Pilot Study of the Pharmacokinetics of Cefotaxime in Critically Ill Patients with Acute Kidney Injury Treated with Continuous Renal Replacement Therapy

Joost B. Koedijk,^a Corinne G. H. Valk-Swinkels,^b Tom A. Rijpstra,^c Daan J. Touw,^d Paul G. H. Mulder,^e Peter H. J. van der Voort,^{f,g} Nils E. van 't Veer,^h Nardo J. M. van der Meer^{c,g}

Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands^a; Department of Clinical Pharmacy, Bravis Hospital Bergen op Zoom and Roosendaal, Roosendaal, The Netherlands^b; Department of Intensive Care, Amphia Hospital Breda, Oosterhout, and Etten-Leur, Breda, The Netherlands^c; University Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, The Netherlands^d; Amphia Academy, Amphia Hospital Breda, Oosterhout, and Etten-Leur, Breda, The Netherlands^e; Department of Intensive Care, OLVG Hospital, Amsterdam, The Netherlands^f; Tias School for Business and Society, Tilburg University, Tilburg, The Netherlands^g; Department of Clinical Pharmacy, Amphia Hospital Breda, Oosterhout, and Etten-Leur, Breda, The Netherlands^h

The objective of this study was to describe the pharmacokinetics of cefotaxime (CTX) in critically ill patients with acute kidney injury (AKI) when treated with continuous renal replacement therapy (CRRT) in the intensive care unit (ICU). This single-center prospective observational pilot study was performed among ICU-patients with AKI receiving ≥ 48 h concomitant CRRT and CTX. CTX was administered intravenously 1,000 mg (bolus) every 6 h for 4 days. CRRT was performed as continuous veno-venous hemofiltration (CVVH). Plasma concentrations of CTX and its active metabolite desacetylcefotaxime (DAC) were measured during CVVH treatment. CTX plasma levels and patient data were used to construct concentration-time curves. By using this data, the duration of plasma levels above 4 mg/liter (four times the MIC) was calculated and analyzed. Twenty-seven patients were included. The median CTX peak level was 55 mg/liter (range, 19 to 98 mg/liter), the median CTX trough level was 12 mg/liter (range, 0.8 to 37 mg/liter), and the median DAC plasma level was 15 mg/liter (range, 1.5 to 48 mg/liter). Five patients (19%) had CTX plasma levels below 4 mg/liter at certain time points during treatment. In at least 83% of the time any patient was treated with CTX, the CTX plasma level stayed above 4 mg/liter. A dosing regimen of 1,000 mg of CTX given four times daily is likely to achieve adequate plasma levels in patients with AKI treated with CVVH. Dose reduction might be a risk for suboptimal treatment.

Nosocomial infections are frequently acquired in the intensive care unit (ICU), leading to an increase in morbidity and mortality in patients (1). Systemic antibiotics are used to treat these infections. Also in our ICU, patients are treated to prevent colonization and subsequent infections by selective decontamination of the digestive tract (SDD) (2–4). Widely used systemic agents are broad-spectrum parenteral cephalosporins such as cefotaxime (CTX). CTX is a β -lactam antibiotic that has antimicrobial activity against potential pathogenic microorganisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterobacteriaceae* (5). After administration, CTX undergoes hydrolysis by esterases available in plasma and the liver to form its active metabolite, desacetylcefotaxime (DAC), which is further metabolized into inactive compounds (6). CTX and DAC have half-lives of 1.1 and 1.3 h, respectively, and are mainly excreted in the urine (7).

Since CTX is mainly cleared by the kidneys, acute kidney injury (AKI) may alter its excretion and pharmacokinetic parameters (8). Subsequently, supporting a patients impaired renal function with renal replacement therapy can again significantly alter the elimination of the drugs. Continuous renal replacement therapy (CRRT) substitutes for renal function by effectively removing solutes from the blood. The extracorporeal clearance is especially relevant for drugs with a dominant renal clearance and results in unpredictable pharmacokinetics (8). Dose modifications of CTX might therefore be required, particularly because the bactericidal action of CTX is time dependent, which is why the dosing interval and frequency should result in plasma concentrations that remain above the targeted level for as long as possible. For CTX, this

targeted level is commonly set at 4 mg/liter, which is $4\times$ the MIC against *Enterobacteriaceae* (9, 10).

For CTX, regimes of 1,000 mg twice daily, 2,000 mg twice daily, or 1,000 mg four times daily have all been recommended in patients with severe renal failure (11, 12). However, during continuous renal replacement therapy, the pharmacokinetics may appear completely different compared to intermittent hemodialysis. According to these considerations, and the unpredictable pharmacokinetics in critically ill patients with AKI, it is unknown what dosing will lead to optimal treatment in this population. Routine therapeutic drug monitoring of cephalosporins is still uncommon but might be important in the future to achieve effective CTX target concentrations in certain patient groups.

The objective of this pilot study was to describe the pharmaco-

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Address correspondence to Joost B. Koedijk, j.koedijk@student.maastrichtuniversity.nl.

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kinetics of CTX in ICU patients with AKI when treated with CRRT.

MATERIALS AND METHODS

Setting. This single-center prospective observational pilot study was conducted during an 8 months period in a level 3 intensive care unit of a large nonacademic teaching hospital (Amphia Hospital Breda, Oosterhout, and Etten-Leur, Breda, The Netherlands). The local institutional ethics review board granted waiver from informed consent according to Dutch and European legislation. This was possible due to the observational design and the use of residual material from routine blood sampling without extra blood samples for study purposes.

Study population. All patients admitted to the ICU of the Amphia Hospital were screened for eligibility. ICU patients received intravenous CTX as part of the SDD-prophylaxis protocol when their expected length of ICU stay exceeded 72 h or when their expected time on the mechanical ventilator exceeded 48 h. A total of 25 patients with AKI receiving at least 48 h of concomitant CRRT and CTX were planned for this study. Patients with less than 4 available plasma samples were excluded. Other exclusion criteria were CRRT for other indications than renal failure, deviation of standard CRRT protocol (e.g., different flow rates), and interruption of CRRT longer than 3 h. In order to limit the effect of residual renal function on total clearance, only AKI patients with anuria or oliguria during the entire study period were included (defined as no diuresis or diuresis of <0.5 ml/kg/h during 6 h, respectively, conforming to the RIFLE and AKIN criteria for AKI) (13).

Study protocol. CTX was administered as intravenous bolus injection, 1,000 mg every 6 h for 4 days. Cefotaxime plasma concentrations were targeted at ≥4 mg/liter (4× the MIC against Enterobacteriaceae as defined by the European Committee on Antimicrobial Susceptibility Testing [EUCAST]) (9, 10). Standard prefilter venous blood sampling was done routinely and was independent of time of CTX administration. Left-over plasma samples from these routine laboratory tests were collected and stored at −20°C for 12 to 18 months. CTX and DAC concentrations were determined at the Amphia Hospital with a high-pressure liquid chromatography method (measuring range, 1 to 30 mg/liter) designed and validated by the local hospital pharmacy. Routine clinical chemical parameters (creatinine, urea, and albumin) were obtained from the patient charts. CRRT was executed as continuous venovenous hemofiltration (CVVH). An AN69ST filter (Prima Flex ST150) was used, and anticoagulation with citrate and a flow rate of substitution fluid of 35 ml/kg/h were given in a postdilution mode.

Pharmacokinetic modeling. The CTX plasma levels and patient data were used to estimate individual concentration-time curves using dedicated software (MW Pharm, version 3.70; Medi Ware, Groningen, The Netherlands). The measured plasma creatinine levels were used as an indication of the total (renal plus artificial) clearance. We hypothesize that in this study, as a result of the remaining kidney function and extracorporeal clearance, the creatinine level gives the best available indication of total clearance during treatment. The validated time of administration in the electronic patient record was used as the time of CTX administration. We made the assumption that the actual time of blood sampling was within 15 min from the registered time of blood sampling. All results have been included in the data analysis.

Based on the time data and the assumed time variations, all plasma concentration-time curves were reviewed by two independent reviewers and in a number of situations, adjustments have been made. If a result was clearly different from expected (e.g., a declining plasma concentration immediately after a documented dose), it is assumed that this was the result of a registration error. Therefore, an adjustment was made if possible within the agreed 15-min margin of sampling time. If not, the result was omitted from the analysis. If a distortion arose in a period with considerable fluctuation of distribution volume (derived from the fluid balance and the amount of fluid that was withdrawn by means of CRRT), the value was excluded since MW Pharm is not able to cope with these cir-

TABLE 1 Patient characteristics

Variable	No. (%) of patients (n = 27) ^a
Men	14 (52)
Mean (SD)	
Age (yrs)	70 (12)
Length (cm)	170 (9)
Wt (kg)	79 (18)
Primary diagnosis ^b	
Coronary artery bypass grafting	6 (22)
Coronary artery bypass grafting and valve surgery	3 (11)
Valve surgery	6 (22)
Sepsis	8 (30)
Cardiopulmonary resuscitation	2 (7)
Complication after abdominal surgery	1 (4)
Aortic dissection	1 (4)
Score ^c	
SOFA	12 (3)
SAPS II	60 (19)
APACHE III	99 (40)
Level ^d	
Albumin (g/liter)	24 (6)
Anuria	9 (33)
Creatinine (μmol/liter)	229 (135)
Urea (mmol/liter)	14 (6)
Diuresis (ml/h)	8.8 (7.7)
Diuresis (ml/kg/h)	0.1 (0.1)

^a Values are expressed as the number (%) of patients or the means and standard deviations (SD) and were measured at inclusion, unless indicated otherwise.
^b The term “valve surgery” here includes both valve replacement surgery and valve leakage surgery.
^c SAPS II and APACHE III scores were measured over the first 24 h of ICU admission. SOFA, sequential organ failure assessment; SAPS, simplified acute physiology; APACHE, acute physiology and chronic health evaluation.
^d Diuresis values were measured over the entire study period.

cumstances. For most patients, one or more peak-trough curves have been left out for reasons mentioned above. The most common reason was variation in prescribed or registered times of CTX administration. All changes have been documented, and changes were implemented only when consensus existed between both reviewers.

Pharmacokinetic analysis and statistics. From data of doses administered and CTX concentrations measured, MW Pharm was used to estimate the patient’s concentration-time profile and exponential hourly decay rate *a* using log-linear regression analysis per patient, based on the following model: $C_1 = C_0 \times \exp(-at)$, where C_1 and C_0 , respectively, denote the trough and peak concentrations, and *t* is the time (in hours) between the trough and peak measurements. The decay rate *a* was estimated per patient from a number of patient’s (peak, trough) concentration pairs using linear regression through the origin after rewriting the model as follows: $\ln(C_1/C_0) = -at$.

Based on the estimated decay rate and the peak-value C_0 for CTX after a given dose of a patient, we estimated the time t_4 (in hours) that it would take to reach 4 mg/ml as of the peak value C_0 , using the formula: $t_4 = [\ln(C_0) - \ln(4)]/a$. So, in each patient we obtained as many estimates of time t_4 as there were (peak, trough) pairs. By using the exponential hourly decay rate *a*, we also estimated the elimination half-life $t_{1/2}$ of CTX (in hours) for each patient as follows: $t_{1/2} = -\ln(0.5)/a$. The pharmacokinetic parameters clearance and the volume of distribution were estimated from the concentration-time curves using MW Pharm.

FIG 1 Box plots of peak and trough levels of CTX and DAC levels. A red line at 4 mg/liter ($4\times$ the MIC) is given.

RESULTS

Demographic data. Ninety-two ICU patients were screened for eligibility. A total of 52 patients were not given CTX or else fewer than four residual blood samples were available (57%). Of the remaining 40 patients, 13 were excluded because of no concomitant CTX-CRRT treatment over 48 h or no anuria or oliguria during the same period. A total of 27 patients (mean age in years, 70 ± 12 ; mean SAPS II score, 60 ± 9) were included. Nine patients (33%) were anuric; the other eighteen patients were oliguric. [Table 1](#) depicts the patient characteristics.

Plasma concentration data. Peak and trough levels of CTX have been estimated using individual concentration-time curves computed with MW Pharm. The median peak level of CTX (374 observations) was 55.3 mg/liter with an interquartile range (IQR) of 14.7 mg/liter (47.2 to 61.9). The range of CTX peak value was between 19 and 98 mg/liter. The median trough level of CTX (349 observations) was 12.1 mg/liter, with an IQR of 11.9 mg/liter (7.6 to 19.5). The range of CTX trough levels was between 0.8 and 37 mg/liter. The median DAC plasma level (286 observations) was 14.7 mg/liter, with an IQR of 9.6 mg/liter (9.3 to 19.1) and ranged from 1.5 to 48 mg/liter. Box plots of peak and trough levels of CTX and DAC levels are displayed in [Fig. 1](#).

Individual concentration-time curves were used to identify the part of the dosing interval where the CTX plasma concentration was $>4\times$ the MIC ($t_{>4MIC}$) for each patient. For each subject, between 9 and 20 peak-trough curves were available, depending on duration of anuria/oliguria and concomitant CRRT-CTX treatment. The calculated time to reach 4 mg/liter (based on mean peak levels of cefotaxime) for all patients was mean 10.1 h (standard deviation = 4.1 h) ranging from 4.5 to 19 h. Twenty-two patients (81%) had all CTX plasma levels above the targeted concentration during the whole dosing interval ($t_{>4MIC} = 100\%$). The $t_{>4MIC}$ varied between 83 and 95% of time in the remaining five

patients with at least one trough CTX plasma level below 4 mg/liter. These five patients were the patients with the shortest time to reach the cefotaxime level of 4 mg/liter (4.5 to 6.2 h). In one patient, a missed dose resulted in CTX plasma levels below 4 mg/liter for 6 h. For every patient, we calculated the patient's elimination half-life from peak to trough. The elimination half-life $t_{1/2}$ ranged from 1.44 to 5.04 h, with a median of 2.42 h (IQR = 1.97 to 3.1 h) across the patients. In all five patients with CTX plasma levels below the target level, the elimination half-life ranged from 1.44 to 2.35 h. Clearance ranged between 8.96 and 17.55 liters/h in these five patients, while the median of all patients was 5.79 liters/h (IQR = 4.8 to 7.5). The volume of distribution levels ranging from 21.9 to 33.8 liters were found in the five patients with CTX plasma levels below 4 mg/liter. The median volume of distribution of all patients was 22.5 liters (IQR = 19.8 to 26.9).

DISCUSSION

In this study we show that 81% of the observed patients with CVVH for AKI have CTX levels above $4\times$ the MIC with intermittent dosing of 1,000 mg at a 6-h interval. As a consequence, 19% of patients have insufficient serum levels at certain time points during treatment. However, in at least 83% of the time any patient in our study was treated with CTX, the CTX plasma level stayed above $4\times$ the MIC. Therefore, adequate prophylaxis is assumed. In one patient, a missed dose resulted in CTX plasma levels below 4 mg/liter for 6 h. This shows that in CVVH the current dosing regimen of 1,000 mg of CTX four times daily results in therapeutic levels in all studied patients and that dose reduction might be a risk for suboptimal treatment.

We noted an unexpected high clearance in the five individuals with CTX plasma levels below 4 mg/liter. However, differences in clearance in our population can be caused by multiple factors and do not fall within the scope of this study design. The broad anti-

bacterial spectrum of CTX is partly attributable to the synergistic effect of CTX with its active metabolite DAC. We could not find information in literature about the extent to which DAC is removed from the body by CRRT. In our study, we found DAC levels that are comparable with values found in literature of patients without CRRT and patients treated with other cephalosporins (14). Therefore, we assume that in our population DAC may still have a contribution to the therapeutic effect. Wise et al. report no toxicity in subjects with DAC levels comparable with levels found in this study (14).

This study has several limitations. The patient data management system of the ICU was the main information source in this study. Small time deviations from ordered times for medication administration and blood sampling were allowed and occurred often, depending on the workflow on the ward. Nursing staff was free to perform electronic registration either directly before or after completing activities. However, these variations have been taken in account in the pharmacokinetic modeling. It was assumed that registration errors of a few minutes did not lead to significant changes in computed elimination rates and times the concentration reached target levels.

The strength of this pilot study is the acceptable design as minimal interventions were needed: an accessible and widely applicable design to answer pharmacokinetic questions in this patient population. Since it was not our intention to investigate factors leading to more rapid CTX clearance in some patients, we did not collect sufficient data to conduct additional analyses. Therefore, further research is needed to investigate associations between CTX plasma levels below the target level, patient characteristics (e.g., length, BMI, clearance, volume of distribution, and residual renal function), CVVH, and treatment outcome (e.g., occurrence of breakthrough infections).

Conclusion. Our results indicate that a dosing regimen of 1,000 mg of cefotaxime four times daily is likely to achieve adequate plasma levels in patients with AKI treated with CVVH. In addition, the plasma levels are closer to suboptimal treatment than to toxicity levels, which implies that dose reduction, as is often advocated in kidney failure, is not necessary in this patient group.

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J.B.K. and C.G.H.V.-S. contributed equally to the paper. J.B.K., C.G.H.V.-S., T.A.R., and N.J.M.V.D.M. collected and analyzed data. J.B.K., C.G.H.V.-S., and N.J.M.V.D.M. wrote the main paper. C.G.H.V.-S., T.A.R., and N.E.V.V. designed the study. C.G.H.V.-S. and D.J.T. constructed and reviewed concentration-time curves in MW Pharm. P.G.H.M. and P.H.J.V.D.V. performed the statistical analysis. N.E.V.V. and N.J.M.V.D.M. supervised the study. J.B.K., C.G.H.V.-S., N.E.V.V., D.J.T., P.G.H.M., P.H.J.V.D.V., and N.J.M.V.D.M. commented on the manuscript.

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