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BRIEF REPORT

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Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia

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Abstract *Objective:* To determine the steady-state plasma and epithelial lining fluid (ELF) concentrations of piperacillin/tazobactam (P/T) administered to critically ill patients with severe bacterial pneumonia. *Design:* Prospective, open-label study. *Setting:* An intensive care unit and research ward in a university hospital. *Patients:* Ten adult patients with severe nosocomial bacterial pneumonia on mechanical ventilation. *Interventions:* All subjects received a 30-min intravenous infusion of P/T 4 g/0.5 g every 8 h. The steady-state plasma and ELF concentrations of P/T were determined by high-performance liquid chromatography. *Measurements and main results:* The mean±SD steady-state plasma trough, peak, and intermediate concentrations were 8.5±4.6 μg/ml, 55.9±21.6 μg/ml, and 24.0±13.8 μg/ml for piperacillin, and 2.1±1.0 μg/ml, 4.8±2.1 μg/ml, and 2.4±1.2 μg/ml for tazobactam, respectively. The mean±SD steady-state intermediate ELF concentrations were 13.6±9.4 μg/ml for piperacillin and 2.1±1.1 μg/ml for tazobactam, respectively, showing a mean percentage penetration of piperacillin and tazobactam into ELF of 56.8% and 91.3 %, respectively, with a P/T ratio of 6.5:1. *Conclusion:* Our results show that during the treatment of severe nosocomial pneumonia, a regimen of P/T 4 g/0.5 g every 8 h might provide insufficient concentrations into lung tissue to exceed the MIC of many causative pathogens. This suggests that higher doses of P/T should be administered in order to maximize the antibiotic concentration at the site of infection, or that a second antimicrobial agent should be used in association.

Keywords Piperacillin · Tazobactam · Lung diffusion · Intensive care · Nosocomial pneumonia · Ventilator-associated pneumonia

Introduction

Piperacillin/tazobactam (P/T) is a combination of an ureidopenicillin and a β-lactamase inhibitor at a fixed ratio of 8:1, which confers a broad spectrum of activity including β-lactamase-producing Gram-negative, Gram-positive, and anaerobic microorganisms [1]. Due to this particular broad-spectrum, P/T is indicated during the treatment of severe nosocomial pneumonia [2, 3]. The pharmacokinetics and pharmacodynamics of P/T have been widely studied in in vitro models or in healthy volunteers [4, 5, 6]. Although clinical studies have evaluated the efficacy of P/T during the treatment of nosocomial pneumonia in critically ill patients, only few pharmacokinetic data concerning this subset of patients are available [2, 3, 7].

Most infections occur in the tissues of the body rather than in the blood so that it is accepted today that appropriate antibiotic therapy requires achieving significant concentrations of antibiotics at the sites of infection [8].

Epithelial lining fluid (ELF) has been advocated as a reliable marker of extracellular antibiotic concentration in lung tissue [8, 9, 10]. Although the concentration of P/T administered to critically ill patients with severe nosocomial pneumonia has already been evaluated in bronchial mucosa, no study has thus far evaluated the penetration of P/T in ELF [7, 9]. Therefore, we conducted a study to determine the steady-state plasma concentrations and the percentage penetration into ELF of P/T 4 g/0.5 g administered every 8 h to critically ill patients on mechanical ventilation with severe nosocomial pneumonia.

Patients and methods

This was a prospective, open-label, single-center study approved by the local Ethics Committee. Prior to inclusion in the study, all patients or their closest relative provided written informed consent. Critically ill adult patients who were hospitalized in our intensive care unit for $\geq$72 h prior to diagnosis were considered eligible for inclusion in the study when suspected of having severe nosocomial ventilator-associated pneumonia, defined according to the Centers for Disease Control criteria [11].

The patients were excluded from the study if they were allergic to ß-lactam antibiotics, exhibited renal dysfunction defined by a calculated creatinine clearance (using urine of the past 24 h) of <40 ml/min or a serum creatinine concentration of >200 µmol/l, or had impairment of hepatic function (alanine aminotransferase, aspartate aminotransferase or bilirubin greater than twice the upper limit of normal).

Before initiation of therapy, specimens for microbiologic diagnosis were obtained using a plugged telescoping catheter (Combicath, Plastimed, St-Leu-La-Forêt, France) from all the patients [12]. All patients were on sedation and mechanical ventilation during the procedure, which is simple, non-invasive and easily repeatable at the bedside. Piperacillin/tazobactam was then administered as empirical therapy in addition to amikacin, until identification of the pathogen and determination of its antibiotic susceptibility.

All subjects received 30-min intravenous infusions of P/T 4 g/0.5 g every 8 h at 7:00 a.m., 3:00 p.m., and 11:00 p.m. All samples for P/T concentration determinations were obtained at steady-state after 2 days of therapy. Blood samples were collected at three predetermined time points at 7:00 a.m. (trough concentration), 8:00 a.m. (peak concentration), and 12:00 p.m. (intermediate concentration) and were immediately centrifuged at 3,000 rpm for 5 min. The serum was removed and stored at −80°C until analyzed. As previously described, each subject underwent one standardized bronchoalveolar microlavage (BAL) procedure [13] simultaneously to blood sampling at 12:00 p.m. A standard bronchial brush tube (Combicath, Plastimed) was inserted in the endotracheal tube, and used to perform a mini-BAL with 40-ml of sterile 0.9% normal saline solution. The aspirate was immediately centrifuged at 3,000 rpm for 5 min and a single aliquot of supernatant was separated and frozen for the urea assay. The remaining volume was frozen at −80°C until the assays were performed. All blood and BAL samples were assayed within 6 months from the time of their collection.

Piperacillin and tazobactam in plasma and BAL were measured simultaneously by high-performance liquid chromatography (HPLC). The detection chosen for the HPLC assay was an ultraviolet detection set at a wavelength of 214 nm. Mean within- and between-day reproducibilities were less than 4.2% and 7.8%, and 5.4% and 10.4%, respectively, for piperacillin and tazobactam in plasma and BAL. Mean accuracy was higher than 97% for both drugs. The recovery of both piperacillin and tazobactam in BAL ranged from 95% to 102%. The limits of quantification of piperacillin and tazobactam were 0.25 µg/ml in serum and 0.50 µg/ml in BAL.

As previously described, the concentration of P/T in ELF (P/T_{ELF}) was determined as follows, using urea as an endogenous marker [13]: $P/T_{ELF}=P/T_{BAL}\times urea_{SER}/urea_{BAL}$, where P/T_{BAL} is the measured concentration of P/T in BAL fluid, $urea_{SER}$ is the concentration of urea in plasma, and $urea_{BAL}$ is the concentration of urea in the BAL fluid.

Results

Ten adult subjects (six men and four women) with severe nosocomial ventilator-associated pneumonia, completed the study (Table 1). Piperacillin/tazobactam administration and microlavage procedures were well tolerated and no serious adverse effects were observed. Of the ten patients undergoing P/T sampling, seven (70%) had at least one organism recovered using the plugged telescoping catheter technique. In total, nine pathogens were isolated

Table 1 Patients characteristics at enrolment (n=10). *SAPS II* Simplified Acute Physiology Score II [15]. Data are expressed as mean±SD or %

Age, years	61±19
Gender, M/F	6/4
Weight, kg	66±12
SAPS II	30±10
Creatinine clearance, ml/min	77±34
Main diagnosis, %	
Pneumonia	50
Abdominal surgery	40
Urinary tract infection	10
PO_2/F_iO_2 ratio	190±57

Table 2 Steady-state plasma and ELF concentrations and ELF/plasma percentage penetration of piperacillin/tazobactam 4 g/0.5 g administered in 30-min infusions every 8 h. *ELF* Epithelial lining fluid. Data are expressed as mean±SD

Sampling time	n	Piperacillin concentration, µg/ml		ELF/plasma percentage penetration, %	Tazobactam concentration, µg/ml		ELF/plasma percentage penetration, %
		Plasma	ELF		Plasma	ELF	
7 a.m.	10	8.5±4.6	-	-	2.1±1.0	-	-
8 a.m.	10	55.9±21.6	-	-	4.8±2.1	-	-
12 a.m.	10	24.0±13.8	13.6±9.4	56.8±33.6	2.4±1.2	2.1±1.1	91.3±27.7

in this study population (five *Pseudomonas aeruginosa*, three *Enterobacteriaceae,* and one *Staphylococcus aureus*). After determination of the causative pathogen susceptibility, the narrowest spectrum antibiotic combination was administered whenever possible.

The mean±SD plasma trough (before the beginning of infusion), peak (1 h after the beginning of infusion) and intermediate (5 h after the beginning of infusion) concentrations at 7:00 a.m., 8:00 a.m., and 12:00 p.m. were 8.5±4.6 μg/ml, 55.9±21.6 μg/ml, and 24.0±13.8 μg/ml for piperacillin, and 2.1±1.0 μg/ml, 4.8±2.1 μg/ml, and 2.4±1.2 μg/ml for tazobactam, respectively (Table 2). The mean±SD intermediate ELF concentrations at 12:00 p.m. were 13.6±9.4 μg/ml for piperacillin and 2.1±1.1 μg/ml for tazobactam, respectively, showing a mean percentage penetration of piperacillin and tazobactam into ELF of 56.8% and 91.3 %, respectively, with a P/T ratio of 6.5:1 (Table 2).

Discussion

Piperacillin/tazobactam is a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity encompassing most Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria, including many pathogens producing β-lactamases and major nosocomial pathogens such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii* [1]. Clinical trials have shown that P/T is an effective treatment for patients with severe nosocomial infections including ventilator-associated pneumonia (VAP), usually in combination with an aminoglycoside [2, 3].

Pharmacokinetics and pharmacodynamics of P/T have been extensively studied in various in vitro and human models [5, 6]. These studies suggest that the administration of P/T during the treatment of severe nosocomial infections appears to provide serum concentrations in excess of the MIC of most causative pathogens [5, 6]. However, these studies were generally carried out in healthy volunteers, and only few pharmacokinetic data concerning infected patients are available [7].

This is the first study to report the steady-state serum and ELF concentrations and the ELF percentage penetration of P/T 4 g/0.5 g administered to patients with severe nosocomial pneumonia. Our results show a mean steady-state plasma concentration 1 h after the beginning of infusion of 55.9 μg/ml for piperacillin (and 4.8 μg/ml for tazobactam), which exceeds the susceptibility breakpoint for Gram-positive bacteria (8 μg/ml) and Gram-negative bacteria (16 μg/ml) other than non-fermentative bacilli such as *P. aeruginosa* or *A. baumanii* (64 μg/ml) [1]. The mean percentage penetration of P/T in ELF is 56.8% for piperacillin and 91.3% for tazobactam, showing a better diffusion of tazobactam than piperacillin in ELF with a mean P/T ratio of 6.5:1.

Considering the targeted micro-organisms frequently encountered in VAP [14] and the reported range of these pathogens MIC_{90} values in nosocomial infections (*P. aeruginosa*, 8-256 μg/ml; *S. aureus* oxacillin-susceptible, 0.5–8 μg/ml; Enterobacteriaceae, 0.5–256 μg/ml, and *Acinetobacter* spp., 8–256 μg/ml) [1], it appears that a regimen of P/T 4 g/0.5 g every 8 h might provide insufficient concentrations into lung tissue to exceed the MIC of many of these pathogens. Considering the high mortality rate of nosocomial pneumonia reaching 76% when the infection is caused by high-risk pathogens such as *P. aeruginosa* [14], our data suggest that doses higher than P/T 4 g/0.5 g every 8 h should be administered to critically ill patients in order to maximize the antibiotic concentration at the site of infection, or that a second antimicrobial agent should be used in association.

Our results, however, only provide pharmacokinetic and pharmacodynamic data to support these hypotheses. Further randomized, controlled clinical trials comparing the outcomes of critically ill patients with severe nosocomial pneumonia caused by pathogens with high MICs are warranted to determine the appropriate dose of P/T in this particular subset of patients.

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