AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Cefepime Pharmacokinetics in Critically Ill Pediatric Patients Receiving Continuous Renal Replacement Therapy

Gideon Stitt,[a,b] Jennifer Morris,[b] Lindsay Schmees,[b] Joseph Angelo,[c] Ayse Akcan Arikan[c,d]

[a]Department of Pharmacy Services, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA
[b]Department of Pharmacy Services, Texas Children's Hospital, Houston, Texas, USA
[c]Department of Pediatrics, Renal Section, Baylor College of Medicine, Houston, Texas, USA
[d]Department of Pediatrics, Section of Critical Care Medicine, Baylor College of Medicine, Houston, Texas, USA

ABSTRACT This retrospective study included pediatric intensive care unit patients receiving continuous veno-venous hemodiafiltration (CVVHDF) being treated with cefepime. The free drug concentration above one time the MIC ($fT>1\times$MIC) and four times a presumed MIC ($fT>4\times$MIC) of 8 μg/ml were calculated. Four patients received doses ranging from 48 to 64 mg/kg of body weight every 6 to 12 h. Three patients achieved 100% $fT>1\times$MIC, with the fourth patient achieving 98% $fT>1\times$MIC. Therapeutic drug monitoring should be considered for critically ill patients receiving cefepime on CVVHDF.

KEYWORDS intensive care units, pediatrics, pharmacodynamics, pharmacokinetics, renal replacement therapy

Continuous renal replacement therapy (CRRT) has become the standard of care for patients in an intensive care unit (ICU) who experience acute kidney injury (AKI), fluid overload, or electrolyte or acid-base derangements (1). Volume of distribution (V_d) and clearance (Cl) are pharmacokinetic (PK) parameters affected to various degrees in CRRT patients depending on patient size, residual renal function, and modality of CRRT clearance delivered, among other factors (2, 3). Contrary to data for adults (4–7), there are currently no published CRRT pharmacokinetic data for cefepime in pediatric patients.

Cefepime is a fourth-generation cephalosporin with broad Gram-negative activity, including activity against *Pseudomonas aeruginosa*, and is commonly used empirically in critically ill patients. The pharmacodynamic (PD) parameter which optimizes bacterial killing for β-lactam antibiotics like cefepime is the fraction of the dosing interval for which the free drug concentration remains above the MIC ($fT>$MIC). Traditionally, this goal has been 40% of the dosing interval for bacteriostasis and 70% for bactericidal activity with cephalosporins, largely based on animal model data (8). Further *in vitro* studies suggested increased bacterial killing when an $fT>$MIC of 100% of the dosing interval was achieved (9). Subsequent *in vivo* studies involving critically ill patients demonstrated improved patient outcomes with similarly aggressive PD targets, with optimal free trough concentrations ranging from one to four times the MIC (100% $fT>1-4\times$MIC) (10–14). The aim of this study was to describe cefepime PK and PD in critically ill pediatric patients on continuous veno-venous hemodiafiltration (CVVHDF) across a range of cefepime dosing regimens and CRRT clearances.

A retrospective chart review was performed from 1 January 2014 through 31 July 2017. The electronic health record (EHR) was queried to identify pediatric ICU patients undergoing CVVHDF and receiving intravenous cefepime with at least two quantifiable cefepime serum concentrations from which PK calculations could be performed. Cefepime peak, midinterval, and trough concentrations were measured at steady state. Concentrations that were not drawn in the same dosing interval were extrapolated

Citation Stitt G, Morris J, Schmees L, Angelo J, Akcan Arikan A. 2019. Cefepime pharmacokinetics in critically ill pediatric patients receiving continuous renal replacement therapy. Antimicrob Agents Chemother 63:e02006-18. https://doi.org/10.1128/AAC.02006-18.

Address correspondence to Gideon Stitt, stittg@email.chop.edu.

Received 19 September 2018
Returned for modification 10 November 2018
Accepted 25 January 2019
Accepted manuscript posted online 4 February 2019
Published 27 March 2019

TABLE 1 Patient demographics

Characteristic	Data by patient			
	1	2	3	4
Age (yr)	1.1	0.6	0.5	5
Sex	Male	Female	Male	Male
Hospital admission diagnosis	Liver transplant	Liver failure	Hyponatremia	HLH[a]
Estimated dry wt (kg)	10	6	5.4	25
Body surface area (m^2)	0.45	0.33	0.33	0.94
Baseline SCr (mg/dl)[b]	0.14	Unknown[c]	0.15	0.3
SCr at CRRT initiation (mg/dl)	0.41	0.53	0.59	3.37
Mean urine output at CRRT initiation (ml/kg/h)[d]	1.3	1.6	1.4	0.25
Mean urine output at sampling (ml/kg/h)[e]	0.22	0.64	0.07	0
Cefepime dose (mg/kg)[f]	48	57	55	64
Dosing interval (h)	8	8	6	12
Infusion time (h)	3	0.5	0.5	0.5
No. of samples collected	3	2	3	3
No. of doses received prior to first sample	18	3	7	2

[a]HLH, hemophagocytic lymphohistiocytosis.
[b]SCr, serum creatinine.
[c]Unknown baseline SCr level due to transfer from outside hospital.
[d]24 h prior to CRRT initiation.
[e]48 h around the time of sampling.
[f]Based on estimated dry weight.

using the dose prior to determine the expected steady-state trough. This study was approved by the Baylor College of Medicine institutional review board.

All serum cefepime samples were collected in the course of usual clinical care, with cefepime dosing at the discretion of the primary medical team. Serum cefepime assays were performed by Atlantic Diagnostic Laboratories (Bensalem, PA) using validated liquid chromatography-tandem mass spectrometry.

The following equations were used to calculate patient-specific steady-state elimination rate constant (k_e), volume of distribution (V_d), and total body clearance (Cl):

$$k_e\left(\mathrm{h}^{-1}\right) = \frac{ln\frac{C_1}{C_2}}{t_2 - t_1}$$

$$V_d\left(\mathrm{liters/kg}\right) = \frac{\mathrm{Dose} \times \left(1 - e^{-k_e t_{\mathrm{inf}}}\right)}{\mathrm{wt} \times t_{\mathrm{inf}} \times k_e \times \left(C_{\max} - C_{\min} \times e^{-k_e t_{\mathrm{inf}}}\right)}$$

$$\mathrm{Cl}\left(\mathrm{liters/kg/h}\right) = k_e \times V_d$$

where C_1 is concentration 1, C_2 is concentration 2, wt is weight, t_{inf} is infusion time, $C_{\max}$ is the maximum concentration of drug in the serum, and $C_{\min}$ is the minimum concentration of drug in the serum. $fT>1\times$MIC and $fT>4\times$MIC were calculated for each patient using a presumed MIC of 8 μg/ml, as this is the highest MIC one would cover in clinical practice (15). Protein binding was assumed to be 20% based on published references (16).

Renal replacement therapy was delivered in hemodiafiltration mode with prefilter hemodilution using bicarbonate-based commercial fluids with an HF1000 filter (Gambro, Baxter, Deerfield, IL). All circuits were regionally anticoagulated with citrate. The minimum starting clearance dose was 2,000 ml/1.73 m^2/h with 50% diffusive and 50% convective clearance. For liver failure and hyperammonemia, the minimum starting dose was 3,000 ml/1.73 m^2/h, as per institutional protocol, with escalation as needed. Further modification in individual CVVHDF doses was prescribed by the attending nephrologist if necessary, such as in situations of uncontrolled hyperammonemia.

Four patients were included (Table 1). Cefepime was used as empirical therapy in three patients and for *Klebsiella pneumoniae* pneumonia in the fourth patient. Patients 1, 2, and 3 were in the ICU due to complications of liver failure, for which high CVVHDF clearance was prescribed to aid in ammonia clearance in addition to AKI and fluid

TABLE 2 CVVHDF parameters

Parameter	Data by patient			
	1	2	3	4
Dialysate (ml/h)	1,500	1,000	550	650
Pre-filter replacement (ml/h)	500	450	500	600
Post-filter replacement (ml/h)	50	50	50	50
Blood flow (ml/min)	90	40	70	100
Blood flow (ml/kg/min)	9	6.7	13	4
Normalized effluent rate (ml/1.73 m^2/h)	8,750	8,593	6,089	3,076
Effluent urea/BUN ratio[a]	0.75	0.75	0.75	0.77
Delivered CVVHDF clearance (ml/1.73 m^2/h)[b]	6,563	6,445	4,567	2,369
Circuit age (h)[c]	22.6	33.8	15.2	11.2

[a]BUN, blood urea nitrogen.
[b]Delivered CVVHDF clearance = normalized effluent rate × BUN/effluent urea nitrogen ratio.
[c]Measured from circuit change to time of cefepime dose prior to sampling.

overload. Patient four received CVVHDF for AKI and fluid overload. Urine output was low or absent in all patients around the time of therapeutic drug monitoring, likely minimizing the effect of intrinsic renal clearance on cefepime PK. Delivered CVVHDF clearance rates ranged from 2,400 to 6,500 ml/1.73 m^2/h (Table 2).

Individually calculated PK parameters are summarized in Table 3. Overall, three patients reached 100% $fT>1\times$MIC, with the fourth patient achieving 98.3% $fT>1\times$MIC. Only one patient (patient 4) achieved the more aggressive PD goal of 100% $fT>4\times$MIC. Of note, this patient had the lowest CVVHDF clearance and blood flow rates when normalized for body weight. No adverse effects directly attributable to cefepime were noted in any patient.

This report represents the first published PK data for cefepime in critically ill pediatric patients receiving a range of CVVHDF clearances. Sepsis represents a significant source of morbidity and mortality in pediatric patients (17), with patients on CRRT demonstrating even higher mortality rates (18–20). With numerous reports suggesting improved patient outcomes by achieving more aggressive PD targets (10–14), optimal dosing data in pediatric patients on CRRT are vital. Although limited by the number of patients included, these data suggest that therapeutic drug monitoring may aid in achieving more aggressive PD targets of 100% $fT>1$–$4\times$MIC in pediatric patients receiving CVVHDF, especially with higher prescribed clearance. Patient 4's disparate apparent V_d compared to the other patients cannot be fully explained, but the relatively lower prescribed CVVHDF clearance and normalized blood flow rate likely contributed to the achievement of 100% $fT>4\times$MIC in this patient.

Several limitations are present in this study. The limited number of cefepime concentrations gathered, while adequate for clinical use, does not allow for more specific calculations to be performed, such as sieving coefficient, dialysate saturation, membrane adsorption, and nonrenal clearance. Calculated V_d and half-life ($T_{1/2}$) values

TABLE 3 Calculated PK and PD parameters

Parameter	Data by patient			
	1	2	3	4
k_e (h^{-1})	0.24	0.44	0.67	0.31
$T_{1/2}$ (h)[a]	2.9	1.6	1	2.2
V_d (liters/kg)	0.23	0.17	0.12	0.04
Cl (liters/h/kg)	0.055	0.075	0.08	0.012
Calculated free C_{max} (μg/ml)[b]	138.6	244.8	306.4	1,268.2
Calculated free C_{min} (μg/ml)[c]	22.7	9.1	7.7	38.6
%$fT>1\times$MIC[d]	100	100	98.3	100
%$fT>4\times$MIC[d]	82.3	63.8	65	100

[a]$T_{1/2}$, half-life.
[b]Back-extrapolated to the end of the infusion.
[c]Extrapolated to the end of the scheduled dosing interval.
[d]Based on a presumed MIC of 8 μg/ml.

were similar to values published for pediatric patients without renal impairment, but a more definitive relationship between delivered CVVHDF clearance and cefepime clearance cannot be inferred from these limited data. The retrospective nature of data collection relies on accurate charting in the EHR. Differences in actual timing of dose administration and serum drug concentration collection from the charted time cannot be captured retrospectively. Additionally, the HF1000 hemofilter set has a blood volume of 165 ml, so depending on the size of the patient, this may or may not change the effective V_d to a clinically significant degree compared to patients who are not critically ill or undergoing CRRT. Changes in protein binding are also seen in critical illness, so the assumed protein binding of 20% may be different in clinical practice, which would then impact $fT>$MIC. However, free drug concentrations were not available for analysis. Finally, due to the small number of patients in this report, more specific dosing recommendations cannot be made. Despite having a large pediatric critical care nephrology program, patient volume at our center remains significantly lower than that in adult programs, making subject accrual a lengthy process. However, this report does underscore the need for therapeutic drug monitoring of β-lactam antibiotics in critically ill patients. Further studies are necessary to more specifically characterize cefepime clearance across a range of CVVHDF clearance rates, as well as to study the effect of different filter types and sizes in addition to other CRRT modalities.

In conclusion, aggressive pharmacodynamic targets of 100% $fT>1–4\times$MIC may be difficult to reach in critically ill pediatric patients undergoing CVVHDF using standard cefepime doses of 50 mg/kg every 12 h. Therapeutic drug monitoring should be strongly considered.

ACKNOWLEDGMENTS

G. Stitt, J. Morris, L. Schmees, and J. Angelo declare no conflicts of interest. A. Akcan Arikan has consulted for Baxter, Medtronic, and La Jolle Pharmaceuticals and receives research funding from the NIH NIAID.

REFERENCES

1. Westrope CA, Fleming S, Kapetanstrataki M, Parslow RC, Morris KP. 2018. Renal replacement therapy in the critically ill child. Pediatr Crit Care Med 19:210–217. https://doi.org/10.1097/PCC.0000000000001431.
2. Choi G, Gomersall CD, Tian Q, Joynt GM, Freebairn R, Lipman J. 2009. Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med 37:2268–2282. https://doi.org/10.1097/CCM.0b013e3181aab3d0.
3. Seyler L, Cotton F, Taccone FS, De Backer D, Macours P, Vincent JL, Jacobs F. 2011. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 15:R137. https://doi.org/10.1186/cc10257.
4. Allaouchiche B, Breilh D, Jaumain H, Gaillard B, Renard S, Saux MC. 1997. Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. Antimicrob Agents Chemother 41:2424–2427. https://doi.org/10.1128/AAC.41.11.2424.
5. Malone RS, Fish DN, Abraham E, Teitelbaum I. 2001. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother 45:3148–3155. https://doi.org/10.1128/AAC.45.11.3148-3155.2001.
6. Isla A, Gascon AR, Maynar J, Arzuaga A, Toral D, Pedraz JL. 2005. Cefepime and continuous renal replacement therapy (CRRT): in vitro permeability of two CRRT membranes and pharmacokinetics in four critically ill patients. Clin Ther 27:599–608. https://doi.org/10.1016/j.clinthera.2005.05.004.
7. Wilson FP, Bachhuber MA, Caroff D, Adler R, Fish D, Berns J. 2012. Low cefepime concentrations during high blood and dialysate flow continuous venovenous hemodialysis. Antimicrob Agents Chemother 56:2178–2180. https://doi.org/10.1128/AAC.05987-11.
8. Craig WA. 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10. https://doi.org/10.1086/516284.
9. Mouton JW, den Hollander JG. 1994. Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 38:931–936. https://doi.org/10.1128/AAC.38.5.931.
10. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J. 2010. Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 36:332–339. https://doi.org/10.1016/j.ijantimicag.2010.06.008.
11. Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL. 2002. Pharmacodynamics of cefepime in patients with Gram-negative infections. J Antimicrob Chemother 50:425–428. https://doi.org/10.1093/jac/dkf130.
12. McKinnon PS, Paladino JA, Schentag JJ. 2008. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31:345–351. https://doi.org/10.1016/j.ijantimicag.2007.12.009.
13. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J, DALI Study. 2014. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58:1072–1083. https://doi.org/10.1093/cid/ciu027.
14. Aitken SL, Altshuler J, Guervil DJ, Hirsch EB, Ostrosky-Zeichner LL, Ericsson CD, Tam VH. 2015. Cefepime free minimum concentration to minimum inhibitory concentration (*f*Cmin/MIC) ratio predicts clinical failure in patients with Gram-negative bacterial pneumonia. Int J Antimicrob Agents 45:541–544. https://doi.org/10.1016/j.ijantimicag.2014.12.018.
15. Clinical and Laboratory Standards Institute. 2015. Performance standards for antimicrobial susceptibility testing; 25th informational supplement.

CLSI document M100-S25. Clinical and Laboratory Standards Institute, Wayne, PA.
16. Lexi-Comp. 2019. Lexicomp online, pediatric and neonatal Lexi-drugs online. Wolters Kluwer Clinical Drug Information, Inc., Hudson, OH.
17. Weiss SL, Parker B, Bullock ME, Swartz S, Price C, Wainwright MS, Goodman DM. 2012. Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. Pediatr Crit Care Med 13:e219–e226. https://doi.org/10.1097/PCC.0b013e31823c98da.
18. Sakhuja A, Kumar G, Gupta S, Mittal T, Taneja A, Nanchal RS. 2015. Acute kidney injury requiring dialysis in severe sepsis. Am J Respir Crit Care Med 192:951–957. https://doi.org/10.1164/rccm.201502-0329OC.
19. Riyuzo MC, Silveira LV, Macedo CS, Fioretto JR. 2017. Predictive factors of mortality in pediatric patients with acute renal injury associated with sepsis. J Pediatr (Rio J) 93:28–34. https://doi.org/10.1016/j.jped.2016.04.006.
20. Santiago MJ, López-Herce J, Vierge E, Castillo A, Bustinza A, Bellón JM, Sánchez A, Fernández S. 2017. Infection in critically ill pediatric patients on continuous renal replacement therapy. Int J Artif Organs 40:224–229. https://doi.org/10.5301/ijao.5000587.