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Saturable elimination of piperacillin in critically ill patients: implications for continuous infusion

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ABSTRACT

The study aimed to evaluate saturation of piperacillin elimination in critically ill adult patients. Seventeen critically ill adult patients received continuous and intermittent infusion of piperacillin/tazobactam. Piperacillin plasma concentrations ($n = 217$) were analysed using population pharmacokinetic (PopPK) modelling. Post-hoc simulations were performed to evaluate the type I error rate associated with the study. Unseen data were used to validate the final model. The mean error (ME) and root mean square error (RMSE) were calculated as a measure of bias and imprecision, respectively. A PopPK model with parallel linear and non-linear elimination best fitted the data. The median and 95% confidence interval (CI) for the model parameters drug clearance (CL), volume of central compartment (V), volume of peripheral compartment (V_p) and intercompartmental clearance (Q) were 9 (7.69–11) L/h, 6.18 (4.93–11.2) L, 11.17 (7.26–12) L and 15.61 (12.66–23.8) L/h, respectively. The Michaelis–Menten constant (K_m) and the maximum elimination rate for Michaelis–Menten elimination (V_{max}) were estimated without population variability in the model to avoid overfitting and inflation of the type I error rate. The population estimates for K_m and V_{max} were 37.09 mg/L and 353.57 mg/h, respectively. The bias (ME) was −20.8 (95% CI −26.2 to −15.4) mg/L, whilst imprecision (RMSE) was 49.2 (95% CI 41.2–56) mg/L. In conclusion, piperacillin elimination is (partially) saturable. Moreover, the population estimate for K_m lies within the therapeutic window and therefore saturation of elimination should be accounted for when defining optimum dosing regimens for piperacillin in critically ill patients.

1. Introduction

The ureidopenicillin piperacillin combined with the β-lactamase inhibitor tazobactam is frequently used to treat serious infections in critically ill patients [1,2]. In line with other β-lactam antibiotics, piperacillin has time-dependent killing properties. The time (T) for which the free (f) concentration of piperacillin remains above the minimum inhibitory concentration (MIC), i.e. $\%fT_{>MIC}$, is the pharmacokinetic/pharmacodynamic (PK/PD) index of choice [3].

In the past few years, a wealth of evidence has emerged demonstrating that the pharmacokinetics of antimicrobial drugs in critically ill patients is profoundly different from the pharmacokinetics of antimicrobial drugs in healthy volunteers or non-critically ill patients [4]. For β-lactam antibiotics specifically, changes in volume of distribution and/or changes in renal function in critically ill patients may lead to considerable between- and within-patient PK variability [5]. Previously, a PK point-prevalence study of β-lactam

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antibiotics in intensive care units (ICUs) reported that 16% of the ICU patients did not achieve the PK/PD target of 50%$fT_{>MIC}$ [6]. As suboptimal antimicrobial use may lead to poor infection outcome, efforts are made to optimise the use of β-lactam antibiotics [7–9]. Because β-lactam antibiotics have time-dependent killing properties, prolonging the duration of β-lactam infusion and thereby extending the time the concentration remains above the MIC was recently introduced in clinical practice [10,11].

Currently, there is ongoing debate on whether or not piperacillin elimination is saturable at therapeutic plasma concentrations [12–19]. This mechanism is particularly relevant in the context of the recent introduction of prolonged infusion of β-lactam antibiotics. Indeed, saturation of piperacillin elimination at therapeutic plasma concentrations implies that, for the total antibiotic exposure in a patient to be the same, a higher daily dose could be necessary when piperacillin is infused continuously as opposed to intermittently. In clinical practice, however, the total daily dose of piperacillin is usually not adapted based on the mode of infusion [11,20].

The aim of this study was to investigate saturation of piperacillin elimination in critically ill adult patients receiving both intermittent and continuous infusion of piperacillin.

2. Patients and methods

2.1. Patients

This prospective interventional study was conducted in the Department of Critical Care Medicine of Ghent University Hospital (Ghent, Belgium). Ethical approval was obtained from the Ghent University Hospital Ethics Committee. Informed consent was signed by patients or their representatives. Patients were eligible for inclusion if they were admitted to the surgical or medical ICU and received piperacillin/tazobactam (TZP) in continuous infusion. Patients aged <18 years and those receiving extracorporeal membrane oxygenation or renal replacement therapy during antibiotic therapy were excluded from the study. Creatinine clearance (CL_{Cr}) was determined by measuring urinary creatinine concentrations from an 8-h urinary collection using an indwelling urinary catheter. Piperacillin antibiotic concentrations and additional data such as biochemistry, demographic data, modified Sequential Organ Failure Assessment (SOFA) score on the day of sampling, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, and ICU survival were prospectively recorded via REDCap [21].

2.2. Administration of piperacillin antibiotic therapy and sampling

All patients received both continuous and intermittent infusion of TZP. TZP dosing was as follows: loading dose of 4/0.5 g over 30 min immediately followed by continuous TZP infusion according to measured CL_{Cr} as follows: CL_{Cr} <15 mL/min, 8/1 g over 24 h; CL_{Cr} 15–29 mL/min, 12/1.5 g over 24 h; and CL_{Cr} ≥30 mL/min, 16/2 g over 24 h. At the end of the antibiotic course as indicated by the treating physician, after a 3-h washout period a short infusion (0.5 h, 4500 g) of TZP was administered. In total, 13 samples were collected from every patient. The first two samples were taken 2 h prior to and immediately before stopping the continuous infusion. Samples 3–13 were collected immediately before administration of the intermittent infusion and after 5, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min (Fig. 1).

2.3. Bioanalysis of piperacillin plasma concentrations

Arterial blood collected in 4 mL lithium heparin blood collection tubes (BD Vacutainer® BD Diagnostics, Erembodegem, Belgium) was sent to the core laboratory of the Department of Laboratory Medicine at Ghent University Hospital where they were first stored in a refrigerator at 4 °C until they were collected by the toxicology laboratory technicians. Storage at 4 °C was never longer than 24 h. After transferring to an Eppendorf tube, plasma samples were centrifuged at 16 162 × g for 8 min (Microfuge 16; Beckman Coulter, Brea, CA, USA). Immediately afterwards, plasma samples were stored at −20 °C until analysis. All samples were analysed within 1 week. The plasma concentration of piperacillin was determined by ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS). Tazobactam concentrations were not analysed in this study. The lower limit of quantification (LLOQ) for piperacillin was 1.09 mg/L, the within-run assay imprecision at LLOQ level was 3.7%CV, and the between-run assay imprecision at the LLOQ level was 8.1%CV [22].

2.4. Population pharmacokinetic (PopPK) model building

Piperacillin concentration–time data were analysed using Pmetrics v.1.5.2 (Laboratory of Applied Pharmacokinetics, Los Angeles, CA, USA), an R-based software program for non-parametric and parametric PK/PD population and individual modelling and simulation. The non-parametric adaptive grid (NPAG) algorithm was used to build a PopPK model for piperacillin administered via continuous and intermittent infusion [23]. A digital Fortran compiler was used (GFortran v.6.1; Free Software Foundation, Inc., Boston, MA, USA) and the runs were executed using R v.3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) and RStudio v.1.1.383 (RStudio, Inc., Boston, MA, USA). One- and two-compartment models were fitted to the data using subroutines from the Pmetrics library. Modelling concentration–time data with linear, parallel linear/Michaelis–Menten, and Michaelis–Menten drug clearance was attempted. Subsequently, the statistical error model with the best fit was selected and a covariate model was developed. Covariates a priori considered for inclusion in the model were measured creatinine clearance (mCL_{Cr}), estimated creatinine clearance according to the Cockcroft–Gault formula (eCL_{Cr}-CG), estimated glomerular filtration rate according to the Modification of Diet in Renal Disease formula (eGFR-MDRD), body weight, age, SOFA score and albumin, based on prior knowledge and biological plausibility [4,24–27]. Body weight was included as a primary covariate on all model parameters, except for the Michaelis–Menten constant (K_m) and the maximum elimination rate for Michaelis–Menten elimination (V_{max}), according to the allometric power model [28]:

$$P\theta_i = TVPq_1{}^{*}(WEIGHT/70)^{**}power \quad (1)$$

where P θ_i is the individual parameter value, TVPθ_1 is the parameter value for a typical adult with a body weight of 70 kg, and power is an allometric exponent fixed to 0.75 for drug clearance (CL) and intercompartmental clearance (Q) and fixed to 1 for volume of the central compartment (V) and volume of the peripheral compartment (V_p). As an initial step, the covariates mCL_{Cr}, eCL_{Cr}-CG and eGFR-MDRD were tested on the CL parameter as this is biologically plausible. However, only one of these was retained, as correlated variables may lead to collinearity and inflation of the parameter's standard error [29]. In a next step, forward selection and backward elimination using the PMstep function in Pmetrics was used to assess the relationship between covariates and model parameters. The log-likelihood ratio test (LRT) and the Akaike information criterion (AIC) were considered during model building. More specifically, a difference of 3.84 in the log-likelihood was considered significant at the 5% level when performing the LRT for comparing nested models. Estimated parameters are reported as mean, percent coefficient of variation (%CV) and median with interquartile range (IQR). The %CV is reported as a measure of between-subject variability in the model parameters. The 95%

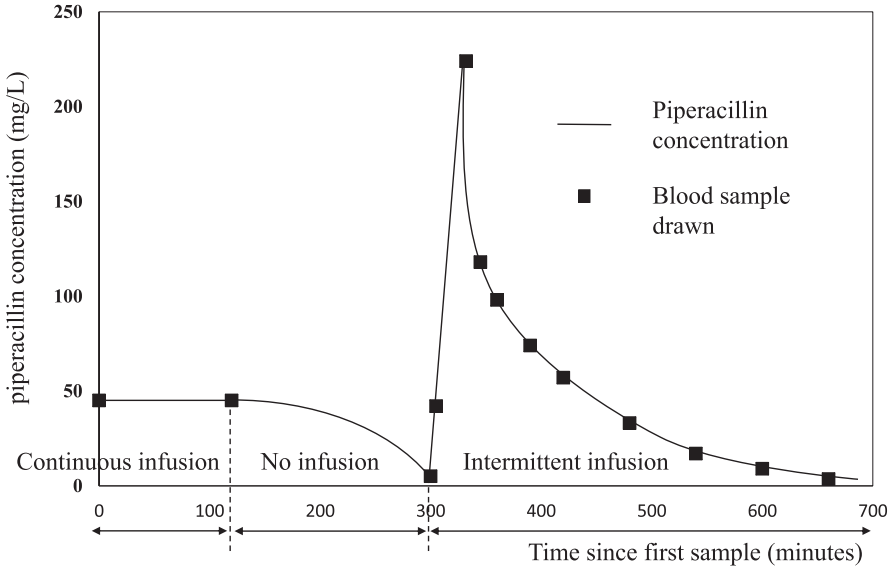

Fig. 1. Administration of piperacillin and timing of sampling.

confidence interval (CI) was estimated via a non-parametric bootstrap ($n = 1000$) and quantifies the uncertainty on the parameter estimates.

2.5. Pharmacokinetic model diagnostics

The PopPK model was assessed by visual evaluation of the goodness of fit of the observed versus a posteriori predicted plots and the coefficient of determination of the linear regression of the observed–predicted values (r^2 close to 1, intercept close to 0) from each run. The predictive performance was assessed on mean prediction error (bias) and mean bias-adjusted square prediction error (imprecision) of the population predictions.

Internal model validation consisted of a visual predictive check (VPC) plot. The VPC ($n = 10\,000$) was performed by overlaying the 95% CI of the simulated profiles for 0.05, 0.5 and 0.95 quantiles with the corresponding quantiles of the observed data.

For external model validation, the final model population parameter distributions were used to predict concentrations for an independent validation data set. We refer to Dhaese et al. [30] for a detailed description of this validation data set. Prediction errors were evaluated based on the absolute bias (ME) and imprecision (MSE) as described in Eqs. 2 and 3:

$$\text{Absolute bias}\left[\hat{\theta}\right](\text{ME}) = \text{E}\left[\hat{\theta} - \theta\right] \quad (2)$$

$$\text{Absolute imprecision}\left[\hat{\theta}\right](\text{MSE}) = \text{E}\left[\left(\hat{\theta} - \theta\right)^2\right] \quad (3)$$

where $\hat{\theta}$ is the predicted piperacillin concentration and θ is the observed concentration. The root mean square prediction error (RMSE) was calculated by taking the square root of MSE.

2.6. Comparative AUC_u simulations for intermittent and continuous infusion dosing regimens

Monte Carlo simulations ($n = 1000$) were performed with the final PopPK model to compare the unbound (u) area under the concentration–time curve (AUC_u) as a measure of total (unbound) drug exposure between intermittent and continuous infusion dosing regimens. Using AUC as a basis to compare intermittent and continuous infusion of β-lactam antibiotics was previously reported by Firsov and Mattie [31]. Free piperacillin concentrations were calculated assuming a 30% level of protein binding in accordance with previous findings [32]. Four different scenarios were evaluated, i.e. a daily dose of 12/1.5 g TZP for a patient with a measured CL_{Cr} of 20 mL/min, 16/2g TZP for a patient with a measured CL_{Cr} of 70 mL/min, 16/2 g TZP for a patient with a measured CL_{Cr} of 130 mL/min and 16/2 g TZP for a patient with a measured CL_{Cr} of 200 mL/min. The body weight for all patients was fixed at 70 kg. For each of these four scenarios, both intermittent and continuous infusion dosing regimens were simulated and compared. The AUC_u was calculated using linear trapezoidal approximation. A 24-h interval for AUC_u calculation was chosen after six doses for intermittent infusion and one bolus and five maintenance doses for continuous infusion.

2.7. Post-hoc estimation of type I error rate

A type I error rate analysis was performed to evaluate the probability to reject the null hypothesis (H_0) in favour of the alternative hypothesis (H_1) given that it is true, where H_0 = piperacillin kinetics are best described by linear elimination and H_1 = piperacillin kinetics are best described by non-linear elimination [27].

In short, concentrations for 17 patients were simulated according to the design of this study (drug administration, blood sampling, etc.). For this, the PopPK model by Landersdorfer et al. [12] served as the H_1, i.e. piperacillin pharmacokinetics are non-linear and elimination is characterised by a parallel first-order and Michaelis–Menten process. The H_0 was simulated by fixing the V_{max} estimate in the model by Landersdorfer to zero, i.e. removing the non-linear component in piperacillin elimination. This process was repeated 5000 times, resulting in 10 000 simulated data sets. All simulated data sets were fitted with a two-compartmental model with linear elimination and a two-compartmental model with parallel linear and Michaelis–Menten elimination. Both models were compared using the LRT according to Eq. 4:

$$\text{LRT} = 2^*(\text{LL}_c - -\text{LL}_r) \quad (4)$$

where LL_c is the log-likelihood (LL) for the more complex model and LL_r is the LL for the reduced model. The difference in the number of parameters between both models was four when between-subject variability was included in the estimation of K_m and V_{max} and was two otherwise. When considering the 5% level of

Table 1
Patient characteristics ($n = 17$), laboratory data and infection characteristics

Patient characteristic	Median (IQR) or *n* (%)
Male sex	11 (64.7%)
Age (years)	64 (51–70)
Weight (kg)	75 (69–80)
APACHE II score	20 (14–24)
SOFA score	7 (5–8)
Duration of TZP therapy (days)	5.8 (4.3–6.8)
Mechanical ventilation during TZP therapy	13 (76.5%)
Vasopressor therapy during TZP therapy	6 (35.3%)
ICU length of stay (days)	17.9 (14.1–31.5)
ICU survival	15 (88.2%)
Albumin (g/L)	
72 h prior to sampling	26.5 (22–29.5)
48 h prior to sampling	26 (21–27.5)
24 h prior to sampling	26.5 (22.8–30.3)
Day of sampling	27 (21.5–30.5)
24 h post-sampling	27 (21.5–30.8)

Timing	eCL_{Cr}-CG (mL/min) [median (IQR)]	eGFR-MDRD (mL/min) [median (IQR)]	mCL_{Cr} (mL/min) [median (IQR)]
72 h prior to sampling	82.9 (52.3–147.3)	97.9 (49.8–145.6)	70 (30–138)
48 h prior to sampling	85.2 (41.1–139.2)	92.9 (36.5–140.9)	49.5 (16.8–141.5)
24 h prior to sampling	84.7 (39.9–119.3)	70.3 (59.8–78.6)	87 (43–120)
Day of sampling	86.1 (40.8–139.2)	101.1 (35.2–140.9)	82 (32.5–98)
24 h post-sampling	100.1 (48.3–139.2)	72.9 (60.6–81.5)	83.5 (36–149.3)

IQR, interquartile range; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; TZP, piperacillin/tazobactam; ICU, intensive care unit; eCL_{Cr}-CG, estimated creatinine clearance according to the Cockcroft–Gault formula; eGFR-MDRD, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease formula; mCL_{Cr}, measured creatinine clearance.

significance, the critical values from the χ^2 distribution were 9.49 and 5.99, respectively.

The type I error rate was calculated from the number of times the complex model was declared superior over the reduced model for the simulated data sets according to the H_0.

2.8. Statistical analysis

All statistical analyses were performed using R and RStudio. Continuous data are presented as the median (IQR) and categorical data are presented as counts (%).

3. Results

3.1. Patients and samples

In total, 17 patients were included and 221 samples were collected (Table 1). All patients were enrolled between 5 February 2018 and 18 October 2018. Samples 5–7 were lost for Patient 13, and sample 8 was lost for Patient 15, therefore only 217 samples were analysed and used for PK model building. The focus of infection was respiratory in 11 patients, abdominal in 5 patients and bacteraemia in 1 patient.

3.2. Pharmacokinetic model building and model diagnostics

Table 2 summarises the log-likelihood (LL) values, the coefficients of determination (r^2 values), the AICs and the predictive performance of linear, parallel linear and Michaelis–Menten, and Michaelis–Menten models (without covariates). Comparison of the coefficient of determination, bias, imprecision and AIC indicated that the model with parallel linear and Michaelis–Menten kinetics was superior compared with both a model with linear elimination and a model with Michaelis–Menten elimination alone (Table 2).

Including mCL_{Cr} normalised to 100 mL/min as opposed to eCL_{Cr}-CG or eGFR-MDRD provided the model with the lowest AIC value (Table 3). Forward selection and backward elimination further revealed a relationship between albumin and CL. However, when including albumin as a covariate on CL, no model improvement in terms of ΔAIC or LRT was noted, hence albumin was not retained as a covariate in the final model.

Table 2
Predictive performance of linear and non-linear piperacillin population pharmacokinetic models[a]

Model	−2LL	Linear regression of observed–predicted for each patient					AIC
		Intercept	Slope	r^2	Bias	Imprecision	
L	1842	3.73	0.98	0.977	−0.078	0.995	1852
L/MM	1748	5.33	0.96	0.975	−0.147	1.31	1797
MM	2197	38.9	0.933	0.647	−0.457	0.779	2207

LL, log-likelihood estimate; r^2, coefficient of determination for the best-fit linear regression for the predicted–observed plot; AIC, Akaike information criterion.
[a] Predictive performance of linear (L), parallel linear and Michaelis–Menten (L/MM) and Michaelis–Menten (MM) model.

Table 3
Predictive performance of piperacillin population pharmacokinetic models incorporating renal clearance as a covariate[a]

Model	−2LL	Linear regression of observed-predicted for each patient					AIC
		Intercept	Slope	r^2	Bias	Imprecision	
mCL_{Cr}	1796	4.87	0.97	0.986	−0.136	1.25	1806
eCL_{Cr}-CG	1805	6.08	0.959	0.97	−0.172	1.29	1815
eGFR-MDRD	1904	5.5	0.98	0.962	−0.12	0.96	1915

LL, log-likelihood estimate; r^2, coefficient of determination for the best-fit linear regression for the predicted–observed plot; AIC, Akaike information criterion; mCL_{Cr}, measured creatinine clearance; eCL_{Cr}-CG, estimated creatinine clearance according to the Cockcroft–Gault formula; eGFR-MDRD, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease formula.
[a] Predictive performance of linear, parallel linear and Michaelis–Menten, and Michaelis–Menten model.

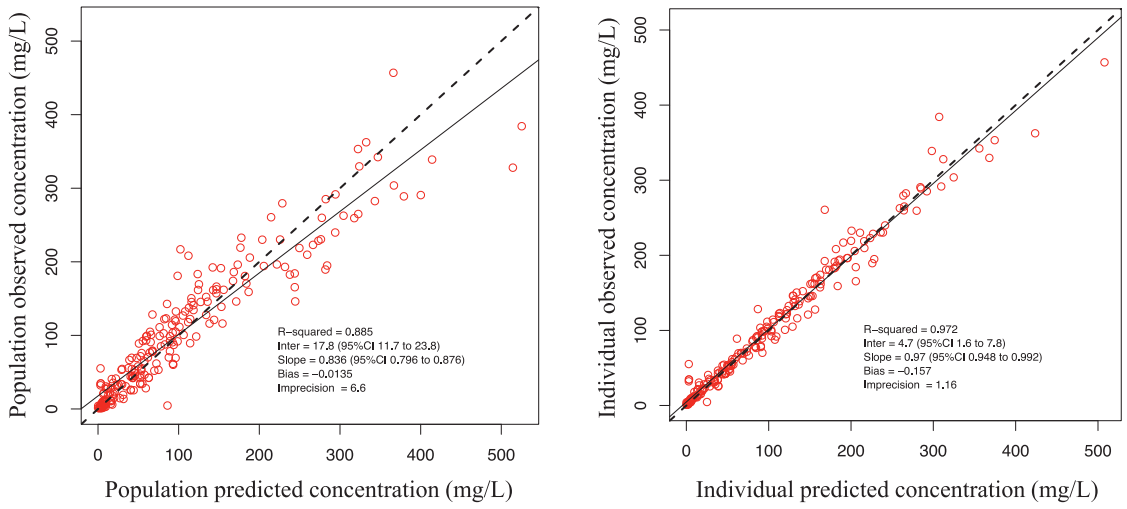

Fig. 2. Diagnostic plots of population predicted versus observed concentrations (left) and individual predicted versus observed concentrations (right) for the final pharmacokinetic model. The dashed line is the line of unity and the solid line is the line of best linear fit.

Table 4
Mean, %CV, median (IQR) and 95% CI parameter estimates for the final population pharmacokinetic model

Parameter	Mean	%CV	Median (IQR)	95% CI around the median
V (L)	9.74	87.27	6.18 (5.76–6.52)	4.93–11.2
CL (L/h)	9.29	26.19	9 (8.68–9.43)	7.69–11
Q (L/h)	21.47	59.81	15.61 (13.38–20.29)	12.66–23.8
V_p (L)	9.8	34.11	11.17 (10.7–11.69)	7.26–12

%CV, percent coefficient of variation; IQR, interquartile range; CI, confidence interval; V, volume of the central compartment; CL, drug clearance; Q, intercompartmental clearance; V_p, volume of the peripheral compartment.

The final model was described as:

$$CL = TVCL^{*}(mCL_{Cr}/100)^{*}(WEIGHT/70)^{**}0.75 \quad (5)$$

$$V = TVV^{*}(WEIGHT/70) \quad (6)$$

$$V_p = TVVp^{*}(WEIGHT/70) \quad (7)$$

$$Q = TVQ^{*}(WEIGHT/70)^{**}0.75 \quad (8)$$

where CL is piperacillin clearance, V is volume of distribution of the central compartment, V_p is volume of distribution of the peripheral compartment and Q is intercompartmental clearance. TVCL refers to the population typical piperacillin clearance for a 70 kg patient with a mCL_{Cr} of 100 mL/min; and TVV and TVVp refer to the population typical volume of distribution of the central and peripheral compartments, respectively, for a 70 kg patient.

The mean, %CV, median (IQR) and %95 CI around the median for the population parameter estimates are listed in Table 4. The typical values for K_m and V_{max} were 37.09 mg/L and 353.57 mg/h, respectively.

Between-subject variability was not estimated on K_m and V_{max} as this resulted in an over-parameterised model and an unacceptable inflation of the type I error rate (for further details see section 'Post-hoc estimation of type I error rate'). Based on the diagnostic plots, the γ multiplicative error model was selected for modelling assay variance. In all model-building runs, each observation was weighted by $1/(\gamma \times SD^2)$. We set γ equal to 1 initially and allowed Pmetrics to fit the value for the population. The final-cycle γ value was 1.26, indicating some additional process noise. The formula for the γ error model is error= $\gamma \times$ SD, where SD is the standard deviation of each observation. SD is modelled by Eq. 9 and was based on earlier validation work by Carlier et al. [33].

$$SD = 2 + 0.1 \times C \quad (9)$$

where C is the concentration of piperacillin.

The a posteriori individual and population predicted versus observed plots and the VPC plots are shown in Figs. 2 and 3, respectively. Results of the Shapiro–Wilk test of normality for the normalised prediction distribution error (NPDE) indicated no violation of normality ($P = 0.195$).

The final PopPK models showed a bias (ME) in predicting serum concentrations from the validation data set of –20.8 (95% CI –26.2 to –15.4) mg/L, whilst imprecision (RMSE) was 49.2 (95% CI 41.2–56) mg/L. The Bland–Altman plot is shown in Fig. 4.

3.3. Comparative AUC_u simulations for intermittent and continuous infusion dosing regimens

In all four scenarios, patients receiving continuous infusion had lower AUC_u values compared with simulated patients receiving the same dose via intermittent infusion (Fig. 5).

3.4. Post-hoc estimation of type I error rate

If the between-subject variability was estimated for all model parameters, the type I error rate was 47.9%. If the between-subject variability was estimated for CL, Q, V and V_p and not estimated for K_m and V_{max}, the type I error rate was reduced to 6.6%.

4. Discussion

A PopPK model with parallel linear and Michaelis–Menten elimination of piperacillin best described these data collected from 17 critically ill patients receiving both intermittent and continuous infusion of TZP. These findings are in agreement with previous studies in healthy volunteers and non-critically ill patients [12,13,17] but are in disagreement with other studies in healthy volunteers and critically ill patients [14,30,34].

Renal excretion of piperacillin is the major pathway of elimination. Approximately 74–89% of the administered dose of piperacillin is eliminated from the body by renal excretion [2,35]. More specifically, Tjandramaga et al. reported that 56–73% of the

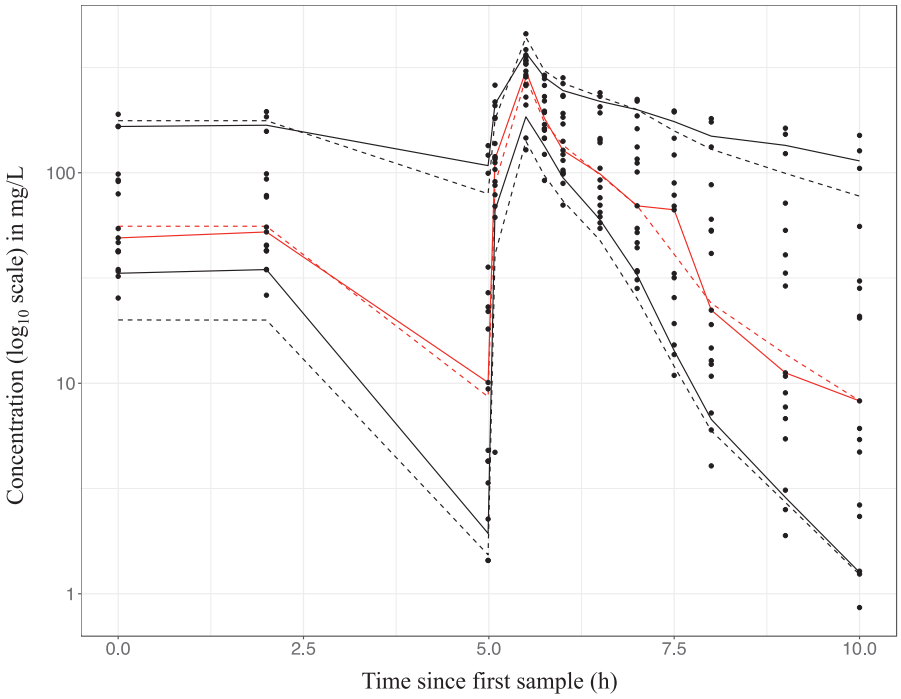

Fig. 3. Visual predictive check plot of piperacillin plasma concentration (log_{10} scale) versus time for the final population pharmacokinetic model. Black dots represent observed data, solid lines represent quantiles of the observed data, and dashed lines represent quantiles of the simulated data.

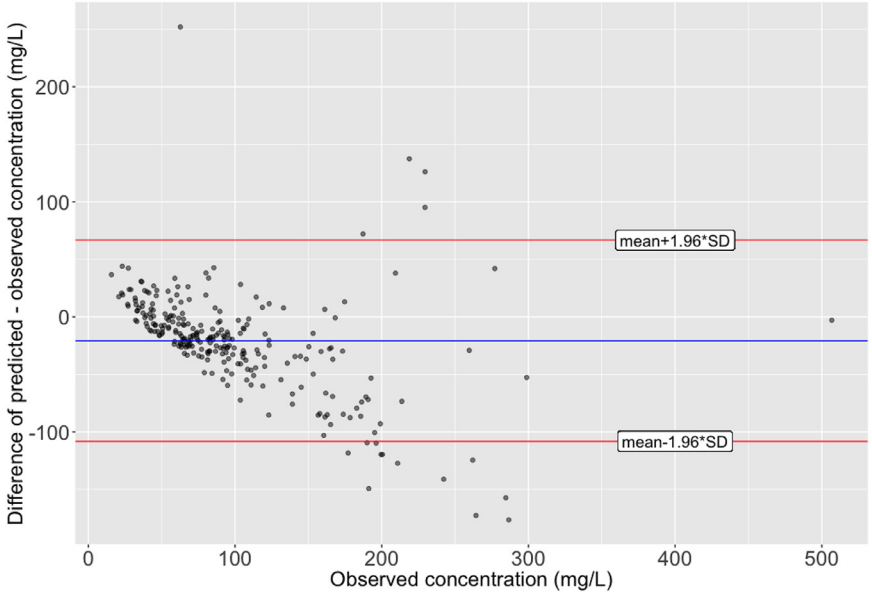

Fig. 4. Bland–Altman plot for comparison of predicted versus observed piperacillin concentrations from a validation data set. The blue line represents the mean difference in concentrations. Red lines are mean−1.96 × SD (lower line) and mean+1.96 × SD (upper line). SD, standard deviation.

renally cleared piperacillin is eliminated through tubular secretion [35], which is a saturable process.

V_{max} is the maximum elimination rate for Michaelis–Menten elimination, and the drug concentration at which the elimination rate is half of the maximum elimination rate is called the Michaelis–Menten constant (K_m). Whether or not non-linear elimination of a drug is clinically relevant depends on the value of V_{max} and K_m. Non-linear elimination is a clinically relevant process if saturation occurs at therapeutic concentrations (i.e. K_m within the therapeutic window) and if V_{max} is high relative to CL, indicating a substantial contribution of the non-linear elimination process to total body clearance. It is postulated that the non-linear elimination pathway should contribute to ≥20% of the total body clearance for it to be clinically relevant [36]. If K_m is very high, then saturation occurs but not at relevant plasma concentrations and it will therefore have no impact on the optimal dosing regimen [12]. Other researchers have reported K_m estimates of 36.1 mg/L [12], 47.9 mg/L [13] and 90.13 mg/L [17], all well within the range of therapeutic piperacillin plasma concentrations and in line with our estimate of 37.09 mg/L.

The implications of these findings remain to be determined. Several institutions recently moved towards prolonged infusion of β-lactam antibiotics, yet conclusive evidence in favour of prolonged infusion is lacking and new clinical trials are in the pipeline

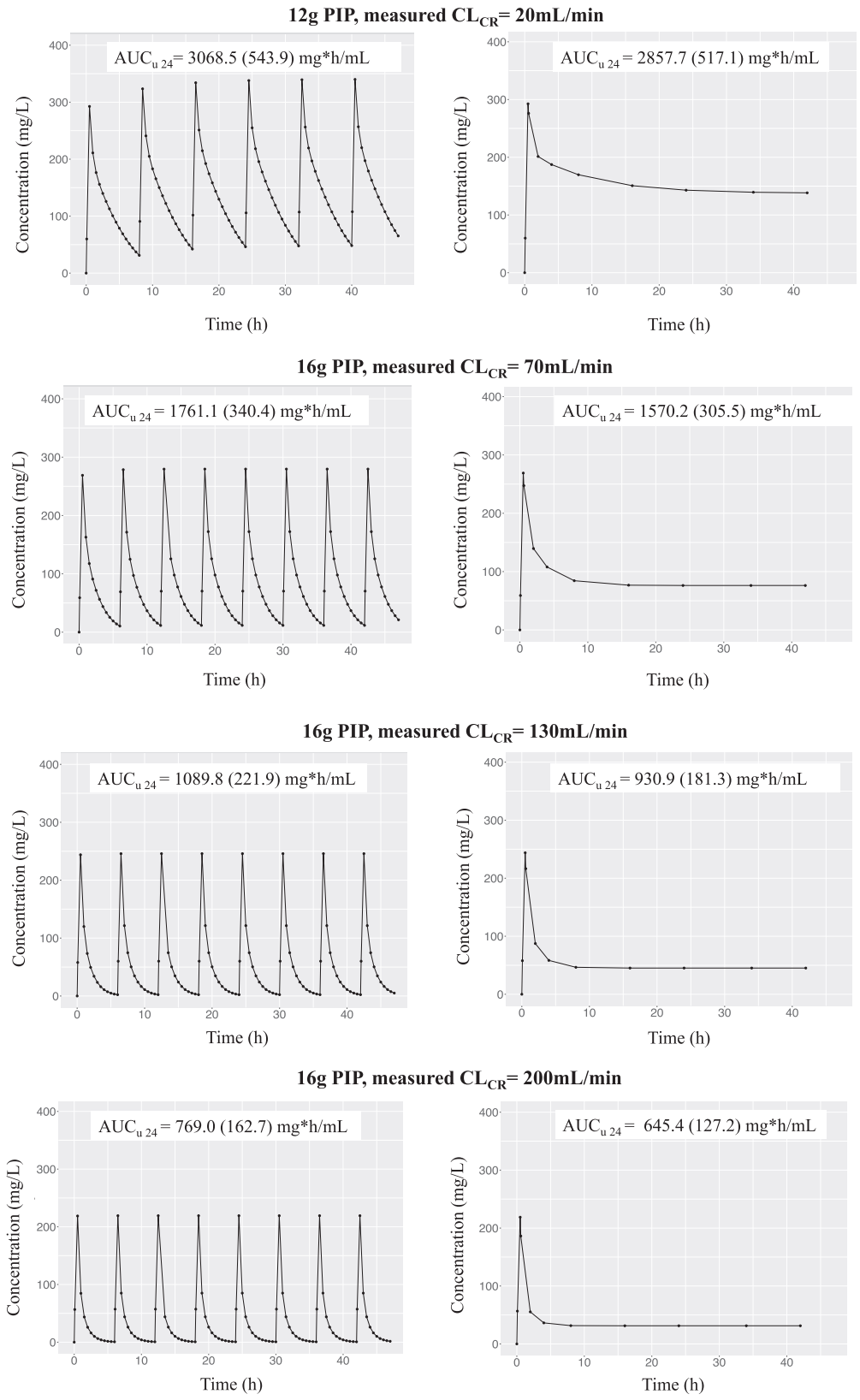

Fig. 5. Simulations of mean (SD) AUC_u values and time–concentration curves for a total daily dose of 12 g piperacillin (upper graph) or 16 g piperacillin (lower graphs) via intermittent (left) or continuous (right) infusion for a patient with a body weight of 70 kg and a measured CL_{Cr} of, respectively, 20, 70, 130 and 200 mL/min. AUC_u values were calculated for a 24-h interval after the sixth dose ($AUC_{u\ 24}$). SD, standard deviation; AUC_u, unbound area under the concentration–time curve; CL_{Cr}, creatinine clearance.

[10,11,20,37]. Saturation of piperacillin elimination at therapeutic plasma concentrations is of particular relevance when randomised clinical trials compare intermittent versus continuous infusion of piperacillin. Indeed, if saturation of piperacillin elimination occurs at therapeutic concentrations, clinical trials comparing the same daily dose of intermittent and continuous infusion piperacillin may unwillingly introduce a bias towards intermittent infusion as patients receiving the same daily dose of piperacillin via intermittent infusion may have a higher total antibiotic exposure compared with patients receiving the same dose of piperacillin via continuous infusion, as is demonstrated in the $AUC_{u\ 24}$ calculations using the final PopPK model (Fig. 5). Whilst AUC_u/MIC may not be the PD index of choice for β-lactam antibiotics, the phenomenon of non-linear kinetics may impact antibiotic concentrations and indirectly also other PD indices such as $T_{>MIC}$. This study focused on piperacillin, but tubular secretion of other β-lactam antibiotics such as amoxicillin, oxacillin, flucloxacillin, cefazolin and cefuroxime has also been reported [38,39].

When performing hypothesis testing and PK model selection, control of the type I error rate is pivotal to avoid false-positive conclusions. Inflation of the type I error rate is expected when dealing with (very) small data sets [40,41]. In this study, including the between-subject variability on K_m and V_{max} resulted in an over-parameterised model and an unacceptable type I error rate (for further details see the section 'Post-hoc estimation of type I error rate']. Therefore, the between-subject variability for K_m and V_{max} was not estimated. As few piperacillin population PK studies incorporate type I error calculations, it is difficult to determine how the current findings with regard to the non-linear kinetics of piperacillin relate to the findings of other studies.

This study has several limitations. Whilst the primary goal was to detect non-linear elimination of piperacillin with a low probability of falsely rejecting H_0, the between-subject variability was not estimated on K_m and V_{max} as this led to an unacceptable type I error. Determining urinary concentrations of renally eliminated drugs is helpful when non-linear kinetics is expected, however in this study piperacillin concentrations were not measured in the urine and no distinction could be made between the renal and non-renal clearance of piperacillin. The validation results indicate that the final model has a bias towards underpredicting antibiotic concentrations. While no bias is to be preferred, in case of underprediction, physicians may be inclined to increase the dose or dosing frequency. Given the low toxicity of β-lactam antibiotics and the important risk of underdosing in ICU patients, models that underpredict concentrations of β-lactam antibiotics are usually preferred over models that have bias towards overprediction [42]. In addition, the sequence of the infusion modes never changed and all patients received continuous infusion first, followed by intermittent infusion. Hence, a trend in piperacillin clearance over time could not be excluded.

In conclusion, piperacillin elimination was best described by a PopPK model incorporating parallel linear and Michaelis–Menten elimination. Nevertheless, in the literature conflicting evidence is found on the importance of non-linear elimination for piperacillin pharmacokinetics. Non-informative study designs and statistical inference based on over-parameterised models likely contribute to these conflicting findings. Future studies, appropriately powered and with a low type I error rate, should be conducted to provide conclusive evidence on the potential influence of non-linear elimination for piperacillin pharmacokinetics in critically ill patients.

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Declarations

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Competing interests: JL has been a consultant for MSD, Australia and Pfizer; JAR has been a consultant for Accelerate Diagnostics, Astellas, Bayer, bioMérieux and MSD as well as having received investigator-initiated grants from MSD, The Medicines Company and Cardeas Pharma; JJDW has been a consultant for Accelerate Diagnostics, Bayer Healthcare, MSD and Pfizer. All other authors declare no competing interests.

Ethical approval: Ethical approval was obtained from the Ethics Committee of Ghent University Hospital (Ghent, Belgium) [2017/1354].

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