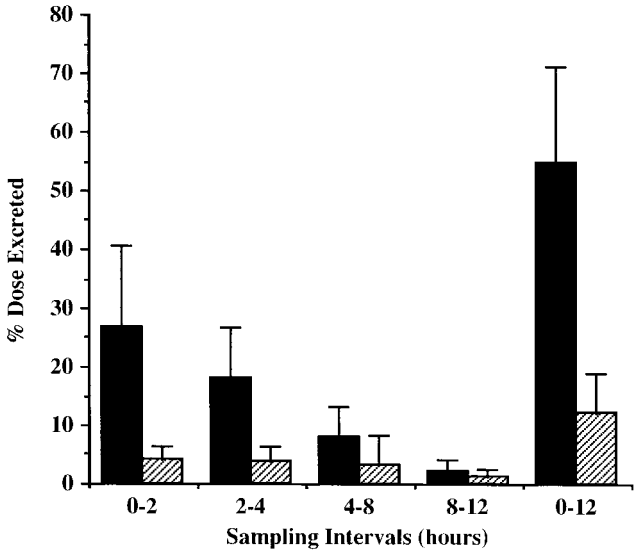

FIG. 2. Recovery of meropenem and the ICI 213,689 metabolite in urine. Urine was collected in aliquots as depicted and analyzed for meropenem and its major metabolite. Each bar represents the mean ± standard deviation of the amount excreted expressed as a percentage of the dose of meropenem administered. ■, meropenem ▨, ICI 213,689.

cause of assay interference (seven patients), inadequate blood sampling (two patients), and renal functional impairment identified just after drug administration (one patient).

Effect of dose on meropenem pharmacokinetics. Patients were enrolled sequentially into one of three dose groups. Plasma concentration-time curves for these three dose groups showed that the peak concentration in plasma (Cp_{max}) and AUC increased proportionately from 10 to 20 mg of meropenem per kg (Fig. 1). The increments in Cp_{max} and AUC from 20 to 40 mg meropenem per kg were somewhat blunted, changing from 56.9 to 92.1 μg/ml and 72.4 to 133.7 μg · hr/ml, respectively. This blunting may reflect both the small number of patients studied in each dose group as well as the setting of the maximal dose at 1.0 g.

No dose-dependent differences were observed in $t_{1/2}$, V_{SS}, CL, or CL_R among the doses studied (Table 2). There were no statistically significant differences in the urinary recovery of meropenem among the three doses, with approximately 55% of the administered dose recovered as parent drug and 12% recovered as metabolite in the first 12 h following drug administration (Fig. 2). CL_R accounted for almost half of the CL of meropenem.

Effect of age on meropenem pharmacokinetics. Patient enrollment was initially stratified into four groups by age. Between 2 months and 12 years of age, the $t_{1/2}$ fell from 1.67 to 0.8 h ($P = 0.0003$) (Table 3). Changes in V_{SS} showed the expected decreasing trend with age, but this trend failed to achieve statistical significance (Table 3). MRT and CL_R also showed age-dependent decreasing trends which did not reach statistical significance. In contrast, CL showed the kind of pattern frequently seen with renally eliminated drugs (3). That is, CL appeared to increase gradually from 2 months through 5 years of age and then decline. None of these changes were statistically or clinically significant.

Urinary recovery of meropenem and its metabolite as a fraction of the administered dose was also independent of age (Fig. 3). However, the fraction of CL attributed to CL_R showed a decreasing trend with increasing age (Table 3).

Safety and tolerance. Infusions of meropenem were well tolerated by virtually all patients; one child appeared to have some redness at the injection site. Clinical adverse events were limited, and some may not have been entirely drug related. The following adverse events were noted during the study: chest pain ($n = 3$ patients), vomiting ($n = 3$), rash ($n = 2$), fever ($n = 1$), nausea ($n = 1$), injection site reaction ($n = 1$), and hypotension ($n = 1$). No laboratory abnormalities were reported as a result of drug exposure in any patient.

DISCUSSION

Meropenem is a new member of the class of carbapenem antibiotics currently under evaluation for the treatment of moderate to severe infections in adult patients. As with other β-lactam antibiotics, meropenem is bactericidal against susceptible bacteria in vitro because it inhibits bacterial cell wall synthesis (17). Studies of the in vitro activity of meropenem have demonstrated a broad spectrum of antibacterial activity which includes activity against pathogens resistant to aminoglycosides and other β-lactam antibiotics (13, 21, 23). The *trans* configuration of the hydroxyethyl side chain and hydrogens protects the parent β-lactam structure from inactivation by both penicillinase and cephalosporinase, whereas the dimethylcarbamoylpyrrolidinethio chain attached to C-2 enhances the compound's antipseudomonal activity (24, 27).

The spectrum of activity of meropenem includes all of the bacterial pathogens that commonly cause infections in infants and children (13, 23). Therefore, meropenem would seem to be a valuable addition to the pediatric antimicrobial armamentarium. In order to evaluate the efficacy of meropenem in this patient population, a pharmacologically sound dosing strategy must be developed.

The present study evaluated the pharmacokinetics of meropenem after single-dose administration at three dosages. Patients receiving the drug were stratified by age into four groups. Overall, meropenem appeared to exhibit first-order elimination following a 30-min infusion of drug (Fig. 1). Dose proportionality was observed for Cp_{max} and AUC when the dose was

TABLE 3. Effect of age on meropenem pharmacokinetics[a]

Patient age	$t_{1/2}$ (h)	V (liters/kg)	V_{SS} (liters/kg)	MRT (h)	CL (ml/min/kg)	CL_R (ml/min/kg)	CL_R:CL	Fe from 0 to 12 h (% dose)[b]	FeM from 0 to 12 h (% dose)[b]
2–5 mo ($n = 9$)	1.6 (0.6)	0.5 (0.1)	0.4 (0.1)	2.2 (0.4)	4.3 (1.6)	2.6 (2.0)	0.54 (0.26)	59 (13)	12 (5)
6–23 mo ($n = 17$)	1.3 (0.4)	0.6 (0.2)	0.4 (0.1)	1.6 (0.4)	5.3 (1.4)	2.4 (1.0)	0.48 (0.18)	47 (20)	16 (10)
2–5 yr ($n = 19$)	1.0 (0.4)	0.5 (0.2)	0.4 (0.1)	1.4 (0.4)	6.2 (1.9)	2.8 (1.7)	0.46 (0.23)	57 (15)	10 (4)
6–12 yr ($n = 18$)	0.8 (0.2)	0.4 (0.1)	0.3 (0.1)	1.3 (0.2)	5.8 (1.5)	2.1 (1.4)	0.38 (0.25)	64 (1)	8 (1)

[a] Values are expressed as means (± standard deviations).
[b] Fe and FeM, fraction of meropenem excreted from 0 to 12 h expressed as percentage of dose and fraction of metabolite excreted from 0 to 12 h expressed as percentage of meropenem dose administered (complete data only).

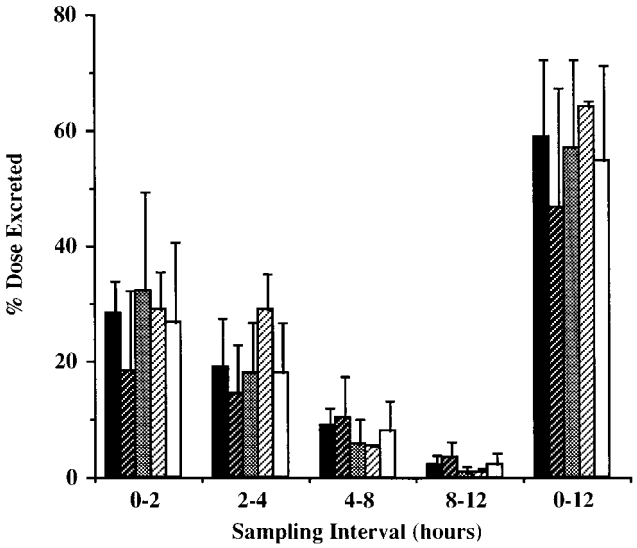

FIG. 3. Effect of age on urinary meropenem recovery. Meropenem excretion in urine expressed as a percentage of the administered dose is shown for each age group studied. Each bar represents the mean ± standard deviation. ■, 2 to 5 months; ▨, 6 to 23 months; ▩, 2 to 5 years; ▨, 6 to 12 years; □, overall.

increased from 10 to 20 mg/kg. Further doubling of the dose from 20 to 40 mg/kg resulted in a slight deviation from this linear relationship. The latter most likely reflects the small sample size used in the study and the fact that in the 40-mg/kg dose group, four patients received the maximal dose and were therefore not truly dosed on a milligram-per-kilogram basis. When the data for these patients were eliminated from the analysis the dose proportionality was only slightly improved. Thus, the loss of dose proportionality in going from 20 to 40 mg/kg may reflect a sampling artifact or may represent a true increase in CL at higher doses.

Among the other pharmacokinetic parameter estimates no effect of dose was observed (Table 2). The elimination $t_{1/2}$ was approximately 1 h, which was very similar to that reported for adult patients (2, 4, 15, 28). Likewise, V_{SS}, CL, and CL_R were all indistinguishable from the values obtained in adult subjects. The stability of meropenem to degradation by renal dehydropeptidase-I was confirmed in children, with approximately 55% of the administered dose recovered unchanged in the urine during the 12 h following drug administration (Tables 2 and 3). This fraction was somewhat less than the 71 percent recovery reported for adult patients, but it far exceeded the 20% recovery reported for imipenem (18) when administered without the renal dehydropeptidase-I inhibitor, cilastatin.

Evaluation of the effect of age on the derived meropenem pharmacokinetic parameter estimates revealed the expected decrease in elimination $t_{1/2}$ with increasing age (3). To some extent this was compensated by a decreasing V_{SS}, so that CL appeared to be age independent. There was a trend toward increasing nonrenal CL with increasing age which was unrelated to the production of the primary meropenem metabolite, ICI 213,689. This is consistent with the ontogeny of biliary excretory function (25).

The results of the present study are consistent with those reported in a similar study of meropenem performed in Japan (7) and in a study of the pharmacokinetics of imipenem performed in a small number of children in the United States (6, 12). Meropenem appears to have a somewhat longer elimination $t_{1/2}$ and a smaller V than those reported for imipenem.

TABLE 4. Predicted duration of effect expressed as time above the MIC for meropenem administered at 20 mg/kg per dose

Representative pathogen	MIC (mg/liter)[a]	Time above the MIC (h)	
		8-h dosing	12-h dosing
Streptococcus pyogenes	0.01	17	15
Neisseria meningitidis	0.25	16	14
Streptococcus pneumoniae, *Neisseria gonorrhoeae*, *Shigella* spp.; *Salmonella* spp. *Salmonella* spp.	0.05	14.2	12
Staphylococcus aureus, group B streptococci	0.10	13	11
Escherichia coli, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Listeria monocytogenes*	0.25	11.5	9.5
Enterobacter cloacae, *Bacteroides fragilis*	0.50	10.2	8.3
Serratia marcescens	1.00	9	7.1
Pseudomonas aeruginosa	2.00	7.8	5.7

[a] Values are taken from references 13, 21, and 23.

The importance of performing pharmacokinetic studies with antimicrobial agents is to use the derived data to determine rational dosing strategies for treating infections. This requires an integration of the pharmacokinetic parameters with pharmacodynamic characteristics determined in vitro. The in vitro pharmacodynamic correlate most commonly used to make these assessments is the MIC (5, 9). By using this and the premise that, for β-lactam antibiotics, drug must be present at inhibitory concentrations at the site of infection throughout the dosing interval, a dosing recommendation can be made on a pharmacokinetic basis. This involves an examination of the time that the serum (plasma) drug concentration is above the MIC for the infecting organism (22). With this approach, at any given dose a dosing interval can be ascertained by projecting the plasma concentration-versus-time curve onto the MIC for a susceptible organism. Such an integrated pharmacokinetic-pharmacodynamic analysis was performed for meropenem administered at 20 mg/kg every 8 or 12 h (Table 4). At this dose all organisms listed should be effectively treated with dosing every 8 h. In fact, with the exception of *Serratia marcescens*, and *Pseudomonas aeruginosa*, 20 mg of meropenem per kg every 12 h would be expected to be an optimal dose on pharmacological principles.

On the basis of the pharmacokinetic parameters derived in the present study, meropenem can be given at doses up to 40 mg/kg at 8-h intervals to infants and children without the risk of drug accumulation. The favorable safety and tolerance profile, as well as the predicted clinical efficacy of the drug, supports its further evaluation for the treatment of infections in children.

ACKNOWLEDGMENT

The study was supported in part by ZENECA Pharmaceuticals.

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