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Analysis of the Achievement of Target Plasma Concentrations and Its Influencing Factors during Piperacillin-Tazobactam Treatment in Elderly Patients with Severe Pneumonia

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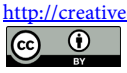

Abstract

Objective: To investigate the achievement of target plasma concentrations and related influencing factors in elderly patients with Severe Pneumonia (SP) during piperacillin-tazobactam treatment. Methods: A retrospective analysis was conducted on the medical records of 82 elderly patients with severe pneumonia admitted to our hospital from August 2023 to August 2025. All enrolled patients received intravenous piperacillin-tazobactam. Piperacillin plasma concentrations were monitored, and multivariate logistic regression was used to analyze factors influencing the achievement of target plasma concentrations for piperacillin-tazobactam. Results: Among the 82 SP patients treated with piperacillin-tazobactam, target plasma concentrations were achieved in 39 cases (47.56%) and not achieved in 43 cases (52.44%). The target achievement group had a higher proportion of q6h dosing frequency, longer infusion time, and higher Albumin (Alb) levels, while C-Reactive Protein (CRP), Serum creatinine (Scr), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total Bilirubin (TBIL), APACHE II score, and SOFA score were lower compared to the control group ($P < 0.05$). Multivariate logistic regression analysis showed that dosing frequency, infusion time, Alb, Scr, APACHE II score, and SOFA score were independent influencing factors for not achieving target plasma concentrations ($P < 0.05$). Conclusion: The achievement rate of target plasma concentrations for piperacillin-tazobactam in SP patients is low. Dosing frequency, infusion time, Alb, Scr, APACHE II score, and SOFA score are independent influencing factors for the achievement of piperacillin plasma concentrations.

Keywords

Severe Pneumonia, Piperacillin-Tazobactam, Achievement of Target Plasma Concentration, Influencing Factors

1. Introduction

Severe Pneumonia (SP) is a common critical illness in clinical practice, and its treatment success is closely related to the rational use of antibacterial drugs [1]. Piperacillin-tazobactam, as a commonly used anti-infective agent, has its efficacy closely associated with whether the plasma concentration achieves effective Pharmacokinetic/Pharmacodynamic (PK/PD) targets [2]. In critically ill patients, complex pathophysiological changes lead to high heterogeneity in drug disposition, often making it difficult to achieve ideal therapeutic plasma concentrations, which may subsequently affect clinical outcomes [3]. Therefore, in-depth exploration of factors influencing the achievement of target plasma concentrations for this drug is of significant clinical importance. Current research suggests that various factors, including the patient's physiological and pathological status, specific dosing regimens, and pathogen characteristics, may significantly impact plasma concentrations [4]. Thus, this study aims to collect clinical data from SP patients, systematically analyze the achievement of target plasma concentrations, and further explore various influencing factors, in order to provide a reference for the development of individualized dosing regimens and optimize treatment efficacy.

2. Materials and Methods

2.1. General Information

A retrospective analysis was performed on the medical records of 82 SP patients admitted to our hospital from August 2023 to August 2025. Inclusion criteria: 1) meeting the diagnostic criteria for SP [5]; 2) steady-state trough concentration of piperacillin-tazobactam achieved; 3) age ≥ 60 years; 4) complete clinical data. Exclusion criteria: 1) undergoing blood purification therapy; 2) combined with malignant tumors; 3) allergic to the treatment drugs; 4) presence of other drugs in the blood that interfere with plasma drug concentration. The 82 patients were aged 60 - 85 years (mean 63.88 ± 7.94), with 50 males and 32 females. This study complied with the requirements of the Declaration of Helsinki.

2.2. Methods

Patients received piperacillin/tazobactam (National Medicine Permit Number H20213899; Suzhou Erye Pharmaceutical Co., Ltd.; specification: 4.5 g). After 3 doses, blood samples were collected within 30 minutes before the administration of the next dose. Two milliliters of elbow venous blood were collected 4 hours post-dose, and piperacillin Cmin (trough concentration) was measured using High-

Performance Liquid Chromatography (HPLC).

Piperacillin-tazobactam is a time-dependent antibacterial agent, and its efficacy primarily depends on the proportion of time that the free drug concentration remains above the Minimum Inhibitory Concentration (MIC) of the pathogen. For critically ill patients, current PK/PD theory emphasizes that β-lactam antibiotics should achieve 100% of the dosing interval with plasma concentrations above the MIC, and some studies suggest that achieving 100% time above 4 to 5 times the MIC may further enhance therapeutic efficacy. When setting the PK/PD target in this study, clinical feasibility and safety were comprehensively considered, and the range where the drug concentration exceeds the MIC but does not exceed 4 times the MIC was selected to optimize efficacy and reduce potential adverse reactions. According to the susceptibility breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI), the MIC for piperacillin-tazobactam is 16 $\mu g \cdot mL^{-1}$, thus the target plasma concentration range was set at 16 - 64 $\mu g \cdot mL^{-1}$ [6].

Data collection: General patient data (age, sex, body mass index) and medication details (dosing frequency, infusion time) were collected. Serum Creatinine (Scr), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total Bilirubin (TBIL), and Albumin (Alb) were measured using an automatic biochemical analyzer. White Blood Cell count (WBC), red blood cells, and Platelet count (PLT) were detected by flow cytometry. Procalcitonin (PCT) was measured by Enzyme-Linked Immunosorbent Assay (ELISA). C-Reactive Protein (CRP) was detected by immunoturbidimetry. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were evaluated.

2.3. Statistical Methods

Data analysis was performed using SPSS 28.0 software. Categorical variables such as gender, dosing frequency, and pathogen type are expressed as n (%), and the chi-square test was used. Continuous variables such as age, body mass index, infusion time, WBC, PCT, CRP, PLT, AST, ALT, TBIL, Scr, red blood cells, Alb, APACHE II score, and SOFA score are expressed as mean ± standard deviation, and the t-test was used. Logistic regression analysis was employed to analyze factors influencing the achievement of target plasma concentrations for piperacillin-tazobactam. The significance level was set at $\alpha = 0.05$.

3. Results

3.1. Achievement of Target Plasma Concentrations in SP Patients during Piperacillin-Tazobactam Treatment

Among the 82 SP patients treated with piperacillin-tazobactam, target plasma concentrations were achieved in 39 cases (47.56%), and not achieved in 43 cases (52.44%).

3.2. Univariate Analysis of Factors Influencing the Achievement of Target Plasma Concentrations in SP Patients during Piperacillin-Tazobactam Treatment

The target achievement group had a higher proportion of q6h dosing frequency, longer infusion time, and higher Alb levels, while CRP, Scr, ALT, AST, TBIL, APACHE II score, and SOFA score were lower compared to the control group ($P < 0.05$). See Table 1.

Table 1. A univariate analysis of factors affecting piperacillin-tazobactam target plasma concentration attainment in patients with severe pneumonia [n (%), $\bar{x} \pm s$].

Variable	Target Concentration Group (n = 39)	Non-Target Group (n = 43)	χ^2/t	P
Age (years)	64.52 ± 8.42	63.05 ± 7.28	0.662	0.511
Gender			0.002	0.963
Male	23 (58.97)	27 (62.79)		
Female	16 (41.02)	16 (37.21)		
BMI (kg/m^2)	23.85 ± 3.15	25.05 ± 3.85	1.200	0.236
Frequency (time/daily)			6.762	0.009
Q6h	29 (74.36)	16 (37.21)		
Q8h	10 (25.64)	27 (62.79)		
Infusion Time (min)	44.65 ± 10.12	30.87 ± 5.68	5.998	<0.001
WBC (×10^9/L)	12.45 ± 3.26	13.75 ± 4.10	1.234	0.223
PCT (ng/mL)	1.85 ± 0.26	2.04 ± 0.64	1.354	0.182
CRP (mg/L)	85.76 ± 12.65	108.76 ± 15.81	5.649	<0.001
Scr (μmol/L)	81.42 ± 14.56	118.79 ± 20.05	7.486	<0.001
Alb (g/L)	32.46 ± 5.24	28.94 ± 4.28	2.610	0.012
ALT (U/L)	35.24 ± 4.26	40.85 ± 5.64	3.943	<0.001
AST (U/L)	40.36 ± 7.25	45.87 ± 8.44	2.465	0.017
TBIL (μmol/L)	15.14 ± 2.03	18.42 ± 1.86	5.963	<0.001
Pathogen			0.015	0.902
Gram-negative bacteria	32 (82.05)	36 (83.72)		
Gram-positive bacteria	7 (17.95)	7 (16.28)		
APACHE II Score (points)	18.46 ± 3.26	22.41 ± 4.05	3.773	<0.001
SOFA Score (points)	6.45 ± 2.12	12.87 ± 2.46	3.712	<0.001

3.3. Multivariate Analysis of Factors Influencing the Achievement of Target Plasma Concentrations in SP Patients during Piperacillin-Tazobactam Treatment

Multivariate logistic regression analysis was performed with dosing frequency

(q8h = 1, q6h = 0), infusion time, Alb, CRP, Scr, ALT, AST, TBIL, APACHE II score, and SOFA score as independent variables, and the achievement of target plasma concentration (not achieved = 1, achieved = 0) as the dependent variable. The results showed that dosing frequency (OR = 0.699), infusion time (OR = 0.694), Alb (OR = 1.525), Scr (OR = 1.631), APACHE II score (OR = 1.477), and SOFA score (OR = 1.499) were independent influencing factors for not achieving the target plasma concentration ($P < 0.05$). Dosing frequency and infusion time (OR < 1) were identified as protective factors against non-achievement of the therapeutic target, whereas Alb, Scr, APACHE II, and SOFA scores (OR > 1) were risk factors.

See Table 2.

Table 2. Multivariate analysis of factors influencing the achievement of target plasma concentrations in SP patients during piperacillin-tazobactam treatment.

Variable	β	SE	Wald	P	OR	95% CI
Frequency	−0.358	0.145	6.096	0.014	0.699	0.526 - 0.929
Infusion Time	−0.365	0.150	5.921	0.015	0.694	0.517 - 0.931
Alb	0.422	0.136	9.628	0.002	1.525	1.168 - 1.991
CRP	0.236	0.198	1.421	0.233	1.266	0.859 - 1.867
Scr	0.489	0.216	5.125	0.024	1.631	1.068 - 2.490
ALT	0.244	0.146	2.793	0.095	1.276	0.959 - 1.699
AST	0.279	0.166	2.825	0.093	1.322	0.955 - 1.830
TBIL	0.345	0.199	3.006	0.083	1.412	0.956 - 2.086
APACHE II Score	0.390	0.186	4.396	0.036	1.477	1.026 - 2.127
SOFA Score	0.405	0.196	4.270	0.039	1.499	1.021 - 2.202

4. Discussion

As a time-dependent antibacterial agent, the core efficacy of piperacillin-tazobactam depends on the percentage of time that the free drug concentration remains above the Minimum Inhibitory Concentration (MIC) of the pathogen, a key PK/PD index referred to as %f T > MIC [7]. In patients with severe infections, to ensure clinical efficacy, piperacillin is typically required to achieve 100% fT > MIC, meaning the trough plasma concentration must consistently exceed the MIC value [8]. However, numerous domestic and international studies have revealed that when Cmin ≥ 16 μg·mL^{-1} is set as the target, the rate of achieving target plasma concentrations in critically ill patients is generally low, at only about 40%, reflecting that current dosing regimens may inadequately cover pharmacokinetic variability under complex pathophysiological conditions [9]. In this study, the observed rate of achieving target piperacillin Cmin in SP patients was 47.56%, consistent with previous research data [10], further highlighting the challenges of unpredictable pharmacokinetic parameters in SP patients, particularly in the ICU population,

potentially affecting the efficacy of anti-infective therapy and increasing the risk of treatment failure. Given this situation, strengthening the implementation of Therapeutic Drug Monitoring (TDM) in clinical practice is particularly urgent. The 2020 expert consensus on antimicrobial concentration monitoring in critically ill patients explicitly recommends routine TDM for β-lactam antibiotics, dynamically adjusting dosage and intervals based on real-time plasma concentration monitoring combined with individual patient characteristics, such as body weight, renal function, and infection site, to optimize the achievement rate of PK/PD targets [11]. This individualized strategy not only helps improve efficacy and reduce the emergence of resistant bacteria but also minimizes drug-related adverse events, ultimately promoting the precision and standardization of severe infection management.

The pathophysiological status of SP patients is complex, and multiple factors can influence the plasma concentration of piperacillin. Analysis of patient general data, medication details, and biochemical indicators in this study revealed that dosing frequency, infusion time, Alb, Scr, APACHE II score, and SOFA score were independent factors affecting piperacillin plasma concentrations. The multivariate analysis results of this study showed that both increased dosing frequency and prolonged infusion time were independent protective factors for achieving target plasma concentrations of piperacillin-tazobactam. This finding is highly consistent with the time-dependent bactericidal characteristics of the drug. The core antibacterial efficacy of piperacillin-tazobactam lies in the percentage of time its free plasma concentration remains above the pathogen's MIC during the dosing interval. Shorter infusion times lead to a rapid peak and subsequent decline in drug concentration, resulting in insufficient duration of effective concentration, whereas lower dosing frequency directly extends the dosing interval, making it easier for the trough concentration to fall below the effective therapeutic level as the drug is continuously cleared from the body. Therefore, increasing the daily dosing frequency replenishes the cleared drug more often, maintaining the plasma concentration within the therapeutic window, while prolonging the infusion time for a single dose allows the plasma concentration to remain steadily above the effective threshold, both of which can significantly optimize the pharmacokinetic target [12]. This conclusion is corroborated by similar domestic and international studies; multiple clinical observations have confirmed that for critically ill patients, especially those with augmented renal clearance or increased volume of distribution, adopting strategies involving multiple daily doses or prolonged infusion can effectively increase the rate of achieving target plasma concentrations, thus providing clear direction for clinically optimizing dosing regimens.

Among patient physiological and biochemical indicators, low Alb status is quite common in SP patients, which may be closely related to enhanced protein catabolism and reduced synthesis caused by systemic inflammatory response. Piperacillin, as a drug with moderate protein binding, has its free drug concentration directly regulated by Alb levels. When serum Alb decreases, the drug's protein

binding rate declines. Although the initial free fraction increases, it also accelerates the overall clearance rate of the drug, ultimately leading to insufficient total drug exposure and difficulty in maintaining a stable effective plasma concentration [13]. Scr level, a key indicator for assessing renal function, when elevated usually suggests decreased glomerular filtration function. However, in SP patients, particularly those with systemic inflammatory response, a transient increase in glomerular filtration rate can often occur, known as augmented renal clearance [14]. In this state, accelerated drug excretion significantly reduces plasma concentrations, making it difficult for conventional dosing regimens to achieve effective therapeutic concentrations. The positive correlation between Scr level and the risk of not achieving the target in this study precisely reflects the impact of this special pathophysiological process on drug metabolism.

The APACHE II and SOFA scoring systems comprehensively reflect the degree of physiological dysfunction and organ dysfunction in critically ill patients. Patients with higher scores often present with more pronounced capillary leakage and third-space fluid retention. These pathological changes significantly increase the apparent volume of distribution of hydrophilic antibacterial agents, leading to a 'dilution' of plasma concentrations. Simultaneously, changes in cardiac output and organ hemodynamics in critical states directly affect the distribution and clearance of drugs. A higher APACHE II score represents more severe physiological dysfunction, while the SOFA score specifically reflects the number and severity of organ dysfunctions [15]. The combined effects of these pathophysiological changes often make it difficult for standard dosing regimens to achieve ideal pharmacokinetic targets in critically ill patients. Multiple prospective studies have also confirmed significant differences in the pharmacokinetic parameters of antibacterial agents between critically ill patients and general patients, which corroborates the findings of this study. Therefore, in clinical practice, for patients with high disease severity scores, their unique pharmacokinetic characteristics should be fully considered, dosing regimens should be adjusted promptly, and therapeutic drug monitoring should be utilized when necessary to achieve individualized precision dosing.

In summary, the rate of achieving target plasma concentrations during piperacillin-tazobactam treatment in SP patients is low. Dosing frequency, infusion time, Alb, Scr, APACHE II score, and SOFA score are independent influencing factors for achieving target piperacillin plasma concentrations. Although APACHE II and SOFA scores are not direct determinants of attaining target piperacillin/tazobactam concentrations, they reflect the severity of the patient's condition and the state of organ function. These factors indirectly influence the pharmacokinetic parameters of the drug, thereby affecting the rate of achieving target plasma concentrations. In clinical practice, physicians need to comprehensively consider the patient's scoring results, organ function status, comorbidities, and other factors, conduct drug concentration monitoring promptly, and individually adjust the dosage and infusion regimen of piperacillin/tazobactam to ensure that

target plasma concentrations are achieved and optimal therapeutic efficacy is attained.

However, this study has several limitations. 1) It is a retrospective, single-center study with a relatively small sample size, which may affect the generalizability of the results. 2) This study focused on piperacillin-tazobactam and evaluated its PK/PD target attainment rate solely based on piperacillin, which has certain limitations. Some studies have highlighted the rationality of the formulation ratio of β-lactam/β-lactamase inhibitor combinations and the issue of pharmacokinetic synchronization between the components. Future research should involve multicenter, large-sample studies that integrate β-lactam and enzyme inhibitors in the evaluation of piperacillin-tazobactam PK/PD, in line with the latest research trends. Further exploration of the mechanisms by which additional potential factors influence the trough concentration of piperacillin-tazobactam is needed to support the advancement of precise clinical drug therapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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