ORIGINAL RESEARCH ARTICLE

An Integral Pharmacokinetic Analysis of Piperacillin and Tazobactam in Plasma and Urine in Critically Ill Patients

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Abstract

Background and Objectives Although dose optimization studies have been performed for piperacillin and tazobactam separately, a combined integral analysis is not yet reported. As piperacillin and tazobactam pharmacokinetics are likely to show correlation, a combined pharmacokinetic model should be preferred to account for this correlation when predicting the exposure. Therefore, the aim of this study was to describe the pharmacokinetics and evaluate different dosing regimens of piperacillin and tazobactam in critically ill patients using an integral population pharmacokinetic model in plasma and urine.

Methods In this observational study, a total of 39 adult intensive care unit patients receiving piperacillin–tazobactam as part of routine clinical care were included. Piperacillin and tazobactam concentrations in plasma and urine were measured and analyzed using non-linear mixed-effects modeling. Monte Carlo simulations were performed to predict the concentrations for different dosing strategies and different categories of renal function.

Results A combined two-compartment linear pharmacokinetic model for both piperacillin and tazobactam was developed, with an output compartment for the renally excreted fraction. The addition of 24-h urine creatinine clearance significantly improved the model fit. A dose of 12/1.5 g/24 h as a continuous infusion is sufficient to reach a tazobactam concentration above the target (2.89 mg/L) and a piperacillin concentration above the target of $100\% f\mathrm{T}_{>1\times\mathrm{MIC}}$ (minimum inhibitory concentration [MIC] $\leq$ 16 mg/L). To reach a target of $100\% f\mathrm{T}_{>5\times\mathrm{MIC}}$ with an MIC of 16 mg/L, piperacillin doses of up to 20 g/24 h are inadequate. Potential toxic piperacillin levels were reached in 19.6% and 47.8% of the population with a dose of 12 g/24 h and 20 g/24 h, respectively.

Conclusions A regular dose of 12/1.5 g/24 h is sufficient in > 90% of the critically ill population to treat infections caused by *Escherichia coli* and *Klebsiella pneumoniae* with MICs $\leq$ 8 mg/L. In case of infections caused by *Pseudomonas aeruginosa* with an MIC of 16 mg/L, there is a fine line between therapeutic and toxic exposure. Dosing guided by renal function and therapeutic drug monitoring could enhance target attainment in such cases.

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1 Introduction

Piperacillin–tazobactam is a broad-spectrum β-lactam and β-lactamase inhibitor combination, active against most *Enterobacterales* and *Pseudomonas* spp., among others [1]. It is one of the most prescribed antibiotics in critically ill patients for the treatment of moderate to severe infections, including severe hospital-associated and ventilator-associated pneumonia, complicated urinary tract infections, complicated intra-abdominal infections, and other causes of sepsis [2, 3]. It is strongly recommended to administer piperacillin–tazobactam as a prolonged (i.e. continuous or extended) infusion to maximize target attainment [4]. A dose of 12/1.5 g/day is generally adequate for infections caused by *Enterobacterales*, anaerobes, and gram-positive bacteria

△ Adis

Key Points

Regular doses of tazobactam (1–2 g/24 h) are sufficient for target attainment.

Piperacillin administered at 12 g/24 h as a continuous infusion is sufficient to treat most infections with minimum inhibitory concentrations (MICs) ≤ 8 mg/L. However, for infections caused by pathogens with an of MIC ≥ 16 mg/L, higher doses of piperacillin are needed, which is accompanied by an increased risk of reaching toxic concentrations.

High concentrations of piperacillin and tazobactam in urine were measured.

(clinical breakpoint for susceptibility ≤ 8 mg/L). However, for *Pseudomonas aeruginosa*, a dose of 16/2 g/24 h is recommended due to higher minimum inhibitory concentrations (MIC) of wild-type *P. aeruginosa* (clinical breakpoint for susceptibility ≤ 16 mg/L) [5].

Most pharmacokinetic studies of piperacillin–tazobactam have focused on piperacillin. However, the efficacy of piperacillin also depends on a sufficiently high concentration of tazobactam in case of β-lactamase-producing strains. Piperacillin–tazobactam is available in a fixed-dose combination (ratio 8:1), and it is therefore desirable that the pharmacokinetic properties of both the β-lactam and β-lactamase inhibitor are similar and remain similar under changing pathophysiological conditions. The efficacy of piperacillin is driven by the time that the unbound drug concentration remains above the MIC of the targeted pathogen (fT$_{>MIC)}$ [6]. Targets of 100% fT$_{>1-5\times MIC}$ are often used in the critically ill population [4, 7]. It is known that pharmacokinetic changes of tazobactam affect the pharmacodynamic outcome [8–10]. Time above threshold is the pharmacokinetic/pharmacodynamic index that appears to correlate best with the efficacy of tazobactam [8].

Both piperacillin and tazobactam are primarily excreted by the kidneys via glomerular filtration and tubular secretion [11]. As a consequence, there is a strong inverse relationship between renal function and systemic exposure of both compounds. It is recommended to adjust the dose of piperacillin–tazobactam based on renal function [1]. Substantial changes in renal function are common in critically ill patients. On the one hand, the glomerular filtration rate (GFR) is lower in patients with acute kidney injury (AKI), and on the other hand, augmented renal clearance (defined as a creatinine clearance of at least 130 mL/min) is increasingly

recognized in ICU patients [12]. Although piperacillin and tazobactam are renally excreted to a major extent, little is known about the urinary pharmacokinetics. Evaluating the urinary pharmacokinetics is even more relevant in the light of piperacillin–tazobactam as a non-carbapenem treatment option in urinary tract infections caused by bacteria producing extended-spectrum β-lactamases (ESBLs).

Although dose optimization studies in critically ill patients have been performed for piperacillin and tazobactam separately [13–16], a combined integral analysis and dose optimization is not yet reported. As piperacillin and tazobactam pharmacokinetics are likely to show correlation, a combined pharmacokinetic model offers the opportunity to predict the exposure of both drugs under different physiological conditions while accounting for this inherent correlation. The aim of this study was to describe the pharmacokinetics of both piperacillin and tazobactam in critically ill patients. An integral population pharmacokinetic model for both piperacillin and tazobactam in plasma and urine was developed and was used to evaluate different dosing regimens based on renal function.

2 Methods

2.1 Study Design and Population

This was a prospective, observational, pharmacokinetic, single-center study performed on the intensive care unit (ICU) of the Radboudumc, Nijmegen, The Netherlands. This study was carried out in accordance with the applicable rules concerning the review of research ethics committees and informed consent in The Netherlands. All patients or legal representatives were informed about the details of this study and could decline to participate (CMO identifier: 2018-4837). The study was registered at ClinicalTrials.gov (identifier: NCT03738683).

All patients admitted to the ICU who were treated with intravenous piperacillin–tazobactam as part of routine clinical care were eligible for inclusion if they were ≥ 18 years of age, started piperacillin–tazobactam therapy ≤ 72 h before inclusion, and were managed with a central venous and/or arterial catheter. Patients were excluded if they received renal replacement therapy or extracorporeal membrane oxygenation. Dose and duration of piperacillin–tazobactam were determined by the attending physician as part of routine clinical care. To estimate pharmacokinetic parameters with sufficient accuracy, we enrolled 40 patients for inclusion, similar to previously published pharmacokinetic studies with piperacillin in critically ill patients [13, 15–17].

2.2 Data Collection

Demographic data and biochemical data were extracted from electronic patient records and processed anonymously. These data included age, sex, height, and total body weight. Biochemical data included creatinine (collected as part of clinical care), cystatin C, urine creatinine collected from urine over a 24-h interval, and serum albumin (collected as part of the study). Furthermore, the indication for piperacillin–tazobactam treatment, identified pathogen and drug dose history were collected. In addition, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on the day of ICU admission and the Sequential Organ Failure Assessment (SOFA) score on the day of inclusion were recorded.

2.3 Pharmacokinetic Sampling

Ethylenediaminetetraacetic acid (EDTA) plasma samples were collected on seven timepoints during a dosing interval: at $t = 0$ (predose) and at $t = 15, 30, 60, 120, 180$ and 360 min post-infusion. To determine the interoccasion variability, we sampled on two occasions, with an interval of 24 h and a total of 14 sampling timepoints, in a subgroup of patients. Furthermore, urinary pharmacokinetics, in 24-h urine, were also determined in a subgroup of patients. All samples were centrifuged at 1900 g for 5 min and were stored in a $- 40\,^{\circ}\mathrm{C}$ freezer until further analysis.

2.4 Bioanalysis of Piperacillin and Tazobactam

Total plasma and urine concentrations for both piperacillin and tazobactam were determined using a validated ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) [XEVO TQ-S, Waters, Etten-Leur, The Netherlands]. The dynamic range for piperacillin concentrations was 0.2–60 mg/L in plasma and 20–6000 mg/L in urine. The dynamic range for tazobactam concentrations was 0.2–30 mg/L in plasma and 15–3000 mg/L in urine. The accuracy range ($n = 15$) in plasma samples, which was dependent on the concentration, was 96–101% for piperacillin and 99–101% for tazobactam. The accuracy range ($n = 5$) in urine samples was 105–110% for piperacillin and 94–101% for tazobactam. Within-day precision of piperacillin varied between 1.8 and 7.6% in plasma samples and 1.0 and 5.0% in urine samples, while within-day precision of tazobactam varied between 2.7 and 10.8% in plasma samples and 2.1 and 3.9% in urine samples. Between-day precision varied between 1.1 and 2.8% in piperacillin plasma samples and 0.3 and 5.3% in tazobactam plasma samples.

2.5 Pharmacokinetic Analysis

Population pharmacokinetic analysis of piperacillin–tazobactam was performed by means of non-linear mixed-effects modeling using the NONMEM® software package (version 7.4.1). Pirana (version 2.9.7) was used as an interface for NONMEM, Perl-Speaks-NONMEM, Xpose and R. Concentration data were log-transformed. The first-order conditional estimation (FOCE) method was used throughout model building. All flow and volume parameters were allometrically scaled to a standardized fat-free mass of 58.2 kg [18], corresponding to a 1.80 m adult male of 70 kg, a priori, with allometric exponents of 0.75 and 1, respectively [19]. Inter- and intraindividual variability were assumed to be log-normally distributed. Residual variability was evaluated using additive error models on a log-scale (which corresponds to proportional error models on a linear scale) separately for each observation compartment: central and urine compartments for both piperacillin and tazobactam. Parameter precision was calculated using the sampling importance resampling procedure as described previously [20].

Structural model selection and covariate analysis were guided by physiological plausibility and objective function value (OFV). A decrease of > 3.84 points in OFV, corresponding to a significance level of $p < 0.05$ for nested models, was considered statistically significant in univariate testing. Non-nested models were compared using the Akaike Information Criterion. Various equations for estimated GFR (eGFR) were evaluated as covariates for renal clearance: Modification of Diet in Renal Disease (MDRD) [21], Chronic Kidney Disease Epidemiology Collaboration based on serum creatinine (CKD-EPI$_{creat}$) [22], based on serum cystatin C (CKD-EPI$_{cysC}$) [23] and on both serum creatinine and serum cystatin C (CKD-EPI$_{creat-cysC}$) [23], and 24-h urine creatinine clearance. No other covariates were evaluated.

2.6 Simulations

The final model was used to perform Monte Carlo simulations to predict the piperacillin and tazobactam concentrations in both plasma and urine. We simulated different dosing regimens in 5000 virtual patients. Total body weight, height, and sex were extracted from 5000 previous ICU patients at our clinic. A uniform distribution of 24-h urine creatinine clearance between 10 and 200 mL/min was simulated, with 10 mL/min increments, resulting in 20 groups of 250 individuals each. For the distribution of 24-h urine output, we used the geometric mean (1585 mL) and coefficient of variation (59.8%) of our study population.

Four different dosing regimens of piperacillin–tazobactam were simulated: 8/1, 12/1.5, 16/2, and 20/2.5 g daily as a continuous infusion, all preceded by a loading dose of 4/0.5 g administered in 30 min. Total piperacillin and tazobactam concentrations were predicted at steady-state.

Pharmacodynamic targets for piperacillin were defined as 100% $fT_{>1\times MIC}$ and 100% $fT_{>5\times MIC}$. We converted the unbound targets to equivalent total concentrations, based on a protein binding of 30% [1]. Probability of target attainment (PTA) was assessed considering the epidemiological cut-off value (ECOFF) from the MIC distribution for *P. aeruginosa*, i.e. 16 mg/L [24]. This can be considered as a worst-case scenario for empirical dosing. In addition, the cumulative fraction of response (CFR) was calculated against the wild-type MIC distribution for *Escherichia coli and Klebsiella pneumoniae* (range 0.008–8 mg/L) [25].

The target for tazobactam was based on an in vitro infection model [8] in which an unbound concentration level of 2 mg/L during 85% of the dosing interval was required to reach a 2-log^{10} CFU/mL reduction for a worst-case scenario, namely high-level β-lactamase-producing *E. coli* strains. Based on these variables, an unbound tazobactam concentration of 2 mg/L corresponds to a total concentration of 2.86 mg/L, assuming a protein binding of 30% [1].

A previously established total piperacillin concentration of 157 mg/L was used as the upper limit for toxicity [26]. The defined threshold has been associated with neurotoxicity in patients receiving a continuous infusion of piperacillin–tazobactam. A much higher neurotoxicity threshold concentration of 361 mg/L and a trough concentration of 453 mg/L for the development of nephrotoxicity in patients administered intermittent infusions of piperacillin has also been reported [27]. In our study, we used the threshold of 157 mg/L, since this is based on patients receiving piperacillin as a continuous infusion. To our knowledge, a relationship between tazobactam concentration and toxicity is not known.

3 Results

3.1 Patient Characteristics

Forty patients were enrolled in the pharmacokinetic study. One patient was excluded for analysis, since the collection times of the pharmacokinetic sampling were not correctly registered. Patients had a median (range) age of 60 (23–83) years, a median (range) total body weight of 80 (48–133) kg, and a median (range) creatinine clearance of 116 (15–377) mL/min. Nineteen of 39 patients had augmented renal clearance (creatinine clearance > 130 mL/min). Details of the patient characteristics are summarized in Table 1. The majority of patients were treated with piperacillin–tazobactam for

sepsis due to pneumonia (43.6%) and sepsis of unknown origin (43.6%). All patients received a dose of 4/0.5 g every 8 h administered in approximately 30 min.

For 30 patients, sampling occurred on one occasion, and for nine patients, sampling occurred on two occasions, with an interval of 24 h. A total of 325 plasma samples for both piperacillin and tazobactam were collected. For 12 patients, 24-h urine was collected for pharmacokinetic sampling during the study period. Plasma concentrations ranging from 0.3 to 428 mg/L (piperacillin) and 0.04 to 51.1 mg/L (tazobactam) were measured. Urinary piperacillin concentrations between 1057 and 8967 mg/L and urinary tazobactam concentrations between 238 and 1503 mg/L were measured.

3.2 Pharmacokinetic Analysis

A very high correlation (Spearman's correlation $r = 0.99$, $p < 0.001$) between piperacillin and tazobactam concentrations in plasma was observed (Fig. 1). Two separate pharmacokinetic models were developed for piperacillin and tazobactam. In addition, piperacillin and tazobactam were modeled simultaneously in a joint pharmacokinetic model, since individual pharmacokinetic parameters of piperacillin

Table 1 Patient characteristics

	Evaluable patients [$n = 39$]
Demographics	
Sex	
Male	26
Female	13
Age, years	60 (23–83)
Total body weight, kg	80 (48–133)
Height, cm	176 (156–198)
Clinical characteristics	
APACHE II score	17 (5–37)
SOFA score	7 (1–13)
Creatinine, μmol/L	70 (25–336)
Cystatin C, mg/L	1.02 (0.44–2.74)
24 h urine output, mL	1735 (560–5110)
24 h urine creatinine clearance, mL/min	116 (15–377)
Albumin, g/L	19 (10–32)
Piperacillin–tazobactam dose	
4/0.5 g q8h	39
Indication	
Sepsis due to pneumonia	17
Sepsis (of unknown origin)	17
Intra-abdominal infection	5

Data are expressed as *n* or median (range)

APACHE II Acute Physiology And Chronic Health Evaluation II, *SOFA* Sequential Organ Failure Assessment, *q8h* every 8 h

and tazobactam showed covariance. For both piperacillin, as for tazobactam, a two-compartment linear pharmacokinetic model with an output compartment for the renally excreted fraction described the data best. Interindividual variability could be identified for non-renal clearance and central and peripheral volume of distribution of tazobactam. Interoccasion variability could be identified for renal clearance for both substances. Equations for eGFR were tested as continuous covariates for renal clearance, assuming a linear relationship (Eq. 1):

$$CL = \theta \, CL_{\text{non-renal}} + eGFR \times \theta \, \text{factor} \, CL_{\text{renal}} \qquad (1)$$

The addition of eGFR as a covariate for clearance improved the model fit for both piperacillin and tazobactam. All eGFR algorithms improved the model significantly ($p < 0.05$). As the introduction of 24-h urine creatinine clearance as a covariate resulted in the greatest reduction in OFV, this estimate was chosen for the final model.

Thereafter, the two separate models were combined into one integral model. A schematic depiction of the integral pharmacokinetic model is shown in Fig. 2, and parameter estimates of the model are shown in Table 2. Renal clearance of piperacillin and tazobactam were highly related. Therefore, in the combined model, renal clearance of tazobactam was described as a function of piperacillin renal clearance (Eq. 2):

$$CL_{\text{renal, tazobactam}} = CL_{\text{renal,piperacillin}} \times \theta \qquad (2)$$

Interindividual variability could be estimated for non-renal clearance and central and peripheral volume of distribution, while interoccasion variability could be estimated for renal clearance. Interindividual and interoccasion variability for both substances were estimated with the same parameters, which resulted in an improved model fit compared with using separate estimates. The introduction of 24-h urine creatine clearance significantly improved the model fit, with
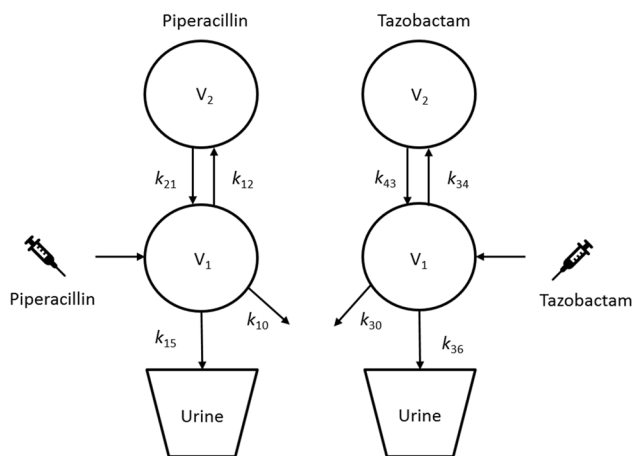
Fig. 2 Schematic depiction of the pharmacokinetic model. The elimination rate constants describing the model are as follows: $k_{12} = Q_{\text{piperacillin}}/V_{1,\text{piperacillin}}$, $k_{21} = Q_{\text{piperacillin}}/V_{2,\text{piperacillin}}$, $k_{10} = CL_{\text{nonrenal,piperacillin}}/V_{1,\text{piperacillin}}$, $k_{15} = CL_{\text{renal,piperacillin}}/V_{1,\text{piperacillin}}$, $k_{34} = Q_{\text{tazobactam}}/V_{1,\text{tazobactam}}$, $k_{43} = Q_{\text{tazobactam}}/V_{2,\text{tazobactam}}$, $k_{30} = CL_{\text{nonrenal,tazobactam}}/V_{1,\text{tazobactam}}$, $k_{36} = CL_{\text{renal,tazobactam}}/V_{1,\text{tazobactam}}$

Fig. 1 Observed piperacillin concentrations versus observed tazobactam concentrations

$r = 0.99$, $p < 0.001$
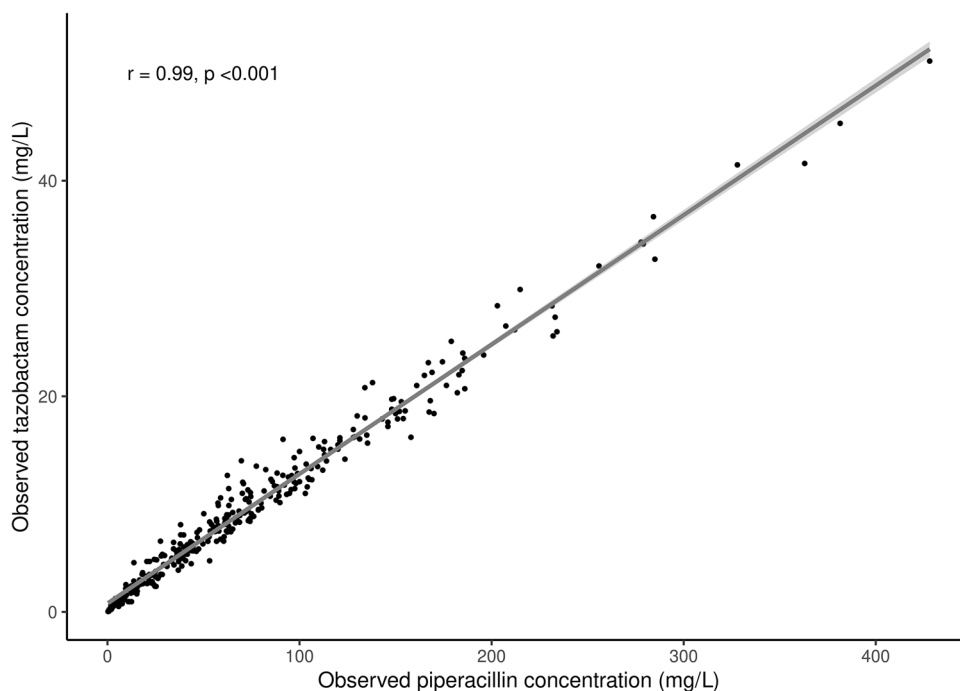
a decrease in objective function of 70 points. Interoccasion variability decreased from 89.6 to 31.5%.

The goodness-of-fit plots are depicted in Figs. 1, 2, 3 and 4 of the electronic supplementary material.

We performed a post hoc design evaluation by means of a stochastic simulation and estimation (SSE) of 250 virtual pharmacokinetic studies. A sample size of 39 patients and a total of 325 plasma samples for both piperacillin and tazobactam resulted in an accurate and precise estimation of the pharmacokinetic parameters (relative bias < 10% and imprecision < 20%).

3.3 Simulations

The simulated piperacillin and tazobactam plasma concentrations for the four dosing regimens (8/1, 12/1.5, 16/2, and 20/2.5 g/24 h) are shown in Figs. 3 and 4. The target concentration for tazobactam (2.86 mg/L) was reached in 100% of

Table 2 Parameter estimates of the final model

	Parameter estimates (95% CI) Final model
Piperacillin	
θ CL$_{\text{non-renal}}$ (L/h)	4.11 (3.04–5.40)
θ factor CL$_{\text{renal}}$	0.0613 (0.0541–0.0697)
CL$_{\text{renal}}$ (L/h) for individual with CreatCL of 116 mL/min	7.11 (6.28–8.09)
$V1$ (L)	29.7 (25.7–31.4)
$V2$ (L)	4.26 (2.22–7.63)
Q (L/h)	3.27 (2.41–4.19)
Tazobactam	
θ CL$_{\text{non-renal}}$ (L/h)	2.49 (1.75–3.32)
θ factor CL$_{\text{renal}}$	0.0674 (0.0631–0.0723)
CL$_{\text{renal}}$ (L/h) for individual with CreatCL of 116 mL/min	7.82 (7.32–8.39)
$V1$ (L)	30.3 (26.4–34.5)
$V2$ (L)	4.56 (2.35–8.30)
Q (L/h)	3.44 (2.45–4.64)
Interindividual variability (%)	
CL$_{\text{non-renal}}$	95.8 (68.1–154)
V1	44.0 (33.8–58.2)
V2	336 (151–1393)
Interoccasion variability (%)	
CL$_{\text{renal}}$	31.5 (24.6–41.9)
Residual error (%)	
Central piperacillin	28.0 (25.9–30.3)
Central tazobactam	25.4 (23.6–27.4)
Urine piperacillin	6.46 (1.02–15.88)
Urine tazobactam	14.2 (9.62–20.6)

Total clearance is defined as: CL = θ CL$_{\text{non-renal}}$ + creatinine clearance × θ factor CL$_{\text{renal}}$

CI confidence interval

the population when a dose of ≥ 2 g/24 h was administered, and in 99.0% and 99.4% of the population with doses of 1 and 1.5 g/24 h, respectively. As the tazobactam target concentration is always achieved, the efficacy of the piperacillin–tazobactam combination is thus mainly dependent on the piperacillin concentration. The PTA for piperacillin, considering an MIC of 16 mg/L, is presented in Table 3. Piperacillin administered at 12 g/24 h is sufficient to attain the target in > 99% of the population when aiming for a target of 100% fT$_{>1\times\text{MIC}}$, even for patients with a creatinine clearance of up to 200 mL/min. In case a target of 100% fT$_{>5\times\text{MIC}}$ is desired, a dose of 20 g/24 h is necessary in patients with a creatinine clearance of 10–60 mL/min, for target attainment in > 90% of the population. Higher doses are required for patients with a creatinine clearance > 60 mL/min.

The CFR for piperacillin against *E. coli* and *K. pneumoniae* is presented in Table 4. The CFR at 100% fT$_{>1\times\text{MIC}}$ was > 90% against *E. coli* and *K. pneumoniae* for all simulated dosing regimens and different classes of creatinine clearance. When aiming for a target of 100% fT$_{>5\times\text{MIC}}$, a dose of 12 g/24 h or more was sufficient for a CFR > 90% against both *E. coli* and *K. pneumoniae*. The CFR was <90% in patients with a creatinine clearance of ≥ 130 mL/min treated with a dose of 8 g/24 h against *K. pneumoniae*.

A limited fraction of 8.0% of the population reached the putative toxicity threshold of 157 mg/L at a dose of 8 g/24 h. In contrast, this threshold was reached in 19.6% with a dose of 12 g/24 h, in 33.3% with a dose of 16 g/24 h, and in 47.8% with a dose of 20 g/24 h.

The simulated piperacillin and tazobactam concentrations in urine are shown in Fig. 5. The median (interquartile range [IQR]) urine piperacillin concentration was 5371 [3110–8,830] mg/L with a dose of 8 g/24 h, 8057 [4665–13,243] mg/L with a dose of 12 g/24 h, 10,742 [6219–17,652] mg/L with a dose of 16 g/24 h, and 13,424 [7774–22,052] mg/L with a dose of 20 g/24 h.

4 Discussion

This study contributes to the knowledge of piperacillin and tazobactam pharmacokinetics and urinary concentrations in critically ill patients. To the best of our knowledge, we are the first to report on a joint pharmacokinetic model with piperacillin–tazobactam in plasma and urine, enabling us to predict the pharmacokinetics of both compounds simultaneously. A high correlation between the pharmacokinetics of both compounds was observed, indicating the necessity of our approach. Neglecting the inherent correlation between the pharmacokinetics of piperacillin and tazobactam would carry this forward in the Monte Carlo simulations, resulting in incorrect target attainment predictions. Moreover, since the pharmacokinetic observations of piperacillin offer
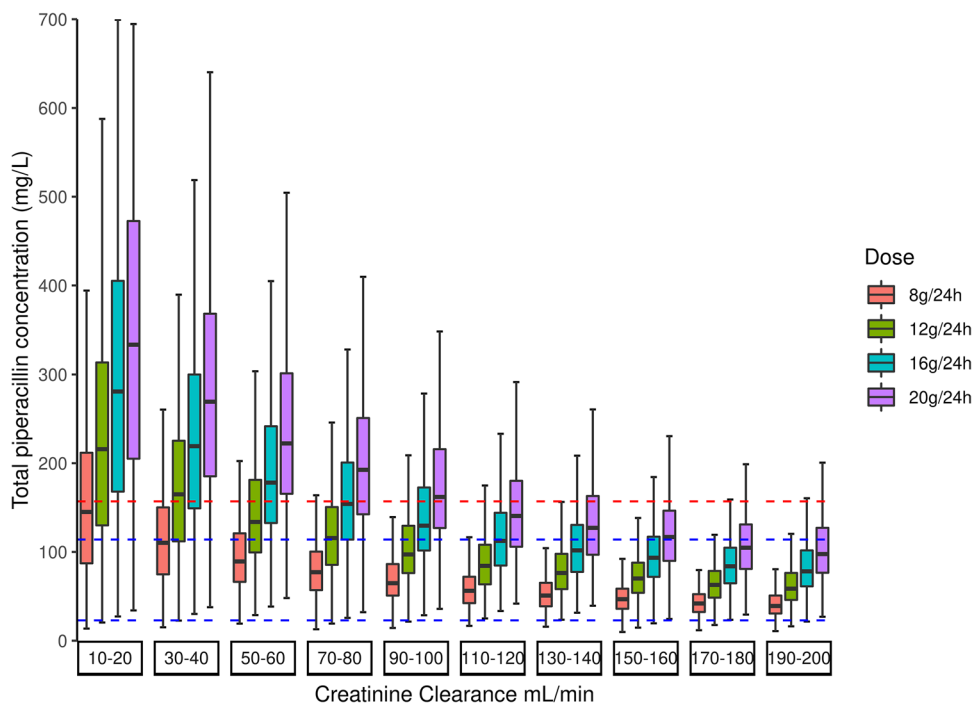
Fig. 3 Simulated piperacillin concentrations for different dosing regimens versus creatinine clearance. The blue horizontal lines represent a target of 100% $fT_{>1\times MIC}$ (22.9 mg/L) and 100% $fT_{>5\times MIC}$ (114 mg/L), assuming an MIC of 16 mg/L. The red horizontal line represents the upper limit of toxicity (157 mg/L). Simulations were performed in 20 groups of creatinine clearance between 10 and 200 mL/min, with 10 mL/min increments. In this figure, pairs of two groups have been combined. *MIC* minimum inhibitory concentration
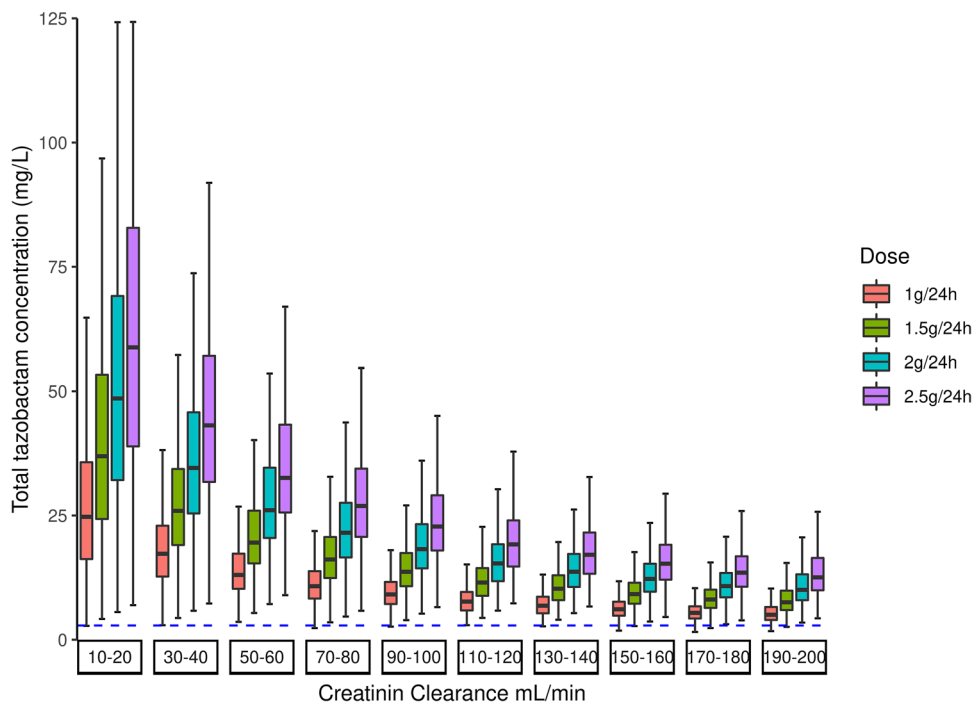

Fig. 4 Simulated tazobactam concentrations for different dosing regimens versus creatinine clearance. The blue horizontal line represents a target of 2.86 mg/L. Simulations were performed in 20 groups of creatinine clearance between 10 and 200 mL/min, with 10 mL/min increments. In this figure, pairs of two groups have been combined

subject-specific information that is helpful in fitting the tazobactam data, and vice versa, using a joint model enlarges the total information density and thus enriches the model. The wide distribution of renal function with a high proportion of subjects in our study with augmented renal clearance (49%) underlines the usefulness of our model in which we have fully characterized the renal clearance by measuring the urine piperacillin and tazobactam concentrations. The proposed dosing recommendations apply to critically ill patients with a creatinine clearance of 10–200 mL/min.

The pharmacokinetic parameters we identified for piperacillin confirm those described in previous papers in critically ill patients [13, 15, 16]. However, total clearance was lower in the current study (11.2 L/h, 95% confidence interval [CI]

Table 3 Probability of target attainment for MIC = 16 mg/L (ECOFF *Pseudomonas aeruginosa*), and probability of reaching the potential toxicity level of 157 mg/L for different doses of piperacillin and different classes of creatinine clearance

Creatinine clearance (mL/min)[a]	Dose piperacillin/ tazobactam (g)	100% $fT_{>1\times MIC}$	100% $fT_{>5\times MIC}$	Toxicity level > 157 mg/L
10–20	8/1	99.4	63.2	45.0
	12/1.5	99.8	80.2	67.2
	16/2	100	89.2	79.0
	20/2.5	100	93.0	86.2
30–40	8/1	98.6	47.4	22.4
	12/1.5	99.8	73.6	54.4
	16/2	100	87.8	72.8
	20/2.5	100	92.6	84.0
50–60	8/1	99.4	29.8	8.0
	12/1.5	100	62.0	34.2
	16/2	100	83.6	59.4
	20/2.5	100	91.2	77.4
70–80	8/1	99.2	16.4	3.6
	12/1.5	99.6	51.0	21.2
	16/2	100	75.0	47.6
	20/2.5	100	87.2	67.6
90–100	8/1	98.2	7.6	1.0
	12/1.5	99.8	35.0	12.4
	16/2	100	62.6	32.6
	20/2.5	100	81.4	53.6
110–120	8/1	97.4	2.6	0.0
	12/1.5	100	22.6	4.2
	16/2	100	48.4	19.6
	20/2.5	100	70.0	37.6
130–140	8/1	96.6	1.0	0.2
	12/1.5	100	13.2	1.8
	16/2	100	39.4	11.4
	20/2.5	100	61.0	29.6
150–160	8/1	95.6	0.2	0.0
	12/1.5	99.6	6.6	0.6
	16/2	99.8	29.8	5.8
	20/2.5	100	52.0	19.0
170–180	8/1	94.8	0.0	0.0
	12/1.5	99.4	3.0	0.2
	16/2	100	19.2	2.0
	20/2.5	100	41.0	11.8
190–200	8/1	93.4	0.0	0.0
	12/1.5	99.6	2.8	0.0
	16/2	99.8	17.4	2.6
	20/2.5	100	37.2	10.8

MIC minimum inhibitory concentration

[a]Simulations were performed in 20 groups of creatinine clearance between 10 and 200 mL/min, with 10 mL/min increments. In this table, pairs of two groups have been combined

9.3–13.5 L/h) than previously reported (17.1 L/h, 95% CI 14.4–20.6 L/h) [16]. This may be explained by the exclusion of patients with plasma creatinine of < 120 µmol/L in the latter study. Considerably less is known about the pharmacokinetics of tazobactam in critically ill patients. The typical total clearance for tazobactam was estimated to be higher (10.3 L/h, 95% CI 9.1–11.7 L/h) than reported in a small study in critically ill patients (5.3 L/h, 95% CI 2.2–9.1 L/h), but similar to reported in patients undergoing colorectal surgery (11.3 L/h, 95% CI 5.1–17.4 L/h) [14, 28].

Piperacillin and tazobactam are predominantly eliminated renally, therefore GFR significantly affects the plasma concentrations. As correct estimation of renal function in critically ill patients is troublesome, we evaluated different equations for GFR to predict renal clearance and found that all tested algorithms for estimating GFR significantly explained the variability in clearance and are useful in predicting piperacillin and tazobactam exposure.

For adequate treatment, it is essential to attain the target for both piperacillin and tazobactam simultaneously. We found that the PTA for tazobactam in regular doses is high,

Table 4 Cumulative fraction of response

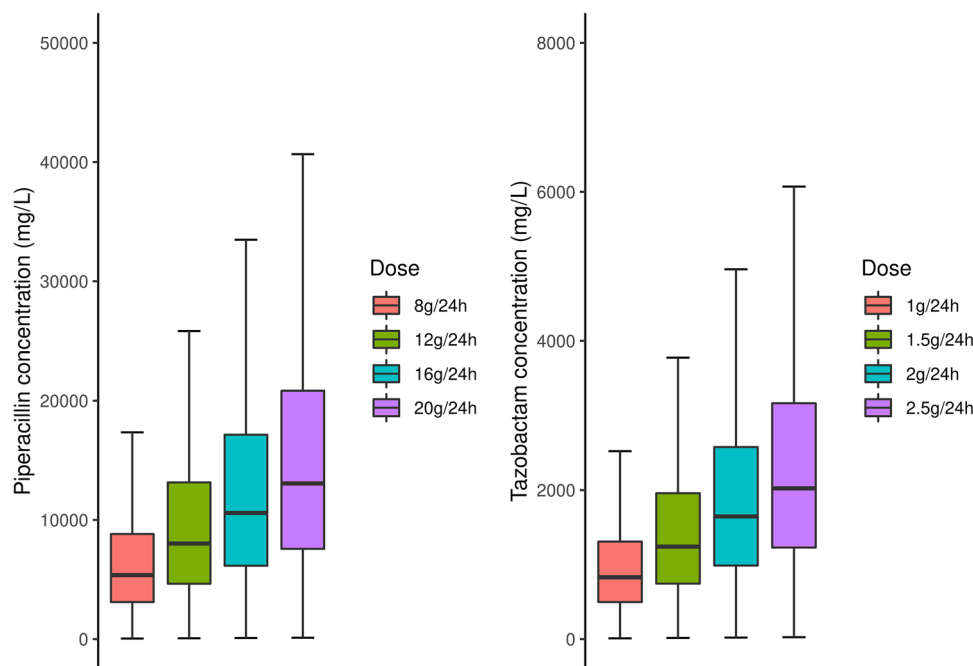| Creatinine clearance (mL/min)[a]	Dose piperacillin/tazobactam (g)	Escherichia coli		Klebsiella pneumoniae	
		100% $fT_{>1\times MIC}$	100% $fT_{>5\times MIC}$	100% $fT_{>1\times MIC}$	100% $fT_{>5\times MIC}$
10–20	8/1	100	99.4	100	96.8
	12/1.5	100	100	100	99.8
	16/2	100	100	100	99.8
	20/2.5	100	99.8	100	100
30–40	8/1	100	99.8	100	97.0
	12/1.5	100	99.4	100	99.0
	16/2	100	100	100	100
	20/2.5	100	100	100	99.6
50–60	8/1	100	99.6	100	98.2
	12/1.5	100	99.8	100	99.6
	16/2	100	100	100	99.8
	20/2.5	100	100	100	100
70–80	8/1	100	98.4	100	97.2
	12/1.5	100	99.8	100	99.0
	16/2	100	100	100	99.8
	20/2.5	100	99.8	100	99.6
90–100	8/1	100	99.6	100	93.6
	12/1.5	100	99.4	100	98.4
	16/2	100	99.6	100	99.7
	20/2.5	100	100	100	99.6
110–120	8/1	100	97.6	100	91.6
	12/1.5	100	98.8	100	98.0
	16/2	100	99.8	100	99.2
	20/2.5	100	100	100	99.4
130–140	8/1	100	97.6	100	**89.6**
	12/1.5	100	99.4	100	96.8
	16/2	100	99.6	100	99.2
	20/2.5	100	99.8	100	99.8
150–160	8/1	100	94.4	100	**90.0**
	12/1.5	100	98.8	100	97.2
	16/2	100	99.2	100	99.2
	20/2.5	100	99.8	100	99.8
170–180	8/1	100	94.2	100	**86.0**
	12/1.5	100	99.2	100	95.6
	16/2	100	99.4	100	98.2
	20/2.5	100	99.8	100	99.0
190–200	8/1	100	96.0	100	**87.4**
	12/1.5	100	98.2	100	94.6
	16/2	100	99.4	100	98.8
	20/2.5	100	100	100	99.2

MIC minimum inhibitory concentration

[a]Simulations were performed in 20 groups of creatinine clearance between 10 and 200 mL/min, with 10 mL/min increments. In this table, pairs of two groups have been combined

i.e. 100% with a dose of 2 g/24 h. Consequently, the efficacy of piperacillin–tazobactam mainly depends on the piperacillin concentration. Piperacillin administered at 12 g/24 h as a continuous infusion is sufficient to treat infections caused by *E. coli*, *K. pneumoniae,* and *P. aeruginosa* when aiming for a target of 100% $fT_{>1\times MIC}$ with creatinine clearances of up to 200 mL/min. The target of 100% $fT_{>1\times MIC}$ is recommended by a panel of experts in the field [4]. Often, higher targets of up to 100% $fT_{>5\times MIC}$ are used in the critically ill population, suggesting to not only maximize efficacy but also to minimize emergence of resistance [7]. In a worst-case scenario,

i.e. an infection caused by *P. aeruginosa* with an MIC of 16 mg/L, a dose of 20 g/24 h is necessary to reach a target of 100% $fT_{>5\times MIC}$ in patients with a creatinine clearance of 10–60 mL/min. Even higher doses are required for patients with a creatinine clearance > 60 mL/min.

However, when aiming for these higher targets, this is accompanied by an increased risk of reaching potential toxic concentrations. Almost half of the population reaches the upper limit of 157 mg/L with a dose of 20 g/24 h. Although β-lactam antibiotics are usually considered to have a wide therapeutic range, this could be argued when a total

Fig. 5 Piperacillin (left) and tazobactam (right) concentrations in urine

piperacillin concentration between 114 and 157 mg/L is aimed for. In patients with a creatinine clearance < 50 mL/min, dose reduction is preferred to prevent toxic concentrations, but this may compromise the effectiveness of antibiotic treatment. Dosing guided by therapeutic drug monitoring could enhance target attainment [29]. Further research on the relationship between piperacillin concentration and toxicity is desirable, since concentrations > 157 mg/L might be tolerated [27].

A relationship between tazobactam concentration and toxicity is not known. We found high tazobactam plasma concentrations. Our data suggest that reduced doses of tazobactam might be possible, while still achieving the unbound target of 2 mg/L.

We demonstrated high urinary concentrations of both piperacillin and tazobactam. These concentrations might be sufficient for the treatment of uncomplicated urinary tract infections caused by *Enterobacterales* with MICs that would conventionally classify them as being resistant to this drug combination. Normally, a clinical breakpoint of 8 mg/L is used for *Enterobacterales* [5], but highly resistant urinary organisms, including carbapenemase-producers, with MICs up to 4096 mg/L could be treated *in vitro* with piperacillin–tazobactam at approximately 50% fT$_{>1\times\text{MIC}}$ [30]. Our data show that these high concentrations are indeed reached in vivo. It should be noted that this applies only to urinary tract infections without microbial invasion in tissue. In case of a bloodstream infection with *E. coli* and *K. pneumoniae* resistant to ceftriaxone, piperacillin–tazobactam appeared inferior compared to meropenem [31].

Several limitations may apply to our study. First, only the total drug concentrations were measured, where it is the unbound concentration that is responsible for the effect. The unbound fraction of both piperacillin and tazobactam is about 30% [1], which is relatively low. Variation in protein binding is therefore of limited significance for interpretation of unbound pharmacokinetics compared to situations in highly protein bound drugs. Second, pharmacokinetic sampling on a second occasion was only performed in a small subset of nine patients. Still, this limited number of patients was sufficient to identify interoccasion variability on clearance. Finally, patients on renal replacement therapy were excluded in our study, thus limiting the extrapolation of our findings to this population. We argued that the role of renal replacement therapy in the pharmacokinetics of piperacillin–tazobactam has already been extensively evaluated [32–34].

There is conflicting evidence on whether or not piperacillin elimination is saturable at therapeutic plasma concentrations. Some previous pharmacokinetic studies found evidence for non-linear, saturable elimination of piperacillin [17, 35, 36], while other studies are in agreement with our findings of linear piperacillin clearance [16, 37]. Piperacillin is cleared through glomerular filtration and tubular secretion. Tubular secretion is a saturable, non-linear, process, while glomerular filtration is a linear process. The extent of saturation of nonrenal clearance was reported to be small [36]. In critically ill patients, the large increases in glomerular filtration and volume of distribution might outweigh the effect of saturable elimination. Also, in the current study all patients received piperacillin 12 g/day. Doses of 12 g/24 h or

lower are less likely to saturate the process of tubular secretion than higher doses. Finding a reliable marker for tubular secretion could be helpful in predicting renal clearance of antimicrobial drugs that are secreted by glomerular filtration and tubular secretion, such as piperacillin.

5 Conclusion

We showed that piperacillin–tazobactam in a dose of 12/1.5 g/24 h as continuous infusion is sufficient to reach a target of $100\% fT_{>1\times MIC.}$. Doses up to 20/2.5 g/24 h are still inadequate to reach the frequently used target of $100\% fT_{>5\times MIC}$ for infections caused by *P. aeruginosa* with an MIC of 16 mg/L. Yet, these high doses may on the other hand lead to toxicity. Since creatinine clearance explains 65% of the variability in piperacillin–tazobactam clearance, target attainment is strongly related to renal function. Thus, dosing should be based on renal function and might be guided by therapeutic drug monitoring. In addition, our data suggest that highly resistant urinary organisms could be treated with piperacillin–tazobactam, as very high urinary concentrations are found, independent of renal function.

Declarations

Transparency declarations None to declare.

Conflicts of interest All authors declared no competing interests related to this work.

Ethics approval This study was evaluated by the local Ethics Committee. The research was conducted in accordance with the Declaration of Helsinki, and national and institutional standards.

Consent to participate All patients or legal representatives were informed about the details of this study and could decline to participate (CMO identifier: 2018-4837). Subsequently, verbal consent was obtained and documented in the patient's medical record. The need for a written informed consent was waived by the local Ethics Committee due to the observational nature of the study.

Consent for publication Not applicable.

Availaility of data and materials Not applicable.

Code availability The NONMEM control stream is provided in the electronic supplementary files.

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