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Pharmacokinetics of piperacillin-tazobactam in plasma, peritoneal fluid and peritoneum of surgery patients, and dosing considerations based on site-specific pharmacodynamic target attainment

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ABSTRACT

Piperacillin-tazobactam (PIP-TAZ) is commonly used to treat intraabdominal infections; however, its penetration into abdominal sites is unclear. A pharmacokinetic analysis of plasma, peritoneal fluid, and peritoneum drug concentrations was conducted to simulate dosing regimens needed to attain the pharmacodynamic target in abdominal sites. PIP-TAZ (4 g-0.5 g) was intravenously administered to 10 patients before abdominal surgery for inflammatory bowel disease. Blood, peritoneal fluid, and peritoneum samples were obtained at the end of infusion (0.5 h) and up to 4 h thereafter. PIP and TAZ concentrations were measured, both noncompartmental and compartmental pharmacokinetic parameters were estimated, and a simulation was conducted to evaluate site-specific pharmacodynamic target attainment. The mean peritoneal fluid:plasma ratios in the area under the drug concentration-time curve (AUC) were 0.75 for PIP and 0.79 for TAZ, and the mean peritoneal fluid:plasma ratios in the AUC were 0.49 for PIP and 0.53 for TAZ. The mean PIP:TAZ ratio was 8.1 at both peritoneal sites. The regimens that achieved a bactericidal effect with PIP (time above minimum inhibitory concentration [MIC] >50%) at both peritoneal sites were PIP-TAZ 4.5 g twice daily for an MIC of 8 mg/L, as well as 4.5 g three times daily, and 3.375 g four times daily for an MIC of 16 mg/L. These findings clarify the peritoneal pharmacokinetics of PIP-TAZ, and help consider the dosing regimens for intraabdominal infections based on site-specific pharmacodynamic target attainment.

1. Introduction

Piperacillin-tazobactam (PIP-TAZ) is an intravenously administered combination of PIP, a penicillin antibiotic, and TAZ, a beta-lactamase inhibitor [1]. PIP-TAZ has broad-spectrum activity against Gram-positive and Gram-negative bacteria. PIP-TAZ is used to treat various infections, including pneumonia, urinary tract infections, and intraabdominal infections [2,3]. Previous pharmacokinetic studies have demonstrated that the serum concentration of PIP-TAZ increases rapidly and achieves a maximum concentration at the end of intravenous infusion [4]. However, the clinical effects of PIP-TAZ depend on its ability to reach the site of infection. Therefore, understanding the pharmacokinetic distribution of PIP-TAZ can help clarify the pharmacodynamic effects of the drug for treating tissue-site infections such as peritonitis.

Shimizu et al [5] measured PIP-TAZ concentrations in peritoneal fluid; however, those authors did not measure plasma concentrations or characterize the peritoneal pharmacokinetics. Additionally, there have been no reports regarding PIP-TAZ concentrations in the peritoneum. Therefore, the present study was conducted to investigate the pharmacokinetics of intravenous PIP-TAZ in the plasma, peritoneal fluid, and peritoneum, and a pharmacokinetic analysis was performed to simulate dosing regimens needed to attain the pharmacodynamic target in abdominal sites.

2. Patients and methods

2.1. Study subjects

This was a prospective, open study on the peritoneal pharmacokinetics of PIP-TAZ conducted at Hiroshima University Hospital

Abbreviations: PIP-TAZ: piperacillin-tazobactam; AUC: area under the drug concentration-time curve; MIC: minimum inhibitory concentration; Cmax: observed maximum concentration; CLSI: susceptible breakpoint MIC by Clinical and Laboratory Standards Institute; EUCAST: epidemiological cut-off MIC by European Committee on Antimicrobial Susceptibility Testing.

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from June 2014 to May 2015. The study protocol and informed consent form complied with the Declaration of Helsinki and were reviewed and approved by the ethics committee of the institution.

Patients undergoing abdominal surgery for the relief of inflammatory bowel disease were chosen as the study subjects as these patients have a sufficient amount of peritoneal exudate for sampling. The inclusion criteria were as follows: elective patients of both sexes aged over 20 years who were amenable to antibacterial prophylaxis for postoperative infections and were willing and able to provide written informed consent. Any patient who was pregnant or hypersensitive to beta-lactams was excluded.

2.2. Drug administration and sample collection

Prophylactic PIP-TAZ (4 g-0.5 g) was administered intravenously by 0.5-h infusion. Venous blood (2 mL), peritoneal fluid (2 mL), and peritoneum (4 mm × 4 mm) samples were planned to be obtained at the end of infusion (0.5 h) and every hour thereafter until the completion of abdominal surgery. The plasma and supernatant peritoneal fluid samples were removed after centrifugation, and the peritoneum samples were rinsed in physiological saline. All samples were stored at –40 °C until assay.

2.3. PIP and TAZ assay

The total concentration of PIP and TAZ in plasma, peritoneal fluid, and the peritoneum was measured via high-performance liquid chromatography as previously reported, with modifications [6]. For PIP, peritoneum samples were homogenized using an overhead mixer with two volumes (w/v) of double distilled water. The homogenate was centrifuged, and the supernatant was collected for further procedures. Plasma, supernatant peritoneal fluid, and peritoneum samples (200 μL each) were added to 800 μL acetonitrile, and the resulting solution was mixed with a vortex mixer and centrifuged. The supernatants (900 μL) were then added to 4 mL dichloromethane and the resulting solution was mixed with a vortex mixer and centrifuged. Next, the supernatants (20 μL) were injected into a chromatograph with a C_{18} column at 40 °C and an ultraviolet absorbance detector at 220 nm. The mobile phase consisted of a mixture of 230 mmol/L potassium phosphate buffer (pH 2.6) and acetonitrile (75:25) with a flow rate of 1 mL/min. The quantification ranges were 0.5–1000 mg/L for plasma and peritoneal fluid and 1.5–1500 mg/kg for peritoneum samples. For intra- and inter-day assays, the precision was 0.69–7.24% and the accuracy was 99.6–107%.

For TAZ, the same measurement methods as those described for PIP were used, except the mobile phase was 230 mmol/L potassium phosphate buffer (pH 2.6) and acetonitrile (95:5). The quantification ranges were 0.5–100 mg/L for plasma and peritoneal fluid and 1.5–150 mg/kg for peritoneum samples. For intra- and inter–day assays, the precision was 1.10–9.49% and the accuracy was 97.5–112%.

2.4. Noncompartmental pharmacokinetic analysis

For each drug, C_{max} was defined as the observed maximum concentration. The area under the drug concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) was calculated based on the trapezoidal rule using the MULTI software program (originally developed by Yamaoka et al [7] and currently maintained by the Department of Biopharmaceutics and Drug Metabolism; Kyoto University, Kyoto, Japan). In the pharmacokinetic analysis, specific gravity of the peritoneum was taken as 1 (kg = L).

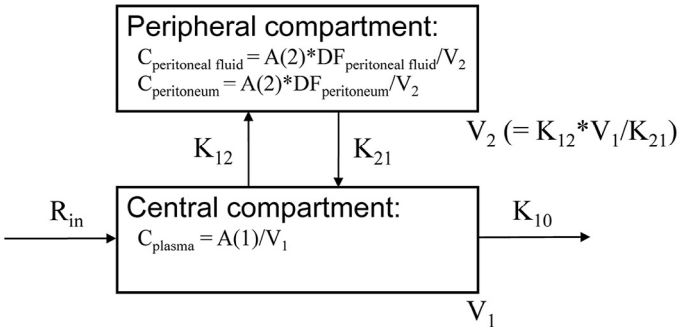

Fig. 1. Hypothetical two-compartment pharmacokinetic model for piperacillin and tazobactam. A(1) and A(2), amounts of drug in the central and peripheral (including peritoneal sites) compartments (mg); V_1 and V_2, volumes of distribution of the central and peripheral compartments (L = kg); C, concentration of drug in plasma and peritoneal fluid (mg/L) and peritoneum (mg/kg); R_{in}, intravenous infusion rate of drug (mg/h), K_{12} and K_{21}, transfer rate constants (1/h); K_{10}, elimination rate constant (1/h); DF, distribution factors to account for drug concentration differences between plasma and peritoneal sites (fluid and tissue).

2.5. Compartmental pharmacokinetic analysis

The preliminary analysis for each drug indicated that a three- or four-compartment model to describe the three drug concentrations (plasma, peritoneal fluid, and peritoneum) was too complicated; rather, a simpler model could be used because of the parallel drug elimination slopes for the peritoneal fluid and peritoneum. Therefore, the concentration-time data were fitted to a hypothetical two-compartment model with distribution factors [8] to account for concentration differences between the plasma and peritoneal sites (Fig. 1). The differential equations for changes in the amount of drug in the central compartment (A[1], mg) and peripheral compartment (including peritoneal fluid and peritoneum) (A[2], mg) regarding time (t) are as follows:

$$dA(1)/dt = R_{in} - (K_{12} + K_{10}) * A(1) + K_{21} * A(2)$$

$$dA(2)/dt = K_{12} * A(1) - K_{21} * A(2)$$

where R_{in} is the intravenous infusion rate of drug (mg/h), K_{12} and K_{21} are the transfer rate constants (1/h) connecting the central and peripheral compartments, and K_{10} is the elimination rate constant (1/h) from the central compartment.

In this model, the distribution volumes are V_1 for the central compartment (L) and V_2 for the peripheral compartment (L) ($V_2 = K_{12}{}^*V_1/K_{21}$). Assuming distribution factors to account for drug concentration differences between the plasma and peritoneal fluid ($DF_{peritoneal\ fluid}$) and between the plasma and peritoneum ($DF_{peritoneum}$), the equations for the drug concentration in plasma (C_{plasma}, mg/L), peritoneal fluid ($C_{peritoneal\ fluid}$, mg/L), and peritoneum ($C_{peritoneum}$, mg/L) are expressed as follows:

$$C_{plasma} = A(1)/V_1$$

$$C_{peritoneal\ fluid} = A(2) * DF_{peritoneal\ fluid}/V_2 = A(2) * DF_{peritoneal\ fluid} * K_{21}/[K_{12} * V_1]$$

$$C_{peritoneum} = A(2) * DF_{peritoneum}/V_2 = A(2) * DF_{peritoneum} * K_{21}/[K_{12} * V_1]$$

These six pharmacokinetic model parameters (K_{12}, K_{21}, K_{10}, V_1, $DF_{peritoneal\ fluid}$, and $DF_{peritoneum}$) were estimated for each patient using the MULTI software program [7].