Cefepime: pharmacokinetics in children (original research)

A pharmacokinetic review of cefepime in children
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Abstract
This paper presents the results of pharmacokinetic evaluations in children who received cefepime after either intravenous or intramuscular administration. The mean total clearance rate, volume of distribution and half-life of cefepime in children, aged two months to less than 12 years, who were given the drug either in a single or in multiple doses were 3.32 mL/min/kg, 0.34 L/kg, and 1.66 hours, respectively. These parameters are similar to what has been observed with other antibiotics that have been used in children. When compared to published pharmacokinetic data in adults, the characteristics of cefepime in infants and children appear to reflect a slightly shortened half-life, a more rapid clearance and a larger volume of distribution. Based on this data, the recommended dose of cefepime in children two months to 12 years is 50 mg/kg every 8 or 12 hours, to a maximum of 2,000 mg per dose. In infants less than two months of age, the dose is 30 mg/kg every 8 or 12 hours.

Key words: cefepime, pharmacokinetics, infants, children, meningitis, half-life, volume of distribution

Introduction
Cefepime, a fourth-generation cephalosporin, is a valuable option in the treatment of lower respiratory tract infection, urinary tract infections, skin and skin structure infections, bacterial meningitis and other infections caused by Gram-positive and Gram-negative microorganisms. While its pharmacokinetics are well documented in adults [Data on file, Bristol-Myers Squibb], new pediatric studies enhance the administration of this antibiotic in that population with data that ensures proper concentrations in many physiological compartments, including the cerebrospinal fluid (CSF). The purpose of this paper is to review the pharmacokinetic data that were obtained following clinical studies using cefepime in the pediatric population in a variety of infections, at different drug dosages and frequencies of administration.

Pharmacokinetic data in adults
Cefepime is administered either intravenously (IV) or intramuscularly (IM). When given IM, cefepime in adult subjects is 100 percent absorbed from the injection site, with mean peak serum concentrations occurring at 1.0 to 1.6 hours. [Barbhaiya, 1990, abstract] Cefepime has a linear pharmacokinetic profile with an elimination half-life of about 2.1 hours. As are other cephalosporins, cefepime is primarily renally excreted, and does not accumulate in persons with normal renal function following multiple dose administration. [Barradell, 1994, p. 486]

Pharmacokinetics profiles do not appear to vary between single and multiple doses of the drug, indicating a lack of drug accumulation in humans with normal renal function. With binding values of approximately 16 to 19 percent, cefepime is not highly bound to plasma protein. More than 80 percent of the administered dose was excreted in the urine as unchanged cefepime in patients with normal renal function. [Okamoto, 1993, abstract] The drug is distributed in various biological tissues and fluids, including maxillary sinus, tonsillar tissue, skin, bronchial mucosal tissue, peritoneal fluid, and breast milk. [Barradell, 1994, p. 486-487] The volume of distribution in healthy adults after a single dose of cefepime is 0.21 L/kg. Barradell, 1994, p. 487, Table VI]

Effects of renal function
Total clearance of cefepime decreases as renal function deteriorates, although the volume of distribution at steady state does not appear to change, regardless of kidney function. [Cronqvist, 1992, abstract] The area under the concentration-time curve also increases as renal function declines. In normal volunteers, the half-life of cefepime was about two hours; in patients with moderate and severe renal impairment, the half-live increased to 4 and 12 hours, respectively. [Barbhaiya, 1991, abstract] Such changes in clearance necessitate dosage adjustments when cefepime is given to patients with renal impairment.

Effects of age
When healthy elderly volunteers, ages 65 to 81 years, were compared to younger volunteers, ages 20 to 40 years, many age-related differences were observed for many pharmacokinetic parameters of cefepime, such as half-life, total and renal clearance, and area under the plasma cefepime concentration-time curve. [Barbhaiya, 1992, abstract]

Pharmacokinetic studies in children are rare in the published literature. One study involved infants and children, aged two months to 15 years, with a diagnosis of meningitis. Here, cefepime 50 mg/kg IV q8h, was infused over 15 to 20 minutes, and produced mean cerebrospinal fluid concentrations of 5.7 and 3.3 micrograms/mL at 30 minutes and eight hours after the first dose, respectively. The cerebrospinal fluid-plasma ratios were 0.09 at 30 minutes and 0.67 at eight hours and greatly exceed the minimum inhibitory concentrations of the patients' meningeal pathogens. [Saez-Llorens, 1995, p. 938, 939]

Multicenter clinical data in the pediatric population
Methods
A total of 411 pediatric patients were enrolled in four studies that included a pharmacokinetic evaluation of cefepime. [Table 1] In the resistant pathogen study (999), 20 patients were treated with cefepime on a compassionate used basis; 19 were treated for multiply-resistant Salmonella Type B infections and one patient was treated with two courses of cefepime for treatment of a bone and joint infection caused by Enterobacter cloacae. [AI411 ISS, 2.1.4, p.19] One study (126) was designed to assess the efficacy of cefepime monotherapy in the treatment of suspected central nervous system (CNS) infections, including bacterial meningitis. Eligibility criteria were based on the presence of meningeal signs (stiff neck, Kerning's or Brudzinski's signs) and other neurologic signs associated with meningitis (headache, focal neurologic deficit) as well as on confirmation by cerebrospinal fluid (CSF) examination (leukocytosis with a predominance of polymorphonuclear forms and an elevated protein level). [AI411 ISS, 2.1.1, p. 18] One study (129) was designed to assess the efficacy of cefepime monotherapy in the treatment of serious bacterial infections, including those involving the urinary tract, the respiratory tract, and skin and soft tissue. Study 129 was an open, non-comparative study that employed cefepime at a dose of 50 mg/kg either q12h or q8h. [AI411 ISS, 2.1.2, p.18] Study 128 enrolled twelve children who were hospitalized for treatment of a non-life-threatening infection; the pharmacokinetics of cefepime were assessed in these patients after receiving single doses of either 30 or 50 mg/kg.

In evaluating cefepime pharmacokinetics in the patients, serial blood and urine samples were collected a single dose and/or at steady state, defined as after at least two days of dosing. Samples were collected over an 8- or 12-hour period, depending on the dosing schedule. Study 129 assessed the penetration of cefepime into sputum while study 126 assessed the antibiotic's penetration into CSF. Validated high performance liquid chromatographic methods with ultraviolet detection were employed to quantify the

amount of cefepime in plasma, sputum, CSF and urine samples. To generate pharmacokinetic parameters, concentration-versus-time data were analyzed using noncompartmental methods. [AI411 ISS, 2.3, p. 29]

Results

In the meningitis study, the penetration of cefepime into CSF was assessed after two or three days of treatment with a 50 mg/kg regimen, thus approximating steady state. In the serious bacterial infection study, the pharmacokinetic profile was based on the administration of a single 30 or 50 mg/kg dose of cefepime, given to children, age two months to less than 12 years, [AI411 ISS, p. 61] who were being treated for a non-life-threatening infection. In the non-comparative study that used cefepime to treat serious bacterial infections in children, pharmacokinetic parameters were noted following single and multiple doses of the drug at 50 mg/kg, dosed either q8h or q12h, to different groups of patients within the study. Suspected bacteremia, serious lower respiratory tract infections such as lobar pneumonia, urinary tract infections such as pyelonephritis, and skin and skin structure infections were included in the diagnoses of the children included in this study. Finally, in the compassionate use study, a limited number of blood samples were collected from three patients after several cefepime doses. [AI411 ISS, 3.0, p. 36]

Pharmacokinetics of cefepime following a single 30 or 50 mg/kg dose

The pharmacokinetics of cefepime were observed in seven and two patients between the ages of 2 and 12 years following a single dose of 30 or 50 mg/kg, respectively. The results demonstrated dose-related increases in maximum concentration (CMAX) and area under the curve (AUC). Both doses used showed similar half-lives (T-HALF), total clearance, and volume of distribution at steady state (VSS). Although T-HALF of cefepime was observed as somewhat shorter in children than in healthy non-elderly adults (1.6 hr versus 2.1 hours), urinary excretion was still the primary route of excretion, as in adults. [AI411 ISS, p. 61]

Pharmacokinetics of cefepime dosed at 50 mg/kg q8h

Thirty-seven infants and children, aged two months to 16 years, were evaluated following single and multiple doses of cefepime. Each patient was administered an IV infusion of 50 mg/kg, up to a maximum single dose of 2 g. The drug was infused over 30 minutes every eight hours. In this study, five age groups were assessed: 2 months-<6 months, 6 months-<24 months, 2 years-<6 years, 6 years-<12 years, and 12 years-18 years. In addition, eight children who were at presumed steady state, received cefepime IM instead of the scheduled IV dose.

Tables 2 and 3 show the pharmacokinetic profiles of these patients at both first dose and at steady state. Following IV administration, the mean CMAX was 168.3 g/mL and 188.6 g/mL after the first dose and at steady state, respectively. After IM administration, the mean CMAX was 68.4 g/mL. In the IV cefepime group, significant differences were also observed between the first dose and steady state in AUC, T-HALF, and CLT. Similarly, following IM administration, the mean AUC value was lower than after IV administration (231.1 micrograms.hr/mL versus 313.3 micrograms.hr/mL, respectively). At 1.83 hours, the T-HALF following IM administration was comparable to the value following IV administration. However, in the eight patients who received cefepime intramuscularly, the absolute bioavailability of the drug (F) at steady state was 82.3 percent, as compared to total bioavailability following IM administration in adults. [AI411 ISS, p. 62] Table 4 breaks out pharmacokinetic parameters according to the five age groups and shows both first dose and steady state data following the administration of cefepime at 50 mg/kg TID. The data are pooled with data from all other patients less than 18 years of age analyzed in the serious bacterial infection study (129). The mean CMAX doses were generally greater at steady state than after the first dose, although never greater than 18

percent after the first dose. No statistically significant differences were observed between dosing intervals or among age groups in AUC, T-HALF, CLT, or VSS. Other analyses determined no significant gender differences in T-HALF, CLT, or VSS. Of the three patients administered multiple doses of cefepime 50 mg/kg in the compassionate use study (999), pharmacokinetic data was reasonably consistent with that obtained from the serious bacterial infection study. [AI411 ISS, p. 37]

Pharmacokinetics of cefepime dosed at 50 mg/kg q12h

Table 5 shows data from 13 patients, ranging in age from 2 years to 10 years, who were observed following cefepime IV administration at 50 mg/kg q12h. At this dosing interval, no statistically significant differences were noted between first dose and steady state in CMAX, AUC, T-HALF, CLT, or VSS. [AI411 ISS, p. 37]

Pharmacokinetics of cefepime in children with meningitis

Successful treatment of meningitis involves adequate penetration of the antibiotic into the CSF. Plasma and CSF levels of cefepime were determined in patients with suspected central nervous system infections, ranging in age from 3.1 months to 14.7 years, with a mean (SD+/-) age of 2.9 (+/-3.9 years). These patients were given cefepime 50 mg/kg q8h. At 0.5, 1.0, 2.0, 4.0 and 8.0 hours, paired plasma and CSF samples were collected and analyzed. [Table 6] The CSF/plasma ratios reached equilibrium (1.0) sometime between 4.0 and 8.0 hours. [AI411 ISS, p. 38]

Cefepime concentrations in CSF ranged from 5.7 micrograms/mL 0.5 hours after the first dose to 3.3 micrograms/mL 8 hours after that initial dose. These values represent 12 percent and 117 percent of concentrations in serum, respectively, and exceeded the minimum inhibitory concentrations (MIC) of the patients' pathogens, most commonly type b Hemophilus influenzae and Neisseria meningitidis, many times over. These mean MIC90 values were 0.1 mg/L for H. flu and 0.008 mg/L for N. meningitidis. [Barradell, 1994, p. 476 and 479]

Discussion

The pharmacokinetic profile of cefepime has been documented in healthy adult volunteers, in healthy elderly volunteers, in adults with sepsis, and in patients with impaired renal function. [Table 7] In the adult population, the pharmacokinetics is dose-proportional, with no drug accumulation noted after repeat dosing. Cefepime is excreted unchanged in the urine with 88 percent of the dose recovered within the first 24 hours. [Barbhaiya, 1991, abstract] The data presented here show the results of pharmacokinetic evaluations in children who received cefepime after either intravenous or intramuscular administration.

In the study that enrolled pediatric patients with non-threatening bacterial infections who received a single dose of cefepime, seven at the 30 mg/kg dose and two at the 50 mg/kg dose, dose-related increases were observed in CMAX and AUC. Mean values for T-HALF, CLT, and VSS were similar despite the dose differences. These data imply that the pharmacokinetics of cefepime are dose-independent in pediatric, as they are in adult, subjects. [AI411 ISS, p. 61]

Data from the non-threatening bacterial infection study can be assessed relative to those data collected within the framework of the serious bacterial infection study. This non-comparative study included pharmacokinetic substudies in which parameter values were determined following single and multiple doses of 50 mg/kg, dosed either q8h or q12h. In patients under age 18 years, T-HALF ranged from 1.52 hours to 1.89 hours. [Table [7]] This relatively short T-HALF combined with dosing intervals of eight or twelve hours can result in steady state by the second day of therapy. Based on mean steady state/first dose CMAX and AUC(TAU) ratios, neither the q8h nor the q12h regimen resulted in an

significant accumulation of cefepime. Although significant differences in first dose and steady state pharmacokinetics were observed in a variety of parameters, none of these were considered clinically significant because of the differences were less than 20 percent. As with adults, steady state and first dose pharmacokinetic parameters differed neither in age of the subject nor in the gender of the subject. Intramuscular administration of cefepime was 82.3 percent in the eight pediatric subjects evaluated as compared with 100 percent bioavailability in adults, although this difference is not considered to be clinically significant. [AI411 ISS, p. 62]

The mean CLT, VSS, and T-HALF of cefepime for children in this study ranging from two months to less than 12 years of age were 3.32 mL/min/kg, 0.34 L/kg, and 1.66 hours, respectively. These parameters are comparable to what has been seen with other antibiotics used in children with bacterial infections. [AI411 ISS, p. 62] For example, cefpirome in the pediatric model produced a total body clearance, apparent volume of distribution, and elimination half-life of 2.15 +/- 0.70 ml/min/kg, 0.32 +/- 0.32 liter/kg, and 1.8 +/- 1.3 h, respectively. [Nahata, 1995, abstract] When compared to published pharmacokinetic data in adults, the characteristics of cefepime in infants and children appear to reflect a slightly faster half-life, a more rapid clearance and a larger volume of distribution. [AI411 ISS, p. 62]

Dosing guidelines for cefepime in children

The determination of cefepime dosing guidelines for pediatric patients was based on finding a dose that would be therapeutically equivalent to the dose used in adults. In these pharmacokinetic studies, models were used to describe the relationship between the age or body weight of the child and the clearance of cefepime from the body. In the one-month to 12-year old age range, the cefepime dose increased from approximately 30 to 50 mg/kg. However, in children over age 12 years, the dose decreased to 30 mg/kg, which is similar, after adjusting for a body weight of 70 kg, to a unit dose of 2,000 mg in an adult. Based on the results of these data, and in tandem with the observation that cefepime total clearance was not significantly different between children 2 months-<6 months and children >6 months of age, the dose of cefepime in pediatric patients between the ages of two months and 12 years should be 50 mg/kg, up to a maximum of 2,000 mg, every 8 or 12 hours. In the pediatric patient, a 50 mg/kg dose will result in serum concentrations that are similar to those achieved in adults after a 2,000 mg dose. In infants less than two months of age, this analysis recommends that a 30 mg/kg dose every 8 or 12 hours is appropriate. [AI411 ISS, p. 62-63]

The pharmacokinetic data included in this paper also support the use of cefepime at 50 mg/kg, three times a day, in the treatment of bacterial meningitis in children one month to 12 years of age. In addition, comparative and non-comparative studies have produced data that support the use of cefepime in children to treat other bacterial infections, such as urinary tract infections, pneumonia, and skin and skin structure infections.

References

Arguedas AG, Stutman HR, Zaleska M, et al. Pharmacokinetics and clinical response in patients with cystic fibrosis. Am J Dis Child. 1992;146:797-802.

Barbhaiya RH, Knupp CA, Tenney J, et al. Safety, tolerance, and pharmacokinetics of cefepime administered intramuscularly to healthy subjects. J Clin Pharmacol. 1990;30:900-910.

Barbhaiya RH, Knupp CA, Forgue ST, et al. Disposition of the cephalosporin cefepime in normal and renally impaired subjects. Drug Metab Dispos. 1991;19:68-73.

Barbhaiya RH, Knupp CA, Pittman KA, Effects of age and gender on pharmacokinetics of cefepime.

Antimicrob Agents Chemother. 1992;36:1181-1185.

Barradell LB, Bryson HM. Cefepime. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1994;47:471-505.

Cronqvist J, Nilsson-Ehle I, Oqvist B, Norrby SR. Pharmacokinetics of cefepime dihydrochloride arginine in subjects with renal impairment. Antimicrob Agents Chemother. 1992;36:2676-2680.

Kieft H, Hoepelman AI, Knupp CA, et al. Pharmacokinetics of cefepime in patients with the sepsis syndrome. J Antimicrob Chemother. 1993;32(Suppl B):117-122.

Nahata MC, Barson WJ, Puri SK. Pharmacokinetics of cefpirome in pediatric patients. Antimicrob Agents Chemother. 1995;39:2348-2349.

Okamoto MP, Nakahiro RK, Chin A, Bedikian A. Cefepime clinical pharmacokinetics. Clin Pharmacokinet. 1993;25:88-102.

Saez-Llorens X, Castano E, Garcia R, et al. Prospective randomized comparison of cefepime and cefotaxime for treatment of bacterial meningitis in infants and children. Antimicrob Agents Chemother. 1995;39:937-940.

Wynd MA, Paladino JA. Cefepime: A fourth-generation parenteral cephalosporin. Ann Pharmacother 1996;30:1414-1424.