JPP Journal of Pharmacy and Pharmacology

JPP 2002, 54: 1693–1696

Received May 22, 2002
Accepted August 8, 2002
DOI 10.1211/002235702171
ISSN 0022-3573

Continuous infusion versus intermittent administration of cefepime in patients with Gram-negative bacilli bacteraemia

Sutep Jaruratanasirikul, Somchai Sriwiriyajan and Natnicha Ingviya

Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, 90110 Thailand

Sutep Jaruratanasirikul, Somchai Sriwiriyajan

Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand

Natnicha Ingviya

Correspondence: S. Jaruratanasirikul, Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand. E-mail: jasutep@ratree.psu.ac.th

Acknowledgement and funding: This work was supported by the Songklanagarind Hospital Foundation. Cefepime and cefadroxil were generously donated by Bristol-Myers Squibb, Thailand, as pure powders. Cefepime (Maxipime) was also generously donated by Bristol-Myers Squibb, Thailand. We thank Mr David Patterson for checking our English. These experiments comply with the current laws of the country in which the experiments were performed.

Abstract

The objective of this study was to compare the pharmacokinetics of cefepime administered by continuous infusion and intermittent injection regimens. A prospective, randomized, cross-over study of ten patients with Gram-negative bacilli bacteraemia was conducted. All patients were randomized to receive cefepime either as a 4-g continuous infusion over 24 h for 48 h or a 2-g bolus administered intermittently intravenously every 12 h for 48 h. After 48 h the patients received the alternative dose regimen. Cefepime pharmacokinetic studies were carried out during hours 36–48 after the start of both regimens. All of the pathogens isolated from the blood in 7 patients had a minimum inhibitory concentration (MIC) $< 1\ \mu g\ mL^{-1}$. In both regimens, the serum cefepime concentrations at all time points were higher than the MIC for the pathogens isolated from this study. For the continuous infusion arm, the highest steady-state concentration was $49.80 \pm 18.40\ \mu g\ mL^{-1}$ and the lowest steady-state concentration was $41.42 \pm 16.48\ \mu g\ mL^{-1}$. The steady-state concentrations were greater than 4 times the MIC of $8\ \mu g\ mL^{-1}$. For the intermittent injection regimen, the mean trough concentration was $4.74 \pm 3.99\ \mu g\ mL^{-1}$. The mean serum cefepime concentration was above $8\ \mu g\ mL^{-1}$ for 81.66% of the dosing interval. Therefore, we conclude that either continuous infusion or intermittent injection can be used as an effective mode of cefepime administration to achieve bactericidal activity.

Introduction

The mode of administration of parenteral antibiotics can optimize their bactericidal effects. Aminoglycosides, for example, exhibit concentration-dependent bacterial killing. Thus, increasing the peak serum drug concentration can enhance the bactericidal activity of these agents (Nicolau et al 1992). The bactericidal activity of β-lactam antibiotics, however, is concentration independent and is determined by the time that concentrations in tissue and serum are above the minimum inhibitory concentration (MIC) for the pathogens during the dosing interval, not the peak serum drug concentrations. If the concentration of antibiotics decreases to below the MIC, bacterial growth resumes immediately (Craig & Ebert 1992; Mouton & den Hollander 1994; Nicolau et al 1996; Lipman et al 1999). Therefore, the optimal method to maintain the time that the β-lactam antibiotic is above its MIC for a pathogen would be to administer the agent by continuous infusion.

Cefepime, a β-lactam antibiotic, is a fourth generation cephalosporin that has a broader spectrum of antibacterial activity than the third generation cephalosporins. This agent has been found in-vitro to be effective against Gram-positive and Gram-negative aerobic bacteria. Therefore, it can cover most organisms isolated from critically ill patients (Barradell & Bryson 1994). Theoretically, continuous infusion would be the appropriate method for administration of cefepime to promote the maximal bactericidal effect. However, until now we have had only limited data regarding the time–concentration profile of cefepime administered by continuous infusion (Burgess et al 2000). Thus, the objective of this study was to compare the

pharmacokinetics of cefepime administered by continuous infusion and intermittent injection regimens.

Materials and Methods

Subjects

Ten patients with Gram-negative bacilli bacteraemia (bacteraemia was defined as at least one positive blood culture) participated in this study. Six were male and four were female. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each patient. None of the patients had a chronic illness or were taking chronic medication. Patients were excluded from the study if they were pregnant or in circulatory shock (which was defined as a systolic blood pressure of < 90 mmHg and poor tissue perfusion) or had documented hypersensitivity to cephalosporins or an estimated creatinine clearance (by the method of Cockcroft-Gault) of $\leqslant 60$ mL min^{-1}.

Drugs

Cefepime and cefadroxil were generously donated by Bristol-Myers Squibb, Thailand as pure powders. Cefepime (Maxipime) was also generously donated by Bristol-Myers Squibb, Thailand. All of the solvents were HPLC grade.

Study design

This was a prospective, randomized, cross-over trial. All patients were randomized to receive cefepime either as a 0.5-g intravenous loading dose followed by a 4-g continuous infusion over 24 h for 48 h or as a 2-g bolus administered intermittently intravenously every 12 h for 48 h. After 48 h the patients received the alternative dose regimen. After completion of cefepime therapy for 4 days, all patients were appropriately treated with other antibiotics for 10 days.

Antimicrobial agent administration

Cefepime powder was reconstituted according to the product instructions. The 0.5-g loading doses were diluted with 10 mL of 5% dextrose in water and administered over 2 min. The 4-g continuous infusion doses were diluted with 200 mL of 5% dextrose in water and administered via an infusion pump at a constant flow rate over 24 h. The 2-g intermittent doses were diluted with 20 mL of 5% dextrose in water and administered over 3 min.

Blood sampling

For the continuous infusion regimen, cefepime pharmacokinetic studies were carried out during the 36–48 h after the start of the continuous infusion. Blood samples (approximately 5 mL) were obtained by direct venepuncture at 36, 36.25, 36.50, 36.75, 37, 37.50, 38, 39, 40, 42, 44 and 48 h.

For the intermittent injection regimen, cefepime pharmacokinetic studies were carried out during the 36–48 h after the start of the intermittent injection (the 4th dose of intermittent injection regimens). Blood samples (approximately 5 mL) were obtained by direct venepuncture at 36, 36.25, 36.50, 36.75, 37, 37.50, 38, 39, 40, 42, 44 and 48 h, the same as the sampling times used in the continuous infusion regimen.

Cefepime assay

The concentration of cefepime was determined by reversed-phase HPLC. Cefadroxil (100 μg mL^{-1}) was used as the internal standard and the samples were extracted by the method of Barbhaiya (Barbhaiya et al 1987). A portion of the extracted sample (75 μL) was injected, using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA), onto a Nova-Pak C18 column (Waters Associates). The mobile phase was 0.0023 M 1-octanesulfonic acid sodium salt–acetonitrile (86:14, v/v) pH 2.3, at a flow rate of 1 mL min^{-1}. The column effluent was monitored by UV detection (Waters 486, Waters Associates) at 280 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates, Milford, MA). The limit of detection of cefepime was 50 ng mL^{-1}.

The intra-assay reproducibility characterized by CV was 0.59%, 0.27% and 0.38% for assays of 4, 32 and 128 μg mL^{-1}, respectively. The inter-assay reproducibility precision values calculated by CV were 2.46%, 2.25% and 1.43% for assays of 4, 32 and 128 μg mL^{-1}, respectively.

Pharmacokinetic analysis

Results were expressed as mean $\pm$ s.d. For the intermittent injection regimen, pharmacokinetic parameters were determined by using WinNonlin Version 1.1 (Scientific Consulting Inc., NC).

Results

The characteristics of 10 patients and the MIC of cefepime for pathogens isolated from blood are shown in Table 1. The mean serum cefepime concentration–time data for continuous infusion and intermittent injection from each patient are depicted in Figure 1. In both regimens, the serum cefepime concentrations at all time points were higher than the MIC for the pathogens isolated in this study. For the continuous infusion regimen, the area under the concentration–time curve (AUC_{36-48}) was 524.83 $\pm$ 169.14 μg h mL^{-1}, the highest steady-state concentration was 49.80 $\pm$ 18.40 μg mL^{-1} and the lowest steady-state concentration was 41.42 $\pm$ 16.48 μg mL^{-1}. The steady-state concentrations were greater than 4 times the MIC of 8 μg mL^{-1} (the cefepime susceptibility breakpoint for *P. aeruginosa* $\leqslant 8$ μg mL^{-1}). For the intermittent injection regimen, the mean trough concentration was 4.74 $\pm$ 3.99 μg mL^{-1}. The mean serum cefepime concentration was above 8 μg mL^{-1} for 81.66% of the dosing interval. The

Table 1 The characteristics of 10 patients and the MIC of cefepime for the pathogens isolated from their blood.

Patient	Age (years)	Body weight (kg)	Diagnosis	White blood cells (cells/mm^3)	Creatinine clearance (mL min^{-1})	APACHE II score	Pathogen	MIC (μg mL^{-1})
A-J	35	48.0	Acute cholecystitis	12900	63.64	16	*E. cloacae*	ND
S-T	47	48.0	Common bile duct stone	15300	63.92	25	*E. coli*, *K. oxytoca*, *A. sobria*	ND
A-K	35	44.9	Sepsis	5900	92.22	25	*Salmonella* spp	ND
S-M	46	60.0	Ascending cholangitis	6600	107.31	11	*K. pneumoniae*	0.064
J-K	32	71.1	Systemic lupus erythematosus	13600	115.92	13	*Salmonella* gr D1	0.125
P-K	56	32.7	Lymphoma	14800	62.54	28	*E. cloacae*	0.032
C-C	29	55.4	Sepsis	3300	70.01	6	*E. cloacae*	0.047
N-M	50	52.0	Diabetes mellitus type II	22000	65.00	27	*Salmonella* gr D1	0.094
W-J	25	51.6	Sepsis	50100	74.25	27	*E. agglomerans*	0.094
M-T	37	51.0	Pulmonary tuberculosis	19200	85.83	25	*H. influenzae*	0.250

ND, not done.

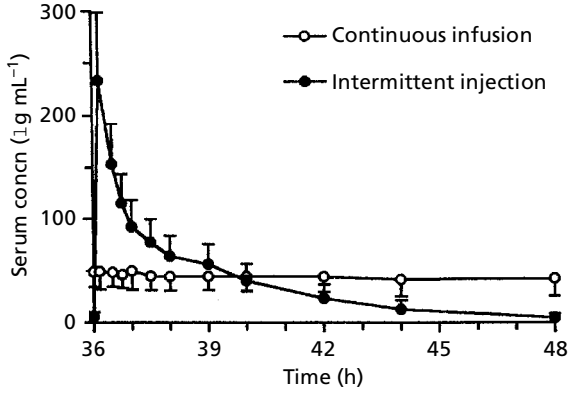

Figure 1 Serum concentrations (mean±s.d.) vs time during hours 36–48 h after the start of cefepime administration of 4-g continuous infusion and 2-g every 12 h intermittent injection in 10 patients with Gram-negative bacilli bacteraemia.

other mean pharmacokinetic parameters during intermittent administration were as follows: the maximum plasma concentration (C_{max}) was 233.09±65.37 μg mL^{-1}, the area under the concentration–time curve over the dosing interval (AUC_{36-48}) was 466.96±157.52 μg h mL^{-1}, the elimination rate constant (K_{el}) was 0.51±0.06 h^{-1}, the serum half-life ($t_{1/2}$) was 2.89±0.78 h, the total clearance at steady state (Cl_{tot}) was 4.49±0.49 L h^{-1} and the volume of distribution at steady state (V_{SS}) was 16.05±2.25 L. No adverse effects were observed in any patient during the study period.

Discussion

Over the last decade, several investigators have attempted to establish the most appropriate administration techniques to optimize bactericidal activity of parenteral antibiotics for the treatment of infections (Craig & Ebert 1992; Mouton & den Hollander 1994). For β-lactams, it is generally accepted that their bactericidal effect is determined by the time that the serum concentrations of antibiotics remains above four or five times the MIC for a pathogen (Craig & Ebert 1992; Mouton & den Hollander 1994; Nicolau et al 1996; Lipman et al 1999). Manufacturers' instructions usually direct that β-lactams be administered by intermittent injections. However, with this mode of administration, the high peak concentrations can not enhance the bactericidal activity of these agents and, during the dosing interval, drug concentrations may fall below the MIC for the pathogens. Therefore, continuous infusion could be a mode of administration that could maintain such concentrations during the whole period of drug administration for most bacterial pathogens, even though there are several modes of administration to optimize the pharmacodynamic properties of β-lactam antibiotics (Craig & Ebert 1992; Nicolau & Quintiliani 1994).

There are several pharmacokinetic and pharmacodynamic studies in animal models to support the use of continuous infusion of β-lactams (Mordenti et al 1985; Livingston & Wang 1993), but only few clinical data exist on man and most of the tests were performed to assess ceftazidime infusions (Benko et al 1996; Nicolau et al 1996; Lipman et al 1999).

A previous study in patients with suspected Gram-negative infections also showed that continuous infusion of ceftazidime consistently resulted in serum concentrations above the MIC and produced a more reliable serum drug concentration than intermittent administration (Benko et al 1996). Moreover, continuous infusion of ceftazidime utilizing one-half the intermittent bolus daily dose was equivalent to the intermittent bolus treatment as judged by pharmacodynamic analysis (Benko et al 1996).

This study was conducted in critically ill patients with Gram-negative bacilli bacteraemia to compare the mode of administration of cefepime, for a total daily dose of 4 g, between continuous infusion and intermittent injection. For the continuous infusion, all patients received 0.5 g of cefepime as a loading dose at the start of continuous

infusion. The serum concentrations obtained from this loading dose were high enough to ensure the rapid onset of antibacterial activity. All of the pathogens isolated from the blood in 7 patients had MIC $< 1\ \mu g\ mL^{-1}$. Both steady-state serum concentrations obtained from continuous infusion regimen and trough concentrations obtained from intermittent injection regimen in each patient can be maintained above the MIC for the pathogens isolated from this study. With continuous infusion therapy, our findings confirmed the results obtained from the previous study suggesting that a continuous infusion regimen provides steady-state serum concentrations above the MIC for most Gram-negative bacilli from clinical isolation throughout the dosing interval (Burgess et al 2000). The serum concentrations in this study were greater than 4 times the MIC only if the MIC was $\leqslant 8\ \mu g\ mL^{-1}$ which was higher than the serum concentration reported in the previous study (Burgess et al 2000). Therefore, in patients infected with pathogens for which the MIC is lower than $1\ \mu g\ mL^{-1}$, the requirement of the total daily dose of cefepime may be reduced by at least one-half. With intermittent injection therapy, the trough concentrations in each patient were higher than the MIC only if the MIC was $\leqslant 4\ \mu g\ mL^{-1}$. In addition, the mean serum cefepime concentrations were above $8\ \mu g\ mL^{-1}$ for 81.66% of the dosing interval. Previous studies in animal infection models showed that antibiotic concentrations did not need to exceed the MIC for 100% of the dosing interval to achieve a significant antibacterial effect. An in-vivo bacteriostatic effect was observed when serum drug concentrations were above the MIC for 30–40% of the dosing interval, whereas maximum killing was approached when levels were above the MIC for 60–70% of the time (Vogelman et al 1988; Craig 1995). This study demonstrated that administration of cefepime by both continuous infusion and intermittent injection can maintain serum levels above $8\ \mu g\ mL^{-1}$ for more than 70% of the dosing interval.

The outcome of cefepime treatment by continuous infusion and intermittent administration could not be evaluated due to the short duration of the treatment. However, after 14 days of antibiotic treatment, haemoculture was negative in all patients. Furthermore, during continuous infusion, no major adverse events related to the use of continuous infusion were observed.

The stability of cefepime is an important consideration if continuous infusion is used. The manufacturer's guidelines state that once cefepime is reconstituted in 5% dextrose solution it is stable for 24 h. Therefore, in this study, the antibiotic solution was changed every 12 h for the continuous infusion group and no problems with stability occurred during the study period.

In conclusion, either continuous infusion or intermittent injection can be used as an effective mode of cefepime administration to achieve bactericidal activity.

References

Barbhaiya, R. H., Forgue, S. T., Shyu, W. C., Papp, E. A., Pittman, K. A. (1987) High-pressure liquid chromatographic analysis of BMY-28142 in plasma and urine. *Antimicrob. Agents Chemother.* **31**: 55–59

Barradell, L. B., Bryson, H. M. (1994) Cefepime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* **47**: 471–505

Benko, A. S., Cappelletty, D. M., Kruse, J. A., Rybak, M. J. (1996) Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected Gram-negative infections. *Antimicrob. Agents Chemother.* **40**: 691–695

Burgess, D. S., Hastings, R. W., Hardin, T. C. (2000) Pharmacokinetics and pharmacodynamics of cefepime administered by intermittent and continuous infusion. *Clin. Ther.* **22**: 66–75

Craig, W. A. (1995) Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn. Microbiol. Infect. Dis.* **22**: 89–96

Craig, W. A., Ebert, S. C. (1992) Continuous infusion of β-lactam antibiotics. *Antimicrob. Agents Chemother.* **36**: 2577–2583

Lipman, J., Gomersall, C. D., Gin, T., Joynt, G. M., Young, R. J. (1999) Continuous infusion ceftazidime in intensive care: a randomized controlled trial. *J. Antimicrob. Chemother.* **43**: 309–311

Livingston, D. H., Wang, M. T. (1993) Continuous infusion of cefazolin is superior to intermittent dosing in decreasing infection after hemorrhagic shock. *Am. J. Surg.* **165**: 203–207

Mordenti, J. J., Quintiliani, R., Nightingale, C. H. (1985) Combination antibiotic therapy: comparison of constant infusion and intermittent bolus dosing in an experimental animal model. *J. Antimicrob. Chemother.* **15** (suppl. A): 313–321

Mouton, J. W., den Hollander, J. G. (1994) Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. *Antimicrob. Agents Chemother.* **38**: 931–936

Nicolau, D. P., Quintiliani, R. (1994) Choosing among the new cephalosporin antibiotics: a pharmacodynamic approach. *Pharmacoeconomics* **5** (suppl. 2): 34–39

Nicolau, D., Quintiliani, R., Nightingale, C. H. (1992) Once-daily aminoglycosides. *Conn. Med.* **56**: 561–563

Nicolau, D. P., Nightingale, C. H., Banevicius, M. A., Fu, Q., Quintiliani, R. (1996) Serum bactericidal activity of ceftazidime: continuous infusion versus intermittent injections. *Antimicrob. Agents Chemother.* **40**: 61–64

Vogelman, B., Gudmundsson, S., Leggett, J., Turnidge, J., Ebert, S., Craig, W. A. (1988) Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. *J. Infect. Dis.* **158**: 831–847