Target-Controlled Infusion of Cefepime in Critically Ill Patients

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TITLE PAGE

Title: Target Controlled Infusion of cefepime in critically ill patients: single center experience

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ABSTRACT

Attainment of appropriate pharmacokinetic-pharmacodynamic (PK-PD) targets for antimicrobial treatment is challenging in critically ill patients, particularly for cefepime, which exhibits a relative narrow therapeutic-toxic window compared to other beta-lactam antibiotics. Target Controlled Infusion (TCI) systems, which deliver drugs to achieve specific target drug concentrations, have successfully been implemented for improved dosing of sedatives and analgesics in anesthesia. We conducted a clinical trial in the Intensive Care Unit (ICU) to investigate the performance of TCI for adequate target attainment of cefepime. Twenty-one patients treated per standard of care with cefepime were included. Cefepime was administered through continuous infusion using TCI for a median duration of 4.5 days. TCI was based on a previously developed population PK model incorporating the estimated creatinine clearance based on the Cockcroft-Gault formula as input variable to calculate cefepime clearance. A cefepime blood concentration of 16 mg/L was targeted. To evaluate the measured versus predicted plasma concentrations, blood samples were taken (median of 10 samples per patient) and total cefepime concentrations were measured using UPLC-MS/MS. Performance of the TCI system was evaluated using the Varvel criteria. Half (50.3%) of measured cefepime concentrations were within ± 30% around the target value of 16 mg L^{-1}. The wobble was 11.4%, median prediction error (MdPE) was 21.1%, median absolute prediction error (MdAPE) was 32.0%, and divergence was -3.72%.h^{-1}. Based on these results we conclude that TCI is useful for dose optimization of cefepime in ICU patients.

KEYWORDS: Target Controlled Infusion, drug infusion system, cefepime, pharmacokinetics, Intensive Care Unit

INTRODUCTION

Inappropriate dosing of antibiotics is a driver for antimicrobial resistance development (1), acute toxicity (2,3) and poor clinical outcome (4-5). This is particularly true for cefepime, a fourth generation cephalosporin, which has shown to exhibit a narrow therapeutic-toxic window (2-3,6). Defining adequate dosing regimens in critically ill patients is challenging as pharmacokinetics (PK) in these patients are known to vary considerably (7-14) and these patients are more likely to be infected by less susceptible bacteria (12).

Traditionally, dosing of antibiotics is based on nomograms which define a dosing regimen based on one or a limited set of patient covariates. In the critically ill, these nomogram-based dosing regimens frequently result in a significant proportion of patients not achieving the therapeutic target (13). Hence, treatment should be individualized using therapeutic drug monitoring and/or population PK (PopPK) models. In recent years several software packages were developed that allow model-based treatment individualization (14). Whilst therapeutic drug monitoring (TDM) linked with Bayesian forecasting provides a powerful opportunity for delivering individualized care for patients (15), several issues in current strategies for dose optimization of antimicrobials have hindered clinical implementation in most ICU's (16,17).

Target-controlled infusion (TCI) is a technique of continuously infusing intravenous drugs and is mainly known in the field of anesthetics (18). TCI allows the clinician to target a predefined concentration in a specific body compartment or tissue of interest. The computer then calculates the optimal infusion rate required to achieve this user-defined target concentration as fast as possible without overshooting the target, based on a PopPK model and patient specific covariates (e.g. age, weight, serum creatinine, etc.) which are integrated in the model. An on-line coupled infusion pump then delivers this optimal infusion regimen to the patient. In comparison to the aforementioned manually controlled infusions, TCI systems might provide a more convenient and performant alternative. Treatment individualization is made easy as the PopPK model and associated covariates are embedded in the TCI devices. Dose adaptations are not limited to practicable changes in infusion rates, dose strengths, dosing intervals, etc. but TCI continuously calculates and adjust the infusion rate to exactly match the distribution and elimination kinetics of the drug during treatment.

In this prospective pharmacokinetic study, we evaluated the performance of a cefepime TCI system in a cohort of critically ill patients. Furthermore, the additional PK data was used to update the earlier presented PopPK model for cefepime (19).

RESULTS

Twenty-one critically ill patients were included in this study. Patients received cefepime for the following indications: suspected or documented respiratory infection (18 of 21; 86%), abdominal infection (1 of 21; 5%), combined respiratory and abdominal infection (1 of 21; 5%) or infection of unknown origin (1 of 21; 5%). Microbiological samples taken before cefepime treatment identified in 16 of 21 (76%) patients one or more pathogens: *Klebsiella* spp. (n = 8), *Escherichia coli* (n = 6), *Citrobacter* spp. (n = 2), *Proteus mirabilis* (n = 1), *Pseudomonas aeruginosa* (n = 1), *Morganella morganii* (n = 1) and *Enterobacter cloacae* (n = 1), *Staphylococcus aureus* (n = 1) and *Haemophilus influenzae* (n = 1). MIC values for cefepime ranged from ≤ 1 mg L^{-1} to 4 mg L^{-1} (75^{th} percentile: ≤ 1 mg L^{-1}). Table 1 shows a the clinical characteristics of the study patients.

The median treatment duration with TCI was 4.0 days (IQR: 2.0 – 5.0 days) and daily cefepime dose was 1.8 g (IQR: 1.6 – 2.5 g) at day 1, 1.3 g (IQR: 1.1 – 2.2 g) at day 2, 1.3 g (IQR: 1.1 – 2.0 g) at day 3 and 1.3 g (IQR: 1.1 – 1.9 g) at day 4. During treatment, a median of 10 blood samples were taken per patient (IQR: 9 – 11) leading to a total of 201 samples. The median of the measured cefepime plasma concentrations was 19.2 mg L^{-1} with an inter-quartile range of 15.3 to 23.3 mg L^{-1} (the mean and SD were 19.5 and 6.36 mg L^{-1}, respectively). The percentage of measured concentrations within ±10, 20, 30, 40 and 50% of the 16 mg L^{-1} target were 20.7, 36.2, 50.3, 66.3 and 77.7%, respectively. Figure 1 shows the measured cefepime concentrations and the predicted concentrations according to the TCI system. The average performance metrics (Varvel criteria) in this patient cohort were: MdAPE: 28.7 %, MdPE: 20.3 %, Wobble: 12.2 %, Divergence: -0.13 % h^{-1}. As seen from Figure 1 performance varies with MdAPEs on an individual basis ranging between 4.1% and 64.2%. Similar variability was found for the other performance metrics; MdPE (range): -25.6% to 64.2%, Wobble (range): 2.12 % to 30.3 % and Divergence (range): -4.43 % h^{-1} to 0.68 % h^{-1}.

By combining the data from this study with the study previously published by our group (19), we were able to improve the PopPK model for cefepime. The following modifications led to a significant improvement in the goodness-of-fit: (i) the implementation of eCrCL as time-varying covariate on CL_{renal}, (ΔOFV: -75.3) and (ii) the addition of between-subject variability (BSV) on the non-renal CL (CL_{other}) (ΔOFV: -54.0). Finally, we made two modifications that slightly worsened goodness-of-fit: a power parameterization for the eCrCL effect on CL instead of the original linear relationship (ΔOFV: +2.2) and scaling of all PK parameters with body weight according to allometric theory (ΔOFV: +2.3) (20). The former was added to the model to avoid the prediction of negative CL_{renal} at very low eCrCL values whereas the latter was included to ascertain sensible behavior of a TCI system based on this model when used in patients with a bodyweight outside the range evaluated in this analysis (50 - 120 kg). None of the other covariates tested in the model (age, plasma albumin levels and C-reactive

protein (CRP)) were found significant. Parameter estimates and associated relative standard errors for the final model are shown in Table 2. The covariate structure for the final model (for a non-dialysis patient) is shown in equations 1-4. Goodness-of-fit plots for the final PopPK model are provided as supplemental material (Fig. S1).

$$CL\ (L\ h^{-1}) = \left(2.29 \cdot \left(\frac{eCrCL\ (mL\ min^{-1})}{60}\right)^{0.943} + 0.795\right) \cdot \left(\frac{weight\ (kg)}{70}\right)^{0.75} \quad \text{Eq.1}$$

$$V1\ (L) = 10.7 \cdot \left(\frac{weight\ (kg)}{70}\right)^{1} \quad \text{Eq.2}$$

$$V2\ (L) = 12.2 \cdot \left(\frac{weight\ (kg)}{70}\right)^{1} \quad \text{Eq.3}$$

$$Q2\ (L\ h^{-1}) = 11.0 \cdot \left(\frac{weight\ (kg)}{70}\right)^{0.75} \quad \text{Eq.4}$$

DISCUSSION

In this study we describe for the first time the use of TCI for the administration of antibiotics in critically ill patients. PK-PD optimized dosing regimens and target attainment are pivotal for effective antimicrobial treatment (4-5). As a result, different approaches to personalized antibiotic dosing have been attempted (15,21-24). TCI systems accomplish this individualization *via* embedded PopPK models and might therefore become a convenient bedside alternative to other approaches. Our prototype TCI system delivers 50.3% of measured cefepime concentrations within ± 30% around the target value of 16 mg L^{-1}. MdPE and MdAPE in this study were 20.3 % and 28.7 %, respectively. This performance is in line with the performance of current PK models used in TCI pumps in anaesthesia (25).

Cefepime was selected as study drug because it is widely used as broad spectrum antibiotic in ICU patients and individualized TCI dosing has a potential benefit given the relatively small therapeutic-toxic window, compared to other beta-lactam antibiotics. It is important to note that there exist no clinically validated target cefepime concentration for continuous infusion. We choose a target (total) cefepime concentration of 16 mg L^{-1} for all patients in our study, which is a compromise between potential toxicity and achieving adequate PKPD targets. The chosen target concentration is well below the recently advocated threshold for cefepime toxicity of 35 mg L^{-1} (6) and is sufficient to achieve free drug above the EUCAST clinical susceptibility breakpoint for the suspected pathogens (e.g. MIC = 1 mg L^{-1} for *Enterobacterales* and MIC = 8 mg L^{-1} for *Pseudomonas* spp.) (http://www.eucast.org). The target resembles the clinical use of cefepime when microbiology results are absent, such as e.g. when used empirically or when cultures remain negative throughout the treatment period (26,27). In these situations population-level assumptions are made about the most likely

organism causing the infection and the distribution of MICs in this population. To achieve true individualization of antibiotic therapy, it might also be necessary to individualize the targeted PKPD index (i.e. more aggressive PKPD targets such as $fT_{>2.1xMIC}$ (28) or $T_{>4.3xMIC}$ (29)) and to account for the susceptibility of the infecting pathogen (once isolated). TCI systems facilitate the use of a patient-tailored target by reducing the complex dose-concentration relationship *via* the embedded PopPK models to the selection of an appropriate plasma concentration target. In our opinion, this practicable flexibility could drive the wide-spread implementation of model-informed precision dosing for antibiotics in the ICU. The use of TCI is not limited to cefepime, but the concept could also be applied to administer any drug that can be give as continuous infusion.

The additional PK data from this study enabled us to update the PopPK model used in our prototype TCI system. From the pooled data analysis V1 was estimated to be 10.7 L and not 18.3 L, as published earlier by our group (19). As a result, loading doses administered by the current version of the TCI system are too high, resulting in an overshoot of the target in the first hour of treatment (as seen from Figure 1). Furthermore, our analysis indicated that within-individual changes in cefepime clearance are (partly) explained by temporal changes in eCrCL. We hypothesize that an updated version of the TCI system based on the new PopPK model and with eCrCL as a control variable to accommodate within-subject variability in CL will perform better than the system evaluated in this study.

The theoretical lower limit for the performance of this new system depends on the magnitude of the unknown BSV in the PopPK model. When targeting a steady-state plasma concentration and assuming that the PopPK model in the TCI system is unbiased, target attainment is limited by the BSV in CL. In our model CL consists of CL_{renal} with a BSV of 24.6% and CL_{other} with a BSV of 69.4%. Consequently, when targeting 16 mg L^{-1} 95% of patients are expected to reach a steady-state concentration between 9.16 and 24.6 mg L^{-1} (based on simulations for a population with an average eCrCL of 60 mL min^{-1}). This translates to a MdAPE of 21.5%, which is, as expected, lower than the MdAPE reported in this study (28.7%). This shows that it is possible to improve the performance of the current TCI system by updating the embedded PopPK model.

Another useful approach for further refining the accuracy of the system is to use model-based feedback-control based on Bayesian forecasting of PK parameters . Open-loop TCI systems (or adaptive TCI systems) (30) where feedback from TDM is used as a control variable in the TCI system are interesting in that respect. Neely *et* al. (21), Matthews *et al*. (23) and Pea *et al*. (24) have shown for aminoglycosides and vancomycin that TDM and Bayesian forecasting of PK parameters results in improved dosing accuracy over conventional dosing strategies. Hence, a TCI system based on the same principles might be advantageous when a higher accuracy is

needed. The lower limit for the performance of such a system is not depending on the BSV in the PK but is governed by the residual variability of the PopPK model, which incorporates both the inaccuracy in the drug assay and model misspecification. For the updated model this would result in a MdAPE of 12.8%. Nevertheless, timely availability of appropriate antimicrobial assays could be problematic as TDM programs for cefepime or other beta-lactam antibiotics are not yet widespread. To this end, biosensor technology could offer an alternative by providing real-time monitoring of antimicrobials in a minimally invasive fashion (31).

There are some limitations to the research presented here: firstly, the small number of patients examined and the fact that all patients originate from only one ICU site. Although patient inclusion was not restricted to any medical condition and all patients receiving cefepime with a eGFR > 15 mL/min were eligible, extrapolation of the results to specific subgroup of patients may not be appropriate. For instance, only few patients with augmented renal clearance were included. Secondly, the model by Jonckheere *et al*. (19) uses only eCrCL to individualize cefepime dosing. A more sophisticated PopPK model, also including patient covariates on the volume of distribution, would have likely resulted in better treatment individualization and potentially better performance. Finally, the TCI performance might be overestimated because the PopPK model which was integrated in the TCI was developed in the same ICU.

In conclusion, novel systems are urgently required to individualize antimicrobial therapy, to address the wide variations in PK currently observed across a range of patient populations, and to minimize the occurrence of sub-optimal dosing. We demonstrated that cefepime TCI is able to deliver antibiotic concentrations within the expected range around the targeted plasma concentrations in a cohort of critically ill ICU patients. In our opinion, TCI offers exciting possibilities for the individualization of antibiotic treatment in ICU patients and could drive the wide-spread implementation of model-informed precision dosing in this vulnerable patient population. Further research is needed to confirm that target attainment is superior and to demonstrate increased clinical efficacy in terms of clinical outcome. The role of TDM in an adaptive TCI approach also requires further investigation.

MATERIALS AND METHODS

Patient inclusion & research ethics. Patients requiring cefepime according to local treatment protocols were included between May 2016 and August 2017. Patients with an estimated glomerular filtration rate (eGFR) (according to CKD-EPI formula) less than 15 mL/min and patients that were on hemodialysis were excluded. This trial was conducted at the Intensive Care department of the OLV Hospital Aalst, Belgium, in accordance with the Declaration of Helsinki and in compliance with Good Clinical Practice and the applicable regulatory requirements. Ethical approval was obtained from the Institution Review Board of the hospital (Belgium registration number: B126201626975). The study was registered in the ClinicalTrials.gov database (NCT02688582) and was monitored by an independent Quality Specialist.

Drug administration. Patients received cefepime i.v. using a TCI system based on a previously developed PopPK model by Jonckheere *et al*. (19). In this model, the estimated creatinine clearance (eCrCl) based on the Cockcroft-Gault formula measured the day of inclusion was used as only input variable and a cefepime blood concentration of 16 mg/L was targeted. There were no adaptations based on changes in eCrCl or measured cefepime concentrations during treatment. Cefepime (20 mg/mL, Fresenius Kabi®, USA) was administered by a syringe pump (Orchestra® Module DPS, Fresenius Kabi®, USA) controlled by RUGLOOPII software (Demed®, Temse, Belgium) on a personal computer. Maximum infusion rate was set to 4 gram of cefepime per hour.

Descriptive statistics. The administered daily cefepime dose was extracted from the case report forms or the RUGLOOPII files. CRP measurements were summarized according to 24h intervals. Measurements up to 24h before inclusion into the study were grouped as baseline measurements. Daily doses of cefepime and CRP levels were analysed for the first 4 days of therapy only, afterwards the number of patients treated was too low to calculate meaningful summary measures. Length-of-stay in ICU/Hospital and mortality are competing risks (i.e. very sick patients who die would have likely had a very long stay in ICU/Hospital), hence the length-of-stay was calculated by replacing length-of-stay for patients who died by the maximum length-of-stay in that patient cohort (32). Presence of neurotoxicity was based on clinical assessment.

Arterial blood and urine sampling and laboratory procedures. Arterial blood was sampled at 0.5, 1, 3, 6, 12, 24, 36, 48, 72, 96 and 120 h after the start of the infusion. The exact timing of blood samples was recorded in the case report form. Samples were collected in lithium heparin tubes, transported immediately to the laboratory and centrifuged at 1000 *xg* for 5 min at 4°C. Subsequently, plasma samples were stored below -70°C until analysis. Urine was collected daily from a urinary catheter over a 12 hour interval. The quantification of

cefepime levels was based on a validated solid phase extraction – liquid chromatography electrospray – tandem mass spectrometry method (33). using a $^{13}C_{12}$-$^{2}H_{3}$-labeled cefepime isotope as internal standard (AlsaChim, Illkirch, France). The range of the analytical method was 0.15 mg L^{-1} to 15 mg L^{-1} with an average bias and imprecision of +5.9 % and 8.6 CV%. Plasma samples were diluted 1/5 in blank human plasma whereas urine samples were diluted 1/50 in blank human plasma prior to analysis. All samples were measured in duplicate. Microbiological samples were taken as per standard of care and analyzed using standard culture procedures. Identification was performed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Germany) and antimicrobial susceptibility testing was performed using the Phoenix system (Becton Dickinson, USA) according manufacturer's instructions.

Calculation of predictive performance. In line with studies on the performance of TCI systems in anesthesia, we used the "Varvel criteria" to evaluate the performance of our TCI system (34). For this, the performance error (PE) is calculated for all samples (j) for the different patients (i) according to equation 5.

$$PEij = \frac{(\text{Cmeas } ij - \text{Cpred } ij)}{\text{Cpred } ij} \text{ x } 100\% \qquad \text{Eq 5.}$$

In this equation $C_{meas\ ij}$ and $C_{pred\ ij}$ are the measured and predicted plasma cefepime concentrations, respectively. Subsequently, the PEs are used to calculate the median PE (MDPE), median absolute PE (MDAPE), wobble, and divergence for each patient. MDPE provides a measure of bias whereas the MDAPE reflects the precision of the system. Wobble is a measure of intra-subject variation in PEs and the divergence quantifies any time-related changes in the imprecision of the TCI system.

Update of previously published population pharmacokinetic model. The plasma and urine cefepime concentration versus time data were fitted using the FOCE-I estimation algorithm in NONMEM® (Version 7.3; GloboMax LLC, Hanover, MD, USA). The "tidyverse" package (Version 1.1.1.; Wickham H. 2017) in R® (R foundation for statistical computing, Vienna, Austria) was used to graphically assess the goodness-of-fit. As a starting point, the model previously published by our group (19), which was used as PopPK model in the presented TCI system, was fitted to the combined dataset (PK data from the pilot study (19) and additional PK data from this TCI study). Modifications to the model were accepted if they resulted in a decrease in the objective function value (OFV). A decrease in OFV was judged statistically significant if inclusion of an additional parameter decreased the OFV with more than 3.84 points.

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416 **FIGURE LEGENDS**

417 **FIG 1** Measured cefepime concentrations (black dots) with non-parametric smoother (blue line) and target

418 window of 16 mg/L of the 21 included patients. Black line represents expected plasma concentrations based on

419 TCI model. Median absolute prediction error (MdAPE) is presented for each patient.

Table 1 Clinical characteristics of study patients (n=21).

Clinical outcome	*n* (%) or median (IQR)
Age	76 (72 – 78)
Male/female	16 (76) / 5 (24)
Body weight (kg)	76 (67 – 86)
BMI (kg/m^2)	26.3 (23.5 – 27.8)
Body surface area (m^2)	1.88 (1.77 – 2.03)
SOFA score at inclusion	7 (3 - 8)
Patients on mechanical ventilation at inclusion	7 (33)
Serum creatinine (mg/dL)	1.49 (0.66 – 2.14)
Cockcroft-Gault (mL/min)	50.4 (29.1 – 100)
MDRD (mL/min/1.73 m^2)	42.3 (30.1 – 106)
CKD-EPI (mL/min/1.73 m^2)	38.8 (26.8 – 83.3)
CRP (mg L^{-1})	
At study inclusion	197 (95.7 – 287)
0 – 24 h	189 (115 – 282)
24 – 48 h	133 (92.6 - 195)
48 – 72 h	89.2 (62.5 - 122)
72 – 96 h	69.0 (46.7 – 88)
Length of stay in ICU (days)[a]	7 (5 – 10)
Length of stay in hospital (days)[a]	21 (13 – 28)
In hospital mortality	5 (24)
Event of neurotoxicity	0 (0)

[a] mortality-corrected length of stay

Table 2 Parameter estimates and associated relative standard errors (RSE%) for the final population PK model derived from simultaneously fitting the data from our previous study (19) (STDY1) and the data from this study (STDY2). Between-subject variability associated with the typical parameters is expressed as CV%. eCrCL was according to Cockcroft-Gault and was interpolated using constant backward interpolation.

PK Parameter	Estimate (RSE%)
CL_{renal} (L h^{-1} 70 kg^{-1})	$\theta_1 \cdot \left(\frac{eCrCL\ (mL \cdot min^{-1})}{60}\right)^{\theta_2}$
θ_1	2.29 (5.4)
θ_2	0.943 (9.6)
CL_{other} (L h^{-1} 70 kg^{-1})	0.795 (9.0)
V1 (L 70 kg^{-1})	10.7 (8.1)
V2 (L 70 kg^{-1})	12.2 (7.2)
Q2 (L h^{-1} 70 kg^{-1})	11.0 (14)
$CL_{dialysis}$ (L h^{-1})	4.48 (8.1)
Between-subject variability (CV%[a])	
CL_{renal}	24.6 (28)
V1	45.7 (31)
CL_{other}	69.4 (32)
Residual unexplained variability (CV%)	
$Plasma_{STDY1}$	31.8 (17)
$Plasma_{STDY2}$	12.8 (25)
$Urine_{STDY1}$	32.5 (27)
$Urine_{STDY2}$	33.3 (42)

V1, volume of distribution of the central compartment; V2, volume of distribution of the peripheral compartment; Q2, inter-compartmental clearance between V1 and V2; CLrenal, renal clearance; CLdialysis, clearance during intermittent haemodialysis; CLother, non-renal clearance. Separate clearance terms are integrated in the model describing renal clearance, non-renal clearance and clearance during haemodialysis. For patients on IHD, we assumed that renal clearance was absent.

[a] CV (%) is calculated according to: $\sqrt{\omega^2} * 100\%$ where ω^2 is the estimated variance in NONMEM

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