Impact of Piperacillin Unbound Fraction Variability on Dosing Recommendations in Critically Ill Patients

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Abstract

A common approach to assess the efficacy of piperacillin is to firstly measure the total concentration, and to afterwards apply a theoretical unbound fraction of 70% to obtain the unbound concentration. However, hypoalbuminemia is a common phenomenon in critically ill patients, resulting in variations in unbound fraction. Therefore, we aimed to simulate the impact of piperacillin unbound fraction fluctuations on the predictive performance of a population pharmacokinetic model and on dosing recommendations of piperacillin. Unbound factors of 70, 75, 80 and 85% were applied to total concentrations of piperacillin administered by continuous infusion from an external dataset. A validated model was used for assessment of predictive performance and to estimate patient clearance. Dosing simulations were performed to evaluate target attainment. Variation in unbound fraction caused minimal impact on piperacillin clearance and target attainment but revealed to influence model evaluation.

Introduction

Piperacillin is a moderately bound, broad-spectrum beta-lactam antibiotic commonly prescribed in intensive care units (ICU) to treat severe infections. The pharmacokinetic/pharmacodynamic (PK/PD) parameter linked to piperacillin antibacterial activity is defined by the time (T) during which the unbound drug concentration (f) remains above the minimum inhibitory concentration (MIC) of the pathogen of interest (f T $>$ MIC) [1]. As a result, piperacillin unbound concentration is required to assess target attainment. This value is obtained with two methods; by either directly measuring the unbound concentration of piperacillin with a validated bioanalytical method; or by firstly measuring the total concentration to afterwards apply a theoretical unbound fraction value to this concentration to obtain the unbound concentration. The latter is often performed with a value of 70%, the typically assumed unbound fraction in healthy subjects [2-8]. However, some studies have used other values to reflect current findings of piperacillin unbound fractions in ICU patients, as it may vary considerably within this population [7-9].

In our previous work, we noticed that the application of an unbound fraction could alter the predictive performance of a population pharmacokinetic (popPK) model evaluated with an independent dataset [10]. In summary, the independent dataset contained total piperacillin concentrations, whereas the model in question, developed by Klastrup et al., used unbound piperacillin concentrations during the development phase [11]. When calculating the predictive performance of the model with both total and unbound concentrations – retrieved by applying a factor of 70% - the latter concluded in favor of the validity of the model, whereas the model was considered unfit for the studied population when using total concentrations. This indicates that a model may perhaps be inappropriately suitable or unsuitable depending on the unbound fraction applied on a dataset in this type of evaluation. No study has clearly shown whether variations in unbound fraction

had an impact on dosing recommendations for piperacillin, nor how it impacted the validity of a popPK model. Additionally, Roberts et al. have stated that more modeling-based research is required to determine whether dosing adjustments would be warranted for drugs that are affected by altered protein binding [12]. The aim of this study was therefore to investigate these potential impacts through simulations by using a previously validated popPK model developed by Klastrup et al. [11].

Methods

With the previously validated model developed by Klastrup et al., two different methodological approaches were used to evaluate the impact of piperacillin unbound fraction variations. In the first approach, we evaluated the predictive performance of this model in multiple simulated scenarios of unbound concentrations within a dataset from a previous study [10]. This dataset contained total concentration values of piperacillin. In the second approach, subjects were selected from the dataset based on certain criteria to assess the impact of unbound fraction variations on target attainment of piperacillin.

Impact of unbound fraction variations on model evaluation

To reflect what has been reported in the literature for piperacillin unbound fraction levels among critically ill patients, total concentrations obtained were applied an unbound fraction ranging from 50 to 100%, by increments of 5% [3, 13, 14]. Afterwards, piperacillin predicted concentrations were obtained by using a previously validated population PK (popPK) model and by using mean population estimates reported by the authors [15]. Prediction error (PE, equation 1) was calculated to assess the predictive performance of the model by comparing predicted concentrations with observed concentrations after application of an unbound fraction [16]. Model bias was determined with median prediction error (MDPE, equation 2) and model imprecision was determined with the median absolute prediction error (MDAPE, equation 3) [17]. The predictive performance of the model was acceptable if MDPE was between ± 20% and if MDAPE [?] 30%. Predicted concentrations were obtained using NONMEM version 7.5 (ICON Development Solutions, Ellicott City, MD, USA), and calculations were performed on R version 4.1.2 using RStudio interface version 1.4.1717.

Bias

$$\text{PE } (\%) = \frac{C_{\text{pred}\,i} - C_{\text{obs}\,i}}{C_{\text{obs}\,i}} \times 100\% \quad (1)$$

$$\text{MDPE } (\%) = \text{median } (\text{PE}_{\text{ij}}, j = 1, N_i) \quad (2)$$

Imprecision

$$\text{MDAPE } (\%) = \textit{median } |\text{PE}_{\text{ij}}, j = 1, N_i| \quad (3)$$

Impact of unbound fraction variations on piperacillin clearance and dosing recommendations

Within the dataset, patients were separated into four renal function categories based on their creatinine clearance (CL): (1) below 30 mL/min, (2) between 30 and 80 mL/min, (3) between 80 and 130 mL/min, and (4) above 130 mL/min. Afterwards, for each category, one patient with median renal function was selected for this evaluation. Thus, four patients with different profiles were retained. To simulate the effect of various unbound fractions of piperacillin in cases of hypoalbuminemia, we applied various factors to the total concentrations of piperacillin for all four subjects. As piperacillin's unbound fraction is estimated at 70%, we started our evaluation with this value. A similar evaluation was performed for unbound fractions of 75, 80 and 85%. This resulted in four different unbound fraction scenarios, each containing four subjects for the assessment of target attainment.

A previously externally validated model was used to estimate piperacillin total CL for each patient within each data set through Bayesian estimation [15]. Individual CL estimation was realized by omitting the estimation step (MAXEVAL =0) and by fixing model parameters to the mean population estimates reported by the authors.

Once individual CL was obtained, dosing simulations were performed to determine whether unbound fraction variations influenced target attainment of piperacillin. Patient PK parameters were inputted on NONMEM, and the simulated piperacillin dose was based on the patient's renal function; i.e., a loading dose of 4 g followed by a maintenance dose of 8, 12 or 16 g if CLCr was below 30, between 30 and 80, or above 80 mL/min, respectively, to reflect the practices reported by Klastrup et al. [11]. Simulations were repeated for the same subject with unbound fractions ranging from 70 to 85%. Target attainment was defined as 100% f T > MIC, for a MIC value of 16 mg/L, corresponding to the EUCAST clinical breakpoint of *Pseudomonas aeruginosa* . Concentration-time plots were generated to compare the various profiles for each subject.

Results

Impact of unbound fraction variations on model evaluation

Results for the variation of the unbound fraction are illustrated in Figure 1. Bias and imprecision values were best with an unbound fraction of 70% but remained acceptable within the range of 65% and 85%. Bias decreased in value as unbound fraction increased.

Impact of unbound fraction variations on piperacillin clearance and dosing recommendations

Individual CL estimates are summarized in Table 1. For example, for the first renal function category, a patient with a CLCr of 24.7 mL/min was selected for this evaluation. The estimated piperacillin CL for this subject decreased as unbound fraction increased, ranging from 5.1 L/h for an unbound fraction of 70% to 4.0 L/h for an unbound fraction of 85%. After simulating a loading dose of 4 g accompanied by a maintenance dose of 8 g, PK/PD target attainment was reached successfully, as illustrated in Figure 2. Similar results were obtained for the other three categories of patients and are available in Table 1 and Figure 2.

Discussion

Variation in protein binding of antimicrobials, including piperacillin, is well documented [18]. Despite being a moderately-bound drug, as a beta-lactam, piperacillin unbound concentration can fluctuate in cases of hypoalbuminemia, therefore affecting the distribution and the excretion of renally eliminated drugs [4, 18]. This is turn may affect the probability of target attainment in critically ill patients.

The present analysis revealed that unbound fraction variations did not significantly affect piperacillin total CL, and simulated concentration-time profiles showed no impact on target attainment, as all concentrations after 24 h (C_{24h}) were above the PK/PD target of 1xMIC of 16 mg/L. However, the profile of the subject with augmented renal clearance (ARC) (subject 4) had a rather low C_{24h}. ARC is becoming more prevalent in ICU and is known to cause lower serum concentrations of drugs that are primarily eliminated by the kidneys, such as piperacillin [9, 19, 20]. Despite successfully achieving a target of 1xMIC, our simulations indicate that patients with ARC may not be able to reliably reach targets of 4xMIC in cases of empirical treatment, which is often the case for piperacillin. This target is commonly used in ICU patients in order to prevent the growth of resistant pathogens [21, 22]. Therefore, while no dosing adjustments seemed necessary in our analysis, it may be in cases where clinicians require the achievement of a more aggressive target of 4xMIC.

While we investigated the impact of unbound fraction fluctuations on a clinical level, we also evaluated the repercussions it could have on the validity of a popPK model. Indeed, after applying various unbound fractions, the model remained valid for values ranging from 65% to 85%. These values are what are mainly reported in studies that determined the unbound fraction of piperacillin in critically ill patients [3, 4, 23]. However, these same studies have also reported values going as high as 95%. Had we used a value of 95% for example, this model would not have been suitable for the external dataset. This indicates that it is important to know the unbound fraction of the population before using a popPK model developed from unbound concentrations of piperacillin. In our case, it is possible that the external dataset had a higher unbound fraction than the value of 70%, indicating that the model may not be suitable at all for this population. This shows the precautions we must take in using theoretical factors in every analysis we perform. Nonetheless, this value offered the best combination in terms of bias and imprecision.

This study has some limitations. Firstly, this study is limited with simulated concentrations. Indeed, only total concentrations were obtained from the external validation dataset, with no knowledge of the real unbound fraction for each subject. Additionally, simulations were performed using a popPK model that only included CLCr as a covariate on CL, not unbound fraction, and CLCr may not fully portray piperacillin's total renal CL, as piperacillin is also eliminated by tubular secretion. To the best of our knowledge, no model currently available in the literature integrated unbound fraction, albumin levels or markers of tubular secretion as covariates on piperacillin CL, making it difficult to adequately evaluate their impact., possibly due to the rarity of such information for clinicians, especially for markers of tubular secretion, as they may not be routinely available in ICU wards.

The present study has shown through simulations that adjustments to piperacillin dosing regimens may not be required in cases of hypoalbuminemia. As a moderately-bound molecule, altered binding may have little impact on piperacillin's PK profile. Thus, despite unbound concentration being the main parameter for target attainment, working with total concentration may suffice for therapeutic drug monitoring of piperacillin. However, considering the real unbound fraction of the dataset is necessary in the case of model evaluation, as the evaluation may be skewed if binding levels were to be assumed in the population. Indeed, it seems it would be best to only evaluate models that used unbound concentrations with external datasets that have real unbound concentrations data available. A clear answer is, however, difficult to give in the case of a molecule such as piperacillin, as opposed to highly bound molecules in the likes of ceftriaxone or ertapenem. Nonetheless, our simulated scenarios offer some insight regarding the possible impact of unbound fraction variability in critically ill patients in hopes of further evaluating this with real clinical studies. Studies with real unbound piperacillin concentrations and unbound fraction values would be warranted before reaching a conclusion.

Conflict of interest statement

The authors have no conflicts of interest that are directly relevant to the content of this article.

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Data availability statement

Patient data obtained are not publicly available. Data related to the model are available in the literature.

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Table 1. Predicted piperacillin total clearance per individual for each unbound fraction scenario.

Subject	**Subject 1**	**Subject 2**	**Subject 3**	**Subject 4**
Creatinine clearance (mL/min)	**24.7**	**63.9**	**104.8**	**183.2**
Administered daily dose (g)	**8**	**12**	**16**	**16**
Measured total concentration (mg/L)	**125.2**	**73.8**	**127.4**	**38.6**
Simulated daily dose (g)	**8**	**12**	**16**	**16**
Unbound fraction (%)	**Predicted individual clearance (L/h)**			
70	5.1	11.9	12.7	25.0
75	4.7	11.2	11.6	23.5
80	4.4	10.6	10.6	22.2
85	4.0	10.0	9.9	21.0

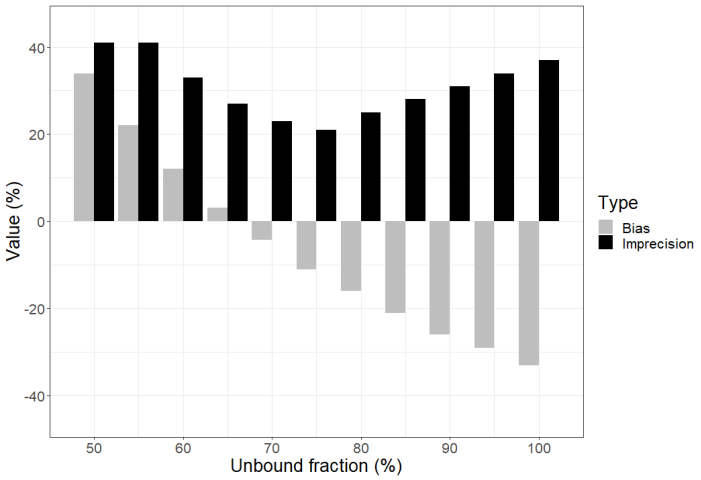

Figure 1. Bias and imprecision per unbound fraction values.

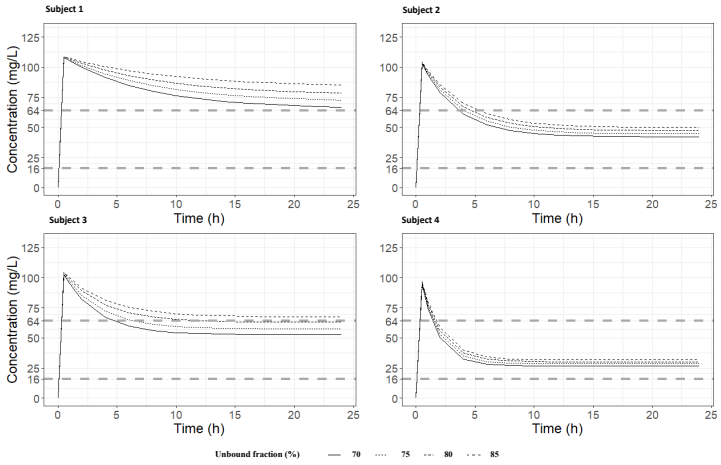

Figure 2. Concentration-time profiles of piperacillin per unbound fraction value for subject 1 (maintenance dose of 8 g), subject 2 (maintenance dose of 12 g), subject 3 (maintenance dose of 16 g) and subject 4 (maintenance dose of 16 g). *Dotted lines correspond to targets of 1xMIC (16 mg/L) and 4xMIC (64 mg/L).*