



Short Communication

Population pharmacokinetics of ticarcillin in critically ill patients receiving extended daily diafiltration



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ABSTRACT

The aim of this study was to describe the population pharmacokinetics of ticarcillin during extended daily diafiltration (EDDf) in critically ill patients with acute kidney injury. Blood samples were collected from critically ill patients prescribed ticarcillin during one to two dosing intervals during which EDDf was performed. Plasma samples were measured using a validated ultra high performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) method. Concentration–time data were analysed using a population pharmacokinetics approach with Pmetrics®. A total of 53 blood samples were collected from six critically ill patients (three male). The mean \pm standard deviation patient age, weight and body mass index (BMI) was 43 ± 22 years, 88 ± 14 kg and 31 ± 5 kg/m², respectively. A two-compartment linear model adequately described the data. Median population pharmacokinetic parameter estimates were as follows: clearance in the presence of EDDf (CL_{EDDf}), 6.41 L/h; clearance of EDDf ($CL_{non-EDDf}$), 4.97 L/h; volume of distribution of the central compartment (V_c), 56.46 L; intercompartmental clearance from the central to peripheral compartment (k_{CP}), 13.54 L/h; and intercompartmental clearance from the peripheral to central compartment (k_{PC}), 21.93 L/h. This is the first population pharmacokinetic model of ticarcillin in patients receiving EDDf. Large pharmacokinetic variability was found, supporting further investigation of the pharmacokinetics of less-studied β -lactam antibiotics in prolonged intermittent renal replacement therapy.

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1. Introduction

Ticarcillin/clavulanic acid (TCC) is an injectable β -lactam/ β -lactamase inhibitor combination belonging to the group of extended-spectrum penicillins with a spectrum of activity against Gram-positive, Gram-negative (including *Pseudomonas* spp.) and anaerobic bacteria. As with other time-dependent antibiotics, the therapeutic success of TCC is reliant on the amount of time the free drug remains above the minimum inhibitory concentration of the infecting pathogen ($fT_{>MIC}$) at the site of infection. Ticarcillin and clavulanate are, respectively, 79% and 41% renally excreted [1] and

undergo a similar rate of clearance from the body. Ticarcillin is 45–65% protein bound with a low volume of distribution (0.17 L/kg), whilst clavulanate is ca. 30% protein bound with a volume of distribution of ca. 0.25 L/kg [2]. Although this drug combination is not currently subject to active marketing or wide use, it is still likely to be used in challenging clinical scenarios, therefore knowledge of how to dose this product, in particular ticarcillin, remains important.

Extended daily diafiltration (EDDf) is the haemodiafiltration setting of prolonged intermittent renal replacement therapy (PIRRT). PIRRT is a modality of renal replacement therapy (RRT) that combines the advantages of using high blood and dialysate flow rates and short treatment times seen in intermittent haemodialysis (IHD) with the haemodynamic stability demonstrated in continuous renal replacement therapy (CRRT). At present, dosage regimens have been defined for TCC during continuous veno-venous

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haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD), continuous veno-venous haemodiafiltration (CVVHDF) and IHD [3]. To date, however, the pharmacokinetics of ticarcillin during EDDf have not been established. Although some pharmacokinetic data in critically ill patients exist for clavulanate by virtue of studies with amoxicillin/clavulanic acid in non-RRT patients [4], few data exist for ticarcillin.

The aim of this study was to describe the population pharmacokinetics of ticarcillin during EDDf in critically ill patients with acute kidney injury.

2. Methods

2.1. Setting

This was an observational pharmacokinetic study conducted in the Department of Intensive Care Medicine at Gold Coast University Hospital (Gold Coast, Australia). Ethical approval to conduct the study was obtained from the local institutional Human Research Ethics Committee. Written informed consent was obtained from all participants or from their substitute decision-makers.

2.2. Study population

The inclusion criteria for this study were: (i) age ≥ 18 years; (ii) admission to an intensive care unit (ICU); (iii) clinical indication for TCC (only the combination formulation was available in Australia at the time of study); and (iv) receiving EDDf. Exclusion criteria were: (i) pregnant women; (ii) patients with active bleeding; or (iii) patients with human immunodeficiency virus (HIV) infection or hepatitis.

2.3. Study protocol

TCC was administered at the direction of the treating physician, with patients receiving their first dose within 24 h of initiating EDDf. TCC dosing was based on the ticarcillin component of the combination therapy in this patient population requiring EDDf due to acute kidney injury; in the absence of published guidelines, patients were dosed at ticarcillin 3 g every 8 h, extrapolated from dosing regimens adopted in patients undergoing CRRT [5,6]. Prior to the first EDDf session, blood samples (3 mL) were taken from each participant to determine plasma ticarcillin concentrations. Blood sampling occurred from the haemodiafilter pre-filter port line. Blood sampling occurred when EDDf was commenced and after 30, 60, 120, 180, 300, 480 and 600 min of the first and third EDDf session. EDDf was commenced at the discretion of the clinician and did not uniformly correspond with the timing of ticarcillin dosing. EDDf was performed in all patients using a 5008s online haemodiafiltration machine (Fresenius Medical Care, Bad Homburg, Germany) with Fresenius polysulfone AV600S 1.4 m² high-flux haemodiafilters (Fresenius Medical Care). The standardised EDDf prescription included a blood flow rate (Q_b) of 300 mL/min, a dialysate flow rate (Q_d) of 200 mL/min, and 50 mL/min predilution with a targeted treatment duration of ≥ 8 h.

Other clinical and demographic data were collected on the day of plasma sampling, including age, sex, total body weight and body mass index (BMI). Clinical data included Acute Physiology and Chronic Health Evaluation (APACHE) II score as well as serum albumin and serum creatinine (SCr) concentrations.

2.4. Sample handling, storage and assay

Blood samples were centrifuged at 3000 rpm for 10 min in a temperature-controlled centrifuge. Plasma samples were stored

at -80 °C until bioanalysis. Ticarcillin was measured using a Shimadzu Nexera X2 ultra high performance liquid chromatography (UHPLC) system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan). The linear range when assaying ticarcillin was 1–200 mg/L, with a precision of 2.6%, 10.6% and 0.9% at 3, 30 and 150 mg/L, respectively, and an accuracy of 1.4% and 2.3% at 1 mg/L and 5 mg/L, respectively.

2.5. Population pharmacokinetic modelling

To describe total ticarcillin concentrations, one- and two-compartment models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the Pmetrics software package for R v.1.5.1 (Keck School of Medicine of USC, Los Angeles, CA). Elimination from the central compartment and intercompartmental distribution into the peripheral compartment (two-compartment model) were modelled as first-order processes.

2.6. Population pharmacokinetic covariate screening

Age, sex, body weight and presence of RRT were evaluated as clinically relevant and physiologically plausible covariates. Covariate selection was performed using a stepwise linear regression from R on all covariates and Bayesian posterior parameters. Potential covariates were separately entered into the model and were statistically tested using the -2 log-likelihood value. If inclusion of the covariate resulted in a statistically significant improvement in the -2 log-likelihood value ($P < 0.05$) and/or improved the goodness-of-fit plot, then the covariate was retained in the final model.

2.7. Model diagnostics

Goodness of fit was assessed by linear regression, with an observed–predicted (both population- and individual-predicted concentrations) plot, coefficients of determination and log-likelihood values. Predictive performance was based on mean prediction error (bias) and mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models. The internal validity of the population pharmacokinetic model was assessed by the bootstrap resampling method ($n = 1000$) and normalised prediction distribution error (NPDE). Using the visual predictive check method, parameters obtained from the bootstrap method were plotted with the observed concentrations. NPDE plots were checked for normal distribution characteristics and trends in data errors.

3. Results

3.1. Demographic and clinical data

A total of 53 blood samples were obtained from six critically ill patients (three male) enrolled in the study. The demographic characteristics of the patients are shown in Table 1.

3.2. Population pharmacokinetic model building

Ticarcillin pharmacokinetics was best described using a two-compartment linear model. The goodness of fit of the model was improved by inclusion of separate clearance parameters for clearance in the presence of EDDf (CL_{EDDf}) and in the absence of EDDf ($CL_{non-EDDf}$). The model was also improved by inclusion of age normalised to the study sample mean value of 43 years as well as the inverse of SCr concentration (in $\mu\text{mol/L}$) normalised to the median value observed before first EDDf (240 $\mu\text{mol/L}$). Addition of these

Table 1
Demographic characteristics of patients included in the study (n = 6)

Patient	Age (years)	Height (cm)	Sex	Weight (kg)	BMI (kg/m ²)	APACHE II score	SCr concentration (μmol/L) ^a
1	19	165	F	65	23.9	27	165
2	29	170	F	80	27.7	17	78
3	52	165	F	100	36.7	29	381
4	24	175	M	85	27.8	29	117
5	61	165	M	100	36.7	23	355
6	75	175	M	98	32.0	27	315
Median	40.5	167.5	–	91.5	29.9	27	240
Quartile 1	25.3	165.0	–	81.3	27.7	24	129
Quartile 3	58.8	173.8	–	99.5	35.5	29	345

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SCr, serum creatinine.

^a SCr concentration values before institution of extended daily dialfiltration.

Table 2

Population pharmacokinetic parameter estimates for ticarcillin during extended daily diafiltration (EDDf) in the final two-compartment covariate model

	Mean	S.D.	CV%	Median
CL _{EDDf} (L/h)	20.27	9.69	104.46	6.41
CL _{non-EDDf} (L/h)	11.19	9.49	86.53	4.97
V _c (L)	56.18	24.43	43.50	56.46
k _{PC} (L/h)	22.62	2.46	14.43	21.93
k _{CP} (L/h)	14.31	3.26	17.15	13.54

S.D., standard deviation; CV%, coefficient of variation; CL_{EDDf}, population clearance of ticarcillin during EDDf; CL_{non-EDDf}, population clearance of ticarcillin off EDDf; V_c, population volume of distribution in the central compartment; k_{PC}, rate constant for ticarcillin distribution from the peripheral to central compartment; k_{CP}, rate constant for ticarcillin distribution from the central to peripheral compartment.

covariates, but not others, each individually resulted in a statistically significant improvement in the -2 log-likelihood from the previous model ($P < 0.05$). Addition of each covariate improved the agreement between the observed and population-predicted concentrations as well as distribution of observed data within the visual predictive check and so was retained in the final model.

The final covariate model was as follows:

$$CL = CL_{EDDf} \times (EDDf) + CL_{non-EDDf} \times (212/SCr) \times (45/age)$$

where CL is the typical value of ticarcillin clearance; CL_{non-EDDf} is the population parameter estimate of ticarcillin CL without EDDf; CL_{EDDf} is the population parameter estimate of ticarcillin CL with EDDf; and SCr is the serum creatinine concentration. The term EDDf becomes 1 when EDDf is on and 0 when EDDf is off.

The mean \pm standard deviation population pharmacokinetic parameter estimates from the final covariate model are shown in Table 2. The diagnostic plots confirm the appropriateness of the final covariate model, as shown in Fig. 1.

4. Discussion

4.1. Key findings

In this descriptive pharmacokinetic study of ticarcillin (co-formulated with clavulanate) in critically ill patients undergoing EDDf, it was found that the median ticarcillin clearance was 6.41 L/h during EDDf and 4.97 L/h when off EDDf. The high clearance described highlights the importance of further investigation of antibiotic pharmacokinetics in patients undergoing this increasingly utilised RRT modality [7,8]. High variability in all pharmacokinetic parameter estimates of ticarcillin was also observed (Table 2), which further emphasises the challenges of using a fixed-dosing approach for drugs that display 'silent' pharmacodynamic profiles

such as antibiotics. Therapeutic drug monitoring (TDM) may contribute in further optimising the dosing of β -lactam antibiotics in individual patients undergoing EDDf.

An important consideration when dosing antibiotics in patients undergoing RRT is the presence of residual renal function and the quantification of removal of renally excreted antibiotics via this process. Factors such as SCr concentration and patient age are used to determine the glomerular filtration rate; as ticarcillin is predominantly excreted by glomerular filtration, it follows that patients of more advanced age and patient's demonstrating higher SCr concentrations are likely to correlate with a reduction in the renal removal of ticarcillin. The presence of vasopressors may also increase cardiac output and the filtration capacity of the kidneys, also affecting ticarcillin removal. Of the six participants who consented to participate in the study, five were receiving vasopressors as part of their treatment. Optimal dosing of ticarcillin in critically ill patients requires an accurate assessment of endogenous renal function and determination of the contribution of non-EDDf ticarcillin removal to clearance.

4.2. Relationship with previous studies

Despite the widespread use of TCC when it was more readily available globally, information on the use of this drug in critically ill patients undergoing different forms of RRT is relatively scarce. No previous data have been presented on the pharmacokinetics of ticarcillin in critically ill patients undergoing EDDf. The dearth of information on the dosing of β -lactam/ β -lactamase inhibitor combinations such as TCC has resulted in dosing estimates based on extrapolation of more widely used formulations such as piperacillin/tazobactam or theoretical application of dosing equations [6,9]. Information on antibiotic dosing may even be extrapolated from similar RRT modalities, e.g. using antibiotic pharmacokinetic data during CVVHDF to guide dosing in EDDf. Whilst these approaches are acceptable with the limited data available, the optimal solution is to guide dosing based on pharmacokinetic studies of the relevant RRT modality and, where available, through clinical use of TDM [10].

Typically, in non-critically ill patients with normal renal function, ticarcillin dosing guidelines vary between 12 g to 18 g daily in divided doses based on indication and severity of infection. In critically ill patients undergoing CVVH, CVVHDF or CVVHD, a loading dose of 3 g has been suggested in some drug dosing reference guidelines to establish therapeutic levels of ticarcillin, followed by 2 g every 6–8 h, 3 g every 6–8 h and 3 g 6 every h, respectively [5]. These dosing regimens reflect the ability of the different forms of RRT to remove ticarcillin to varying extents. Interestingly, the dosage guidelines described in patients undergoing CRRT generally expose the patient to less ticarcillin than would be administered in patients with normal renal function, demonstrating the superi-

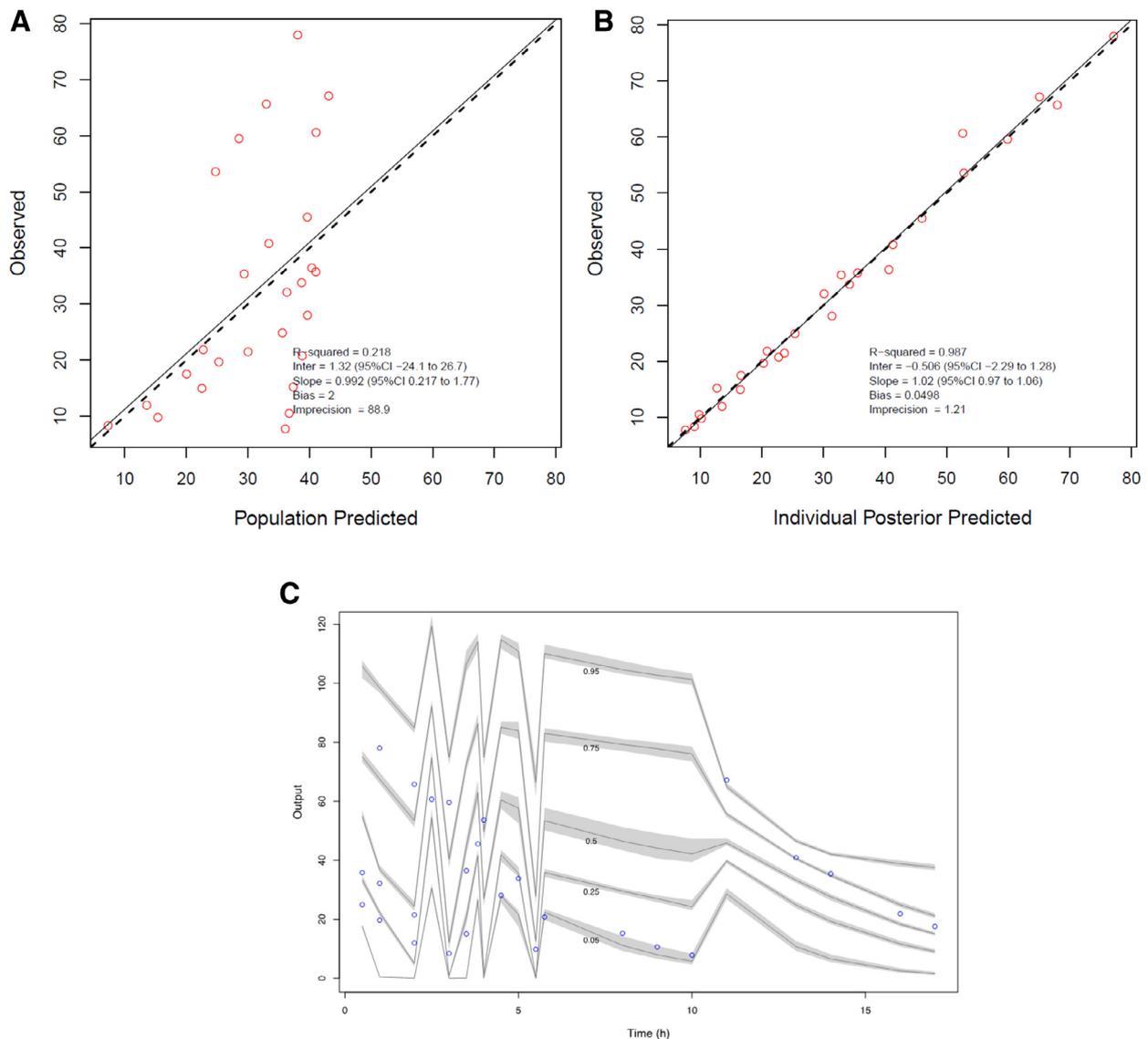


Fig. 1. Diagnostic plots for the final population pharmacokinetic covariate model. (A) Population-predicted concentrations (mg/L) versus observed concentrations (mg/L). The dotted black line is the line of linear regression with an R^2 value of 0.218, and the solid black line is the line of $x=y$. (B) Individual predicted concentrations versus observed concentrations. The dotted black line is the line of linear regression with an R^2 value of 0.987, and the solid black line is the line of $x=y$. (C) Visual predictive check of simulations of concentration (mg/L) versus time (h). Percentiles (with shaded 95% CI) are the lines shown as 0.95, 0.75, 0.5, 0.25 and 0.05 values. CI, confidence interval.

ority of a functioning kidney in removing ticarcillin compared with CRRT.

Subsequent to commencing this pharmacokinetic study, TCC has been withdrawn from active marketing owing to the availability of alternative antibiotics and declining global demand. There is a strong likelihood that TCC will continue to be used in niche clinical scenarios of patients with difficult multidrug-resistant infections with unique susceptibility profiles. This study provides information on the interindividual variability of ticarcillin in a small cohort of patients in the critical care setting. Effective removal during RRT of low-molecular-weight drugs with low volumes of distribution, such as β -lactam antibiotics like ticarcillin, warrants the need for further pharmacokinetic studies during these therapies. This study provides an example of the variability that may be encountered in the clinical setting and potentially the manner in which similar β -lactam antibiotics may demonstrate pharmacokinetic variability during EDDf.

4.3. Implications of the study findings

There is an ongoing need for pharmacokinetic studies to be performed that optimise drug therapy with evolving RRTs around the world. The lack of available data to guide decisions limits patient dosing based on extrapolation of data from other pharmacokinetic studies performed using different RRT modalities that may have far different correlative pharmacokinetic effects. Some ICUs may receive supplementary guidance by the use of TDM to optimise the dosing, however most do not have access to such supplemental tests.

The concentrations of ticarcillin observed in this study demonstrated that current dosing of 3.1 g of TCC every 8 h irrespective of the timing of EDDf achieves drug exposures associated with maximal antibacterial effect, although it may risk some patients manifesting high concentrations.

4.4. Study limitations

Although this study is the first descriptive pharmacokinetic study of ticarcillin in critically ill patients undergoing EDDf, it has some limitations. First, the sample size is small, therefore describing all possible correlations between pharmacokinetic parameters and covariates may not have been possible. Second, ticarcillin plasma concentrations were measured and not concentrations at the site of infection, which may provide better mechanistic data regarding the effectiveness of dosing. Finally, this study was not designed or powered to examine the effect of ticarcillin exposure on patient outcome, and larger studies are required to explore this question further.

5. Conclusion

Like other β -lactam antibiotics, ticarcillin demonstrates highly variable pharmacokinetics in EDDf. Importantly, a strong effect of the patient's endogenous renal function, described using SCr concentration and age, on non-EDDf clearance was observed, confirming that this must be accounted for when choosing drug dosing regimens during PIRRT. We conclude that ticarcillin is cleared to a much greater extent during EDDf than by CRRT and that more studies are needed for all drugs during this increasingly used form of PIRRT to ensure optimal therapy in a patient population at risk of therapeutic failure.

Declaration of Competing Interest

None declared.

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Ethical approval

Ethical approval was obtained from the local institutional Human Research Ethics Committee to conduct the study.

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