Dose optimization of piperacillin/tazobactam in patients with renal dysfunction based on population pharmacokinetic and pharmacodynamic simulations

Chao Zhang1*, Ruohan Xie1, Chuhui Wang1, Chenchen Xi2, Mengjia Ge1

1. Department of pharmacy, Peking University Third Hospital, Beijing 100191, China
2. Center for drug evaluation, China Food and Drug Administration, Beijing 100053, China

Abstract: In the present study, we aimed to investigate the optimal dosage regimens of piperacillin/tazobactam in patients with chronic kidney disease according to their different classes of renal function based on bacterial resistance. A total of 2700 simulations were applied based on a published population pharmacokinetic and pharmacodynamic model using nonlinear mixed effects modeling (NONMEM) software. Permissible optimal dosage regimens were defined as those associated with a less than 10% of patients whose probabilities of target attainment (PTA) were not attain target. For patients with mild to moderate renal injury, 4/0.5 g of piperacillin/tazobactam every 12 h in 30 min intermittent infusion could attain the target. If the MIC (minimum inhibitory concentration) for the pathogen was 8 mg/L or 16 mg/L, either an 8-h or 6-h dosing interval or extended 2–6 h infusion regimen had to be used to achieve the outcome of the therapy. Regarding MIC was up to above 32 mg/L, a high dose of piperacillin (12–24 g/d) in continuous infusion was the only approach that could achieve the effective target in patients with renal dysfunction. A low dose with extended 4–6 h infusion regimen was recommended for patients with severe renal injury. Our study identified permissible optimal piperacillin/tazobactam dosage regimens for patients with renal dysfunction with an MIC up to 64 mg/L. The findings of this study would be helpful for precise administration of piperacillin/tazobactam in clinical practice.

Keywords: Piperacillin/tazobactam; Renal dysfunction; Dose optimization


1. Introduction

Piperacillin/tazobactam is an extended-spectrum β-lactamase inhibitor combination antibiotic. Because of its broad coverage, piperacillin/tazobactam is commonly recommended as a first-line therapy for severe bacterial infections, including intra-abdominal infection, hospital-acquired pneumonia, febrile neutropenia, and skin or soft-tissue infection[1]. As a time-dependent antibiotic, the bactericidal activity of piperacillin/tazobactam is associated with the drug concentrations above the minimum inhibitory concentration (fT>MIC), of which at least 30% to 50% is needed[2-4]. It is evidenced that proper use of antimicrobials can improve clinical outcomes and reduce resistance, maintaining antimicrobial sensitivity in general population[5-8].

Chronic kidney disease (CKD) is a common, progressive illness that has become a global public health problem. About 70% of piperacillin/tazobactam is excreted by the kidney, accordingly leading to excessive accumulation in patients with kidney dysfunction due to impaired renal excretion. In addition, the plasma protein binding of drugs may be significantly reduced, which in turn may influence the pharmacokinetic processes of distribution and elimination to some extent[9]. The activity of several drug-metabolizing enzymes and drug transporters has been shown to be impaired in chronic renal failure. All of above-mentioned facts make dosage adjustment
extremely complex and necessary when piperacillin/tazobactam is administered to patients with renal dysfunction. However, in clinical practice, there is no therapeutic drug monitoring for piperacillin/tazobactam in these patients, and therefore its dosage regimens are too difficult to be optimized. Population pharmacokinetic and pharmacodynamic model in combination with patient covariates can predict antimicrobial efficacy and is used to set targets for regimens and optimization\textsuperscript{[10,11]}. In the present study, we aimed to investigate the optimal dosage regimens of piperacillin/tazobactam in patients with renal dysfunction based on population pharmacokinetic and pharmacodynamic simulations.

2. Materials and methods

2.1. Population pharmacokinetic and pharmacodynamic model

This work was performed using the nonlinear mixed effects modeling software, NONMEM (Version VII), based on previously published models. Available sparse data from 10 patients with renal dysfunction at Peking University Third Hospital were used to fit previously published population pharmacokinetic models and to identify the appropriate model in this study. The final model was qualified with a one-compartment with first-order elimination model. Interindividual variability (IIV) was supported in clearance and volume of distribution, and a combined proportional and additive structure was appropriate for the residual errors\textsuperscript{[12]}. Creatinine clearance and body weight were found as significant predictors of clearance and volume of distribution, respectively\textsuperscript{[12]}. The equations were as follows:

\[ \text{CL} = 5.05 + 9.6 \times \frac{\text{CL}_{\text{CR}}}{89} \]
\[ V = 22.3 \times \frac{\text{WT}}{81.8} \]

Where CL, V, CL\textsubscript{CR} and WT represent the clearance, volume of distribution, creatinine clearance calculated by Cockcroft-Gault formula and body weight, respectively. \( f_{T>MIC} \) has been proven to best predict the clinical outcome of piperacillin/tazobactam and involved in pharmacodynamic model. This study was approved by Institute Ethical Review Board of Peking University Third Hospital.

2.2. Dosage regimen optimization

The plasma concentration-time profiles of 2700 subjects were simulated at steady-state for each dosage regimen based on the defined published population pharmacokinetic model. Probabilities of target attainment (PTA) of patients with different degrees of renal dysfunction were estimated from frequency of achieving the target for each scenario. Optimal regimens for patients with different stages of renal disease were recommended when at least 90% of patients could attain target according to MIC levels. The target breakpoint was defined as the PTA was above 70%.

3. Results

Different piperacillin/tazobactam dosage regimens were evaluated, including intermittent and prolonged or continuous infusion dosing strategies with different dose intervals. In regard to the effective target, the permissible piperacillin/tazobactam regimens predicted acceptable (>70%) PTAs against an MIC of up to 64 mg/L in different degrees of renal function (Table 1). Figure 1 shows the assessments of PTA by MIC for various dosing regimens in 90% percentile of patients with CL\textsubscript{CR} of 15–30 mL/min, 31–60 mL/min, and 61–90 mL/min.
Figure 2 depicts a dosing algorithm for choosing the most advisable piperacillin/tazobactam regimen in relation to different classes of renal function, which may be considered for the empirical treatment of suspected infections. The approach is feasible in clinical settings with predominantly MIC ≤ 4 mg/mL and resistance occurring of MIC ≤ 8 mg/mL to make sure 90% percentile of patients may achieve desirable antimicrobial outcomes. Figure 3 shows the predicted concentrations versus time when the recommended regimens were administered according to different degrees of renal function.
4. Discussion

A proper dose of the right antibiotic therapy is the cornerstone to maximize the successful outcome of treatment. In patients with renal dysfunction, a standard dosage regimen of piperacillin/tazobactam is not suitable due to impaired drug elimination as well as high pharmacokinetic variability, leading to toxicity or therapeutic failure. Piperacillin/tazobactam-induced neurotoxicity has been reported in CKD patients, especially for the patients with renal failure[13]. Dosing errors in CKD patients have also been reported[14]. Dosage adjustments are crucial and necessary in this special population in order to improve efficacy and reduce toxicity.

In this study, we aimed to identify permissible piperacillin/tazobactam regimens for optimal treatment in patients with different degrees of renal function. The resistant strains may occur in clinics, which were considered to further adjust dosage regimens in order to overcome the inadequate efficacy under such circumstance. Our findings showed that if MIC was less than 4 mg/L, for patients with mild to moderate renal injury (CL\textsubscript{CR} was above 31 mL/min), 4/0.5 g of piperacillin/tazobactam every 12 h in 30 min intermittent infusion could attain the target. If the MIC for the pathogen was 8 mg/L or 16 mg/L, either an 8-h or 6-h dosing interval or extended 2–6 h infusion regimen could be used to guarantee the outcome of the therapy. Regarding MIC was up to above 32 mg/L, a high dose of piperacillin (12–24 g/day) in continuous infusion was the only approach, which could possibly achieve the effective target in patients with renal dysfunction. For patients with severe renal injury (CL\textsubscript{CR} was within the range of 15–30 mL/min), reduced piperacillin dosage regimens to 2 g every 8 h and 2 g every 6 h in 30 min infusion were recommended when MIC was 4 and 8 mg/L, respectively. The optional dosage

Figure 3. The simulated concentrations versus time profiles of recommended dosage regimens in relation to different classes of renal function. (A) CL\textsubscript{CR} 61–90 mL/min, (B) CL\textsubscript{CR} 31–60 mL/min, (C) CL\textsubscript{CR} 15–30 mL/min.
regimen of 2 g every 12 h in a 4-h or 6-h infusion could also be used if extended infusion approach was preferred.

Asín-Prieto et al. have built a population pharmacokinetic model of piperacillin/tazobactam in critically ill patients undergoing continuous renal replacement therapy and reported noticeable differences in the PTA among the dosing intervals depending on the MIC, which is similar to our findings. Extended or continuous infusion approach was found to increase the rate of reaching target in our study, which has been proved by many studies. A meta-analysis we did previously, including 14 studies (two prospective studies, seven retrospective studies, and five randomized controlled trials), have demonstrated that the extended or continuous infusion of piperacillin/tazobactam leads to a higher clinical cure rate and a lower mortality rate than the conventional intermittent strategy. If infusion pumps were not fully equipped, which may frequently occur, optional dosing regimens using short infusion were raised in our study based on MIC values according to different classes of renal function. Accordingly, pathogens for which MICs were high could be treated with a short infusion of piperacillin/tazobactam in a large dose. From Table 1, it was found that administration of 2 g/d piperacillin in an extended 12-h infusion in patients exhibiting a CLCR of 15–30 mL/min provided a high probability of success against bacteria for which the MIC values were 2 mg/L, whereas double dose was needed if piperacillin was administered as a short infusion to achieve the similar target. Therefore, when MIC was extremely high or the patients had a high rate of renal excretion, extended or continuous infusion approach would be a better option due to its low dose, conferring safer therapy outcome. Dhaese et al. have recently found that in critically ill patients with a renal clearance higher than 90 mL/min, a high-dose continuous infusion of 24 g/24 h is insufficient to achieve adequate exposure against bacteria (MIC≤16 mg/L). However, our study population was the patients with renal dysfunction, and 24 g/24 h dose of piperacillin was demonstrated to be adequate.

Gilbert et al. have reported high PTAs up to an MIC of 16 mg/L with 4 g of piperacillin every 8 h, which is not same as our results. The same dose was recommended for patients with mild renal dysfunction, but at least an additional 3-h infusion was necessary. In contrast, if traditional 30-min infusion approach was used, 4 g of piperacillin should be given every 6 h. Figure 3 shows the profiles of concentrations were changed with time at recommended dosing regimens (Fig. 2), from which decreased peak concentrations were caused by lower dose or lasting high excretion concentrations were presented when applied extended infusion regimens. Therefore, for patients with severe renal dysfunction, the low dose with extended infusion regimens would be highly recommended considering high sensitivity of adverse drug event for CKD patients.

The population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam have been investigated by several studies. The percentage of the dosing interval that the drug concentration remains above the MIC of the infecting organism is thought to be closely related to antimicrobial outcome. Although the drug concentrations in infected tissue would be the most relevant target, the blood concentrations are usually identified as a substitution since these data are not available in clinical practice. In this study, PTAs were calculated based on population pharmacokinetic and pharmacodynamic simulations. Different dosage regimens were compared according to bacterial MICs and patients’ renal functions (Fig. 1).
Although optimal dosing regimens of piperacillin/tazobactam were investigated in various patient populations, most of the focus is on intensive care patients or critically ill patients[10,15,19,22]. Asín-Prieto et al. have developed the dosing recommendations for critically ill patients undergoing continuous renal replacement therapy[10]. The drug clearance was considered as a non-renal component, a renal component conditioned by the CL\textsubscript{CR} and extracorporeal clearance, which was related to ultrafiltrate flow and unbound fraction. Few studies have assessed the optimal dosing regimens in CKD patients. It has been reported that the pharmacokinetics are likely to be significantly altered in patients with renal dysfunction. The findings of this study could provide a guide when piperacillin/tazobactam was given for CKD patients in clinical practice.

We are aware of potential limits of this study. No clinical application was tested and therefore no clinical effective outcome could be combined to further adjust our recommended dosing regimens. Additionally, we used the published population model without describing much of our observed data, and therefore it was possible to induce biases due to different disease statuses or populations.

In conclusion, our study identified permissible optimal piperacillin/tazobactam dosage regimens for patients with renal dysfunction with an MIC up to 64 mg/L. The findings of this study would be helpful for precise administration of piperacillin/tazobactam in clinical practice.

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Reference


**基于群体药动学和药效学的仿真**

**对肾功能不全病人使用哌拉西林/他唑巴坦进行剂量优化**

张弨¹*, 谢若函¹, 王楚慧¹, 袭辰辰², 戈梦佳¹

1. 北京大学第三医院 药剂科, 北京 100191
2. 国家食品药品监督管理总局 药品审评中心, 北京 100022

**摘要:** 本研究的目的是根据患者不同程度的肾功能损伤和细菌耐药情况，探索哌拉西林/他唑巴坦在肾功能不全患者中的给药方案。本研究基于发表的群体药动学模型，使用非线性混合效应模型(NONMEM)法进行2700次的仿真，最佳的给药方案定义为不达标的患者的概率低于10%。研究发现对于肾功能轻度至中度损害的患者，常规4/0.5 g哌拉西林/他唑巴坦，q12h，30 min给药方案是合适的。但当MIC为8 mg/L或16 mg/L时，需要调整给药方案为q8h或q6h或者延长输注时间为2–6 h。当MIC大于32 mg/L时，12–24 g/天的高剂量哌拉西林持续输注是唯一可以达到目标值的给药方案。对于严重肾损伤的病人，推荐采用低剂量并延长输注4–6 h。本研究中给出不同MIC(直到64 mg/L)下，肾功能不全患者给予哌拉西林/他唑巴坦的具体推荐给药方案，研究结果将会为哌拉西林/他唑巴坦在临床上的精准给药提供帮助。

**关键词:** 哌拉西林/他唑巴坦; 肾功能不全; 剂量优化