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Title

Pharmacokinetics and the most suitable regimen of panipenem/betamipron
in critically ill patients receiving continuous renal replacement therapy - a pilot study

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Running Head

Suitable regimen of PAPM/BP during CRRT

Key words

pharmacokinetics
carbapenems
kidney failure
hemofiltration
metabolic clearance rate

Abstract

Critically ill patients are often complicated with acute renal failure induced by severe infection or sepsis. The patients need administration of broad-spectrum antibiotics as well continuous renal replacement therapy (CRRT). However, there is no uniform pharmacokinetics of antibiotics during the CRRT because CRRT is performed with the various combinations of dialysate flows (Q_D) and ultrafiltrate flows (Q_F). The aims of this study were to estimate the pharmacokinetics of panipenem/betamipron (PAPM/BP) and to determine the appropriate treatment regimens for PAPM/BP in critically ill patients undergoing CRRT. In patients with CRRT, the PAPM total clearance (PAPM CL_{tot}) was calculated as the sum of PAPM clearance dependent on the living body and CRRT and shown as follow:

$$\text{PAPM } CL_{tot} (\text{ml/min}) = (1.2 CL_{cre} + 66.5) + 0.86 (Q_D + Q_F)$$

where CL_{cre} is creatinine clearance. Pharmacokinetic values of PAPM were measured in 4 patients with CRRT. According to these results, the most appropriate treatment regimen regarding PAPM CL_{tot} (ml/min) showed as follows:

PAPM $CL_{tot} < 80$	0.5 g every 12 hr or 1 g every 15 hr
PAPM $CL_{tot} 80\text{-}120$	0.5 g every 8 hr or 1 g every 12 hr
PAPM $CL_{tot} 120\text{-}160$	0.5 g every 6 hr or 1 g every 8 hr

Critically ill patients are often complicated with acute renal failure and thus are hemodynamically unstable. Continuous renal replacement therapy (CRRT) has proven to be a convenient extracorporeal technique to treat renal failure and subsequent fluid overload in critically ill patients. However, there is no uniformity in the pharmacokinetics of drugs used during CRRT because the procedure is performed with the use of many different combinations of dialysate flows (Q_D) and ultrafiltrate flows (Q_F).

Critically ill patients are also often complicated with various severe infections and need to be intravenously administered antibiotics with a broad spectrum. For critically ill patients with various severe infections, panipenem/betamipron (PAPM/BP) is often intravenously administered because it demonstrates good clinical and bacteriological efficacy ¹. Panipenem is carbapenem that has a broad spectrum of activity covering gram-negative and gram-positive aerobic and anaerobic bacteria ^{1,2}. Panipenem is administered with BP, an organic anion tubular transport inhibitor with very low toxicity that inhibits the active transport of PAPM in the renal cortex, thereby reducing the nephrotoxic potential of PAPM ¹. For adult patients with normal renal function, the recommended dosage of PAPM/BP is 0.5 g for a period of at least 30 mins every 12 hours ¹. This dosage may be increased to 1 g for a period of at least 60 mins every 12 hours ¹.

The influences of CRRT on the pharmacokinetics of PAPM/BP are therefore suspected to depend on Q_D and Q_F . The aims of this study were thus as follows: 1) to estimate total PAPM/BP clearance during CRRT based on Q_D , Q_F , and renal function of patients, and 2) to determine the appropriate dose regimens of PAPM/BP based on the total PAPM/BP clearance in critically ill patients during CRRT.

Materials and Methods

In vitro study

An automated CRRT system (ACH-10, Asahi Medical Co., Tokyo, Japan) was used. A CRRT circuit was set up using a cellulose triacetate hollow fiber 1.1 m² hemofilter (UT-110, Nipro, Osaka, Japan) and filled with 5% bovine serum albumin (BSA) (**Figure 1**). The BSA was circulated for 10 mins to adhere proteins to the circuit. Thirty mg each of PAPM and BP was mixed with 200 ml of 5% BSA in a reservoir. The CRRT conditions were as follows: the BSA flow was fixed at 150 ml/min; Q_D was defined from 0, 1, and 2 l/hr; Q_F was defined from 0, 1, and 2 l/hr independently of Q_D ; normal saline was used as a dialysate and also served as a replacement fluid infused post-dilutionally with an equal amount of Q_F . We took samples from the pre-hemofilter and post-hemofilter. Samples from the filtrates were also taken (**Figure 1**). The sampling times were 15, 30, 60, and 120 mins after the start of CRRT. All samples were mixed with an equal amount of 1M MOPS buffer (pH 7.0) and frozen at -80 °C until analysis. These studies were performed repeatedly for eight different combinations of Q_D and Q_F .

Clinical study

This study was performed in the Intensive Care Unit of Hokkaido University

Hospital. Four patients with acute renal failure, who were being treated by CRRT and receiving PAPM/BP intravenously, were studied. Approval for the study was obtained from the Ethics Committee of our institution, and written informed consent was obtained from each patient's next of kin. **Table 1** shows the patients' detailed clinical backgrounds. The creatinine clearances (CL_{cre}) were measured based on the serum and urine creatinine levels, the urine volume for 24 hours, the body weight, and the height of the patients.

In patient 1, 0.5 g of PAPM/BP was intravenously administered during a 60 minute period every 12 hours, 1.0 g during a 60 minute period every 12 hours, and 1.0 g during a 60 minute period every 8 hours. These schedules of PAPM/BP administration were made to investigate the outline of the drug's pharmacokinetics. When 1.0 g of PAPM/BP was intravenously administered over 60 minutes every 8 hours in patient 1, an appropriate concentration of PAPM was obtained. Consequently, this administration schedule was used for all patients. **Table 1** shows the PAPM/BP dose regimens.

Vascular access was obtained by inserting a double-lumen catheter (10 F, Mahurkar, Quinton Instruments, Bothell, WA, USA) into a femoral vein. An automated CRRT system (JUN600, UBE, Tokyo, Japan) was used. The same hemofilter (UT-110, Nipro, Osaka, Japan) as that used in the in vitro study was used. The dialysate and replacement fluid were Sublood-A[®] (sodium 140, potassium 2.0, calcium 1.75, magnesium 0.5, chloride 111, bicarbonate 35, acetate 3.5, and glucose 5.51 mmol/l; Fuso, Osaka, Japan). The CRRT conditions were as follows: The blood circuit pumped a constant blood flow rate of 120 ml/min; Q_F was defined as 1.0 l/h in all patients; Q_D was infused in a countercurrent at rates of 1 l/h in addition to continuing

hemofiltration. The replacement fluid was infused after dilution as clinically indicated.

Samples were collected >48 hours after the start of PAPM/BP administration and CRRT. The sampling points were pre-hemofilter and post-hemofilter. Samples were also taken from the filtrates. Sets of three samples were taken before the start of the next PAPM/BP administration, at 1, 1.5, 2, 4, and 8 hours after the start of the drug administration. The blood samples were promptly centrifuged and plasma was separated. The samples from the plasma and filtrate were mixed with an equal amount of 1M MOPS buffer (pH 7.0) and frozen at -80°C until analysis.

Analysis of PAPM and BP

The concentrations of PAPM and BP in the samples were determined by the high-performance liquid chromatography (HPLC) method. Plasma and filtrate samples (100 μl) were combined with 50 μl of 20 mM MOPS (pH 7.0) and 200 μl of MeOH in a 1.5 ml Eppendorf tube. The samples were vortexed and centrifuged at 12,100 g at 4°C for 20 minutes. Twenty μl of the layers was injected into the HPLC system. A liquid chromatograph (L-7110, HITACHI, Tokyo, Japan) and a reversed-phase column (L-column ODS, 4.6 mm inner diameter x 150 mm) were used. PAPM and BP were detected at 296 nm and at 240 nm, respectively, using a variable wavelength ultraviolet monitor (L-7405, HITACHI, Tokyo, Japan). Protein-bound fractions of PAPM and BP were measured by using the Centrifree[®] Micropartition Device (Millipore, Bedford, MA, USA) with each drug at concentrations of 12.5, 25, 50, and 100 $\mu\text{g/ml}$ in 5% BSA and human plasma.

Pharmacokinetic analysis

A pharmacokinetic analysis was performed using the nonlinear least-squares regression program (MULTI) ³. The parameters were calculated by a two-compartment open model with a constant rate of infusion. The plasma concentration-time data were fitted to the following equation:

$$C_1 = A e^{-\alpha t} + B e^{-\beta t} \quad (1)$$

$$A = \frac{D (\alpha - K_{21} - \beta)}{V_1 (\alpha - \beta)} \quad (2)$$

$$B = \frac{D (K_{21} - \beta)}{V_1 (\alpha - \beta)} \quad (3)$$

where C_1 is the plasma concentration of PAPM or BP, D is the dose of the drug, K_{21} is the rate constant from the peripheral compartment to the central compartment, and V_1 is the volume of the central compartment. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule. The clearances in vivo (CL_{vivo}) and by CRRT (CL_{CRRT}) were calculated as follows:

$$CL_{vivo} = \frac{\text{Total drug dosage}}{AUC} \quad (4)$$

$$CL_{CRRT} = \frac{C_{D+F} (Q_D + Q_F)}{C_{Pre}} \quad (5)$$

where C_{D+F} is the concentration of the drug in dialysate and filtrate and C_{Pre} is concentration of the drug at pre-hemofilter. Because PAMP and BP are low molecular substances, Q_D and Q_F influence similarly to CL_{CRRT} ⁴.

Simulation study

The plasma concentration-time curves of PAMP were simulated using the pharmacokinetics parameters that were determined in this clinical study. Based on the predictive PAMP CL_{tot} , appropriate dose regimens of PAMP/BP were determined to maintain an effective plasma concentration level throughout the dosing intervals. The effective plasma concentration of PAMP was determined to be 4 $\mu\text{g/ml}$ as a breakpoint minimum inhibitory concentration (MIC) ⁵⁻⁷.

Statistical analysis

The StatView 5.0 statistical software package (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculation analyses. Predictive clearances were obtained by using a simple linear regression. Comparisons between the paired groups were made using Student's paired t-test. A p value of < 0.05 was considered to be statistically significant. All data were expressed as the medians (minimum - maximum) or the means $\pm$ SD.

Results

In vitro study

Protein-bound fractions of PAPM in 5% BSA and human plasma were 8.4 (6.3-10.6) % and 7.4 (7.2-8.2) %, respectively. Protein-bound fractions of BP in 5% BSA and human plasma were 55 (53-58) % and 52 (50-55) %.

Figure 2 shows the relationships between CL_{CRRT} and Q_D+Q_F of PAPM and BP. The predictive PAPM and BP CL_{CRRT} were obtained by interpolation into simple linear regression of each CL_{CRRT} against Q_D+Q_F closely correlates with the experimental data as follows (**Figure 2**):

$$\text{PAPM } CL_{CRRT} = 0.86 (Q_D+Q_F) \quad (p < 0.0001, R^2 = 0.93) \quad (6)$$

$$\text{BP } CL_{CRRT} = 0.59 (Q_D+Q_F) \quad (p < 0.0001, R^2 = 0.95) \quad (7)$$

Previous reports ^{8,9} showed a relationship between CL_{cre} and PAPM CL_{vivo} in patients with various renal functions. Based on results of previous reports ^{8,9}, the predictive clearance of PAPM in vivo (PAPM CL_{vivo}) was obtained by interpolation into simple linear regression of PAPM CL_{vivo} against CL_{cre} closely correlates with the data of previous reports as follows (**Figure 3**):

$$\text{PAPM } CL_{vivo} \text{ (ml/min)} = 1.2 CL_{cre} + 66.5 \quad (p = 0.0009, R^2 = 0.95) \quad (8)$$

The predictive total PAPM clearance (PAPM CL_{tot}) in a patient with acute renal failure during CRRT was calculated as follows:

$$\begin{aligned} \text{PAPM } CL_{tot} \text{ (ml/min)} &= \text{PAPM } CL_{vivo} + \text{PAPM } CL_{CRRT} \\ &= (1.2 CL_{cre} + 66.5) + 0.86 (Q_D+Q_F) \end{aligned} \quad (9)$$

Clinical study

The plasma concentration-time curves of PAPM at 0.5 g and 1 g PAPM/BP every 12 hours in patient 1 are shown in **Figure 4**. The peak plasma concentrations of PAPM after the intravenous infusion of 0.5 g and 1 g PAPM/BP over 1 hr were 23.2 $\mu\text{g/ml}$ and 42.9 $\mu\text{g/ml}$, respectively.

The plasma concentrations of PAPM and BP at 1 g PAPM/BP every 8 hours are fitted to a two-compartment model and presented in **Figure 5**. After the intravenous infusion of 1 g PAPM/BP over 1 hr, the peak and trough plasma concentrations of PAPM were 36.8 (25.1 - 48.8) $\mu\text{g/ml}$ and 4.3 (1.8 - 5.2) $\mu\text{g/ml}$, respectively, and the peak and trough plasma concentrations of BP were 69.6 (54.0 - 85.5) $\mu\text{g/ml}$ and 30.6 (16.8 - 49.8) $\mu\text{g/ml}$, respectively. **Table 2** shows the pharmacokinetic parameters of PAPM and BP for each patient. The predicted total clearances of PAPM were almost equal to the actual measured total clearances.

Simulation study

Based on the predictive PAPM CL_{tot} , appropriate dose regimens of PAPM/BP to maintain an effective plasma concentration level throughout the dosing intervals were determined as follows:

PAPM $\text{CL}_{\text{tot}} < 80$ (ml/min) 0.5 g every 12 hr or 1.0 g every 15 hr

PAPM CL_{tot} 80-120 (ml/min) 0.5 g every 8 hr or 1.0 g every 12 hr

PAPM CL_{tot} 120-160 (ml/min) 0.5 g every 6 hr or 1.0 g every 8 hr

The simulated plasma concentration-time curves of PAPM are shown in **Figure 6**.

Discussion

Critically ill patients often undergo CRRT to treat acute renal failure and a subsequent fluid overload. Because CRRT is performed under various conditions, it is difficult to generalize the pharmacokinetics of certain drugs during CRRT. For example, although Giles JL et al.¹⁰ investigated the pharmacokinetics of meropenem in patients during CRRT, they indicated the clearance in their study to be different from that reported in a previous study¹¹. This difference was caused by dissimilarities of CRRT. The pharmacokinetics of drugs during CRRT depend on the following conditions: 1) the pore size and adsorption ability of the hemofilter membrane; 2) the molecular size and protein binding fraction of the drug; 3) Q_D and Q_F in CRRT^{4,12}.

The hemofilter used in this study was a cellulose tri-acetate membrane with large pores and without drug-absorption. In CRRT, high-flux membranes with large pores and no drug-absorption are recommended. We use the recommendable hemofilter not only for the in vitro study but also in clinical settings.

The protein-bound fraction of a drug influences its CL_{CRRT} ¹². A drug having a high protein-bound fraction shows a lower CL_{CRRT} than that of another drug having a low protein-bound fraction when the two drugs have the same molecular sizes¹². In the in vitro study to establish PAPM and BP CL_{CRRT} , we used BSA instead of human plasma. Protein-bound fractions of PAPM and BP in BSA were the same as those in the human plasma. Based on this premise, the results of in vitro study could be applied in clinical settings. Predictive PAPM CL_{CRRT} indicated in this study is applied to various conditions of CRRT in clinically settings, because the formula was based on

the various settings of the CRRT circuit model. In a patient with renal failure, the amount of PAPM elimination decreased in correlation with the patient's CL_{cre} ^{8,9} because PAPM is mainly eliminated by the kidneys¹. We estimated PAPM CL_{vivo} based on the CL_{cre} (i.e., $PAPM\ CL_{vivo}\ (ml/min) = 1.2 \times CL_{cre} + 66.5$). However, PAPM is not eliminated by the kidneys alone. In the predictive formula of PAPM CL_{vivo} , a fixed number, such as 66.5, may thus indicate the non-renal elimination rate. In a patient during CRRT, PAPM CL_{tot} is the sum of the clearance of the patient and CRRT. In this study, we established PAPM CL_{tot} applied to a patient with various renal functions during CRRT with various conditions.

The percentage of PAPM CL_{CRRT} in PAPM CL_{tot} was below 30% in the four patients (**Table 2**). The CRRTs were performed on conditions that the amount of Q_D and Q_F were about 33 ml/min (2 l/hr) in this study. However, the amount of Q_D and Q_F does not have an upper limit. Recent studies^{13,14} showed that high-volume replacement CRRT improved the prognosis of patients with acute renal failure. The influences of CL_{CRRT} on CL_{tot} increase when the high-volume replacement CRRT is performed for a patient with severe acute renal failure.

Panipenem is a carbapenem antibiotic with a broad spectrum of activity against many common pathogens^{1,2}. It is often administered to critically ill patients with severe infections in intensive care units. In β -lactam antibiotics such as PAPM, the most appropriate surrogate marker for predicting the outcome is the duration in which the concentration of the drug in plasma exceeds the MIC¹⁵. Although PAPM demonstrated a post-antibiotic effect in vitro¹, the clinical significance of this effect has not yet been evaluated. Therefore, it is desirable to maintain a concentration above the MIC throughout the dosing interval. The clinical breakpoint MIC of

carbapenem has been shown in several previous reports ⁵⁻⁷. The Japan Society of Antimicrobial Agents showed the breakpoint MIC to be 2 µg/ml in pneumonia and 1 µg/ml in sepsis ⁶. The National Committee for Clinical Laboratory Standards determined the breakpoint MIC to be 4 µg/ml ⁵. Based on these findings, in the present study the breakpoint MIC of PAPM was thus determined to be 4 µg/ml ⁵⁻⁷. In pharmacokinetic simulation, the doses and intervals in PAPM administration were adjusted to maintain the breakpoint MIC throughout the dosing intervals (**Figure 6**).

Betamipron, an organic anion transport inhibitor, is administered with PAPM to reduce the renal toxicity of PAPM ¹. The physicochemical properties of BP include a low molecular weight (193 Da) as same as that of PAPM (339 Da), and high degree of binding to plasma proteins (73%) in contrast to PAPM (7%) ¹. Because of these physicochemical properties, BP is not eliminated at the same rate as PAPM by CRRT, and it accumulates in a patient with renal failure during CRRT (**Figure 5**). Concentration ratio of PAPM/BP significantly decreases also. However, a previous report showed that BP had neither toxicity nor any side effects ¹⁶. The accumulated concentration of BP is sufficient to reduce the renal toxicity of PAPM. We also did not observe any side effects of BP accumulation or decrease of concentration ratio of PAPM/BP during the study period when we monitored several laboratory data and systemic findings.

This pilot study has several potential limitations. First, when the predictive formula of PAPM CL_{vivo} was obtained, we used results of previous reports ^{8,9}. However, our critically ill patients may have had more severe renal failure than that of previous reports ^{8,9}, and may have other organ failures. Second, the clinical CRRT study was performed under similar conditions, although the predictive formula of PAPM CL_{CRRT}

was established by many experimental data in various conditions. Third, our clinical study was a pilot study. Therefore, a larger, more precise clinical study is needed to confirm the accuracy of our predictive formulas and the results of a simulation study.

Conclusion

We established a predictive formula of PAMP CL_{tot} applied to a patient with various renal functions during CRRT with various conditions. On the basis of PAMP CL_{tot} , we arrived at the recommended doses and intervals in PAMP administration to achieve effective concentrations.

When PAMP/BP is administered during CRRT, PAMP CL_{tot} should be calculated based on the formula:

$$\text{PAMP } CL_{tot} (\text{ml/min}) = (1.2 CL_{cre} + 66.5) + 0.86 (Q_D + Q_F)$$

Next, the appropriate dosages and intervals should be selected based on the calculated PAMP CL_{tot} :

PAMP $CL_{tot} < 80$ (ml/min)	0.5 g every 12 hr or 1 g every 15 hr
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PAMP CL_{tot} 80-120 (ml/min)	0.5 g every 8 hr or 1 g every 12 hr
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PAMP CL_{tot} 120-160 (ml/min)	0.5 g every 6 hr or 1 g every 8 hr.
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Figure legends

- Figure 1.** A circuit model of continuous renal replacement therapy and sampling points in the in vitro study.
- Figure 2.** Panipenem (filled circles and solid line) and betamipron (open circles and dotted line) clearance by continuous renal replacement therapy. CL_{CRRT} , clearance by continuous renal replacement therapy; Q_D , dialysate flow; Q_F , ultrafiltrate flow.
- Figure 3.** The predictive clearance of panipenem in vivo (PAPM CL_{vivo}). $PAPM\ CL_{vivo}\ (mL/min) = 1.2\ CL_{cre} + 66.5$, where CL_{cre} is creatinine clearance (mL/min) ($P = 0.0009$, $R^2 = 0.952$). This predictive formula is based on CL_{cre} and PAPM CL_{vivo} in patients with various levels of renal function in previous reports ^{8,9}.
- Figure 4.** The plasma concentration-time curves of panipenem in the administration of 1.0 g panipenem/betamipron every 12 hrs (open circles) and 0.5 g every 12 hrs (filled circles) in patient 1.
- Figure 5.** The plasma concentration-time curves of panipenem (PAPM) and betamipron (BP) at 1.0 g PAPM/BP administration every 8 hrs. The filled circles show the PAPM concentrations and the open circles

show the BP concentrations.

Figure 6. The simulated plasma concentration-time curves of panipenem. The graphs on the left side show the plasma concentration-time curves of 0.5 g panipenem/betamipron (PAPM/BP) administration every 12 hr (upper side) and 1.0 g every 15 hr (lower side) in a patient whose panipenem total clearance (PAPM CL_{tot}) is 80 mL/min. The center graphs show the simulations for 0.5 g PAPM/BP administration every 8 hr (upper side) and 1.0 g every 12 hr (lower side) in a patient whose PAPM CL_{tot} is 120 mL/min. The graphs on the right side show the simulations for 0.5 g panipenem/betamipron administration every 6 hr (upper side) and 1.0 g every 8 hr (lower side) in a patient whose PAPM CL_{tot} is 160 mL/min. In all graphs, the shadow shows 4 μ g/mL as the breakpoint MIC concentration.











