Effects of Peritoneal Dialysis on Pharmacotherapy: A Deductive Pharmacokinetic-model Approach to Predict Drug Concentration Profiles in Plasma and Peritoneal Fluid

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Summary: The aim of this study was to present a deductive compartment pharmacokinetic (PK) model to predict the concentration profiles of drugs in plasma and peritoneal fluid in peritoneal dialysis (PD) rats. PK parameters of model drugs in normal and experimentally induced acute renal failure (ARF) rats not undergoing PD were obtained inductively in a common regression manner with a two-compartment model. In PD normal and ARF rats, PK parameters relating to the transfer of drugs to the peritoneal dialysate and the progress of renal failure were deductively modified to simulate the drug concentration-time profiles in plasma and in the peritoneal fluid in PD rats. The deductively introduced modifiers were the volume of distribution in the peripheral compartment, plasma protein binding, and solvent movement factor to the peritoneal fluid. Predicted profiles of tolbutamide, propranolol and cefazolin in PD normal and ARF rats were compared with the corresponding observed data. This minimal deductive approach yielded satisfactory accuracy in the prediction of both the plasma and peritoneal fluid concentrations of tolbutamide and propranolol.

Keywords: peritoneal dialysis; pharmacokinetics; tolbutamide; propranolol; cefazolin; acute renal failure; rat; deductive PK model; profile prediction

Introduction

Peritoneal dialysis (PD) is a treatment for patients with severe chronic kidney dysfunction and is used as an alternative to hemodialysis. Impaired renal function is supplemented with PD to maintain water and electrolyte homeostasis and to excrete waste products including xenobiotics. PD utilizes the peritoneum of the patient as a semi-permeable dialyzing membrane across which excess body fluids and dissolved substances (electrolytes, urea, glucose, and other small molecules including drug molecules) are removed from the systemic plasma by regular drainage of the dialysate followed by replacement with fresh.

For chronic end-stage renal failure patients, peritoneal dialysis, as an alternative to renal replacement therapy, permits improvement of their quality of life. However, infection and inflammation of the peritoneal membrane attributed to the permanent catheter are major clinical risks of PD.1–4 A variety of pharmacoeconomics for attendant complications, besides antibiotics for the treatment of infectious peritonitis, are frequently prescribed to PD patients. As the contribution of PD to the systemic clearance of drugs is not negligible, characterization of the pharmacokinetics of drugs in patients undergoing PD is indispensable for dose adjustment in rational pharmacotherapy.1–4

We have demonstrated that the plasma concentration of tolbutamide (TB), an antidiabetic drug, was decreased by 23.4% when PD was performed in acute renal failure (ARF) rats, while the profile was not changed by PD in normal rats.5 The contribution of the decreased plasma unbound fraction of TB to the increase of the distribution volume in ARF rats was suggested.5 We have also reported that the increase of the unbound fraction of TB, induced experimentally by the concomitant use of sulfonamides, decreased intrinsic dialysis clearance of TB in ARF rats receiving PD.6 Several pharmacokinetic (PK) analysis studies have clarified the changes of PK characteristics of drugs in PD.7,8 In hydrophilic antibiotic studies, shortening of the plasma half-life has been reported in patients undergoing PD.9 Aoyama et al. presented a peritoneal dialysis PK model to discuss the profiles of fluconazole, a relatively low protein binding (approx. 10%) drug, in plasma and dialyzing fluid in normal and ARF rats.10 In their peritoneal dialysis PK model, the distribution volume of the peripheral compartment was fixed at the volume of the dialyzing fluid.10 However, renal dysfunction is often accompanied by...
The model was attempted using the data sets of model drugs in rats with regarding the utility of the pro infused peritoneal dialysate and parameters representing plasma cardiopulmonary bypass surgery and modiﬁed prophylactic use of antibiotics in children undergoing that such deductive modiﬁcations have implications for individualized prophylactic use of antibiotics in children undergoing cardiopulmonary bypass surgery and modiﬁcation.

Propranolol hydrochloride (PPL), a sympatholytic non-selective β-blocker, is administered to patients to treat hypertension. Cefazolin sodium (CEZ) is clinically effective against infections caused by staphylococci and streptococci of Gram-positive bacteria and is generally used to treat moderately severe bacterial infections involving the lungs, bones, joints, stomach, blood, heart valves, and urinary tract. In the treatment of peritonitis, antibiotics are frequently infused into the peritoneum dissolved in the dialysate.13) There is no systematic clinical research on the variation of pharmacokinetic parameters in renal failure patients undergoing PD beyond a few reports.16,17

In this study, TB, PPL and CEZ were selected as model drugs for investigating the effects of peritoneal dialysate infusion on the transfer kinetics of these drugs from plasma to the peritoneal fluid. Plasma concentrations of TB were quoted from our previous report.5 PK parameters obtained in rats not undergoing PD (non-PD rats) by the conventional two-compartment PK model were applied to the deductive PK model under PD conditions (dedPD-PK model). In the dedPD-PK model, the dialysate compartment in the dedPD-PK model was characterized as belonging to the peripheral compartment, since drug distribution between the circulation and peritoneal fluid requires a certain time after intravenous administration.5) In the dedPD-PK model, three deductive factors, i.e., volume of the infused peritoneal dialysate and parameters representing plasma protein binding and partition characteristics of the dialysate, were introduced to express the peripheral compartment. Discussion regarding the utility of the model prediction by the dedPD-PK model was attempted using the data sets of model drugs in rats with dialysate introduced in the peritoneal cavity.

Materials and Methods

Materials: Tolbutamide was purchased from Sigma-Aldrich (St. Louis, MO). Propranolol hydrochloride and cefazolin sodium were purchased from Nacalai Tesque (Kyoto, Japan). Peritoneal dialysate (Dianeal PD-2 1.5; Baxter Ltd., Tokyo, Japan) was used without modiﬁcation. Other chemicals used in this study were of the ﬁnest grade available from domestic distributors.

Animals: Male Wistar rats (250–330 g) were purchased from Charles River Laboratories Japan, Inc. (Yokohama, Japan). The rats were allowed free access to a standard laboratory diet and water prior to the experiments. To induce acute renal failure, the rats were injected with 10 mL/kg of 50% glycerol into both thighs after 24-h water deprivation. After the glycerol injection, the rats fed normally for another 24 h were used as ARF rats.18) Establishment of acute renal failure was conﬁrmed by increased serum creatinine (Ccr) and blood urea nitrogen (BUN) concentrations. All animal experiments were performed in accordance with the Guidelines for Animal Experimentation of Okayama University.

Evaluation of plasma protein binding of model drugs: After being anesthetized with ethyl carbamate (1 g/kg), normal and ARF rats were ﬁxed on their back. Blood was drawn from an inferior vein and plasma was collected by centrifugation. Ten microliters of model drug solution was mixed with 490 µL of the plasma specimen. Part of the plasma solution was used for high-pressure liquid chromatography (HPLC) determination of the total drug concentration, and the other part was applied to the Centrifree micropartition ultraﬁltration device (Millipore, Billerica, MA). The unbound fraction of the model drug was separated by centrifugation (1,500 × g, 10 min, 4°C) and the model drug concentration was measured with HPLC. To guarantee the blood volume in the pharmacokinetic study, we determined laboratory values (Ccr and BUN) and protein binding of drugs in rats not used for the pharmacokinetic study.

Concentration-time proﬁles of drugs in plasma and in peritoneal ﬂuid after single i.v. dosing: Under deep anesthesia with ethyl carbamate (1 g/kg), each rat was ﬁxed on its back on a thermo-controlled platform. In PD rats, an indwelling 18-gauge needle was inserted into the abdominal cavity. The elastic outer needle was ﬁxed with surgical glue to the abdomen, and was connected to silicone tubing for abdominal infusion. Then, pre-warmed dialysate (100 mL/kg body weight) was slowly infused into the abdominal cavity. Tolbutamide (10 mg/kg), propranolol hydrochloride (2 mg/kg) or cefazolin sodium (5 mg/kg) was administered from the right femoral vein. Blood samples (and peritoneal ﬂuid samples from PD rats) were collected over 4 h (TB, CEZ and PPL in ARF rats) or 2 h (PPL in normal rats) after i.v. dosing. A blood sample was collected from the jugular vein. A peritoneal ﬂuid sample was collected via the silicone tubing connected to the abdomen. The sampling volumes for blood and peritoneal ﬂuid were 250 µL and 300 µL, respectively. The blood samples were centrifuged at 12,000 rpm (approx. 8,000 × g) for 10 min to collect the plasma fraction for determination. The peritoneal ﬂuid sample was ﬁltered through a 0.45 µm pore membrane (Milllex-GV; Millipore).

Measurement of drug concentration: Drug concentrations in the plasma and the peritoneal ﬂuid samples were determined by HPLC (LC-10ATVP; Shimadzu, Kyoto, Japan). The column for the HPLC was an Inertsil ODS-3 column (4.6 × 150 mm; GL Sciences Inc., Tokyo, Japan). The column temperature was maintained at 40°C by using a column oven (CTO-6A; Shimadzu). The samples were injected into the HPLC system by an auto-injector (SCL-10AVP; Shimadzu). TB and CEZ were determined spectrophotometrically by HPLC equipped with a UV-VIS detector (SPD-10AVP; Shimadzu) at 228 nm and 272 nm, respectively. The mobile phase for TB and CEZ was a mixture of 0.05% phosphoric acid/2-propanol/methanol (45:2:53 by volume) and a mixture of methanol/0.1 mol/L potassium phosphate (27:73 by volume),
respectively, at a flow rate of 1.0 mL/min. PPL was determined by HPLC equipped with a spectrofluorometric detector (RF-10AXL; Shimadzu) operated at excitation and emission wavelengths of 293 nm and 356 nm, respectively. The mobile phase was a mixture of methanol/10 mmol/L phosphate buffer (pH 2.15) (37:63 by volume) at a flow rate of 1.2 mL/min.

Pharmacokinetic parameters in non-PD rats: Pharmacokinetic parameters of drugs in non-PD rats were estimated inductively by fitting the plasma concentration profiles to an inductively obtained two-compartment model in which the time-course of the plasma concentration was expressed as the following bi-exponential equation (Eq. 1), using a non-linear least squares regression program (MULTI9):

\[ C(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]  

(Eq. 1)

where \( C(t) \) is the plasma concentration of the drug at time \( t \). From the best-fitting parameters in Eq. 1, a model describing pharmacokinetic parameters was calculated. The calculated inductive PK parameters for tolbutamide, propranolol and cefazolin are listed in Table 2.

Deductive PD-PK model (dedPD-PK model): The dedPD-PK model, a compartment-based PK model for prediction of the concentration profiles of drugs in plasma and peritoneal fluid in PD rats, was established deductively by the addition of three deductive factors, i.e., volume of the infused peritoneal dialysate (\( V_{PD} \)), the parameters representing plasma protein binding (\( f_b \)) and the apparent solvent movement factor (\( F \)) generated by the introduction of hypertonic peritoneal dialysate. These factors specified the effects of PD on the peripheral compartment of the inductively obtained PK model in non-PD rats (Fig. 1). In the dedPD-PK model, peritoneal fluid was connected to the peripheral compartment. In our preceding studies,6,8) the delay in concentration-time profile of tolbutamide in the peritoneal fluid compared to that in plasma was evident.

Modification of PK parameters in the dedPD-PK model: \( V_{PD} \) and \( f_b \) were used for the modification of PK parameters connected with the peripheral compartment in the dedPD-PK model. Conceptual volume increase was introduced into the distribution volume of the peripheral compartment (\( V_e \)). \( V_2 \) in the dedPD-PK model (\( V_{2PD} \)) was assumed as Eq. 2 under ideal conditions:

\[ V_{2PD} = V_2 + V_{PD} \cdot (1 - f_b) \]  

(Eq. 2)

where the volume change of the peritoneal fluid during PD was negligible and the transfer of drugs from the systemic plasma to peritoneal fluid was rapid enough to treat the \( V_{2PD} \) as kinetically well-stirred.

When the solvent movement to the peritoneal cavity owing to the dehydration of systemic circulation generated by the introduction of hypertonic peritoneal dialysate was taken into account, \( V_{2PD} \) could be expressed as in Eq. 3 in the deductive modification.

\[ V_{2PD} = V_2 + F \cdot V_{PD} \cdot (1 - f_b) \]  

(Eq. 3)

where \( F \) was an apparent solvent movement factor.

As the relative osmotic ratio of Dianeeal PD-2 1.5 is approximately 1.2,20) the \( F \) value was considered to be between 1.0 and 1.2. In the simulation of drug concentrations in the peritoneal fluid, the \( F \) value was fixed as 1.0 or 1.2 to discuss the effects of solvent movement on the simulations.

In the dedPD-PK model, plasma concentration profiles (\( C_{1ded}(t) \)) in PD rats can be expressed as another biexponential equation (Eq. 4). The abbreviation, \( ded \), means the prediction by the dedPD-PK model. The following relations (Eqs. 5 to 11) among these parameters, \( P, Q, \gamma, \delta \) in Eq. 4 can be derived from basic PK principles for a 2-compartment model.21)

\[ C_{1ded}(t) = P \cdot e^{-\alpha t} + Q \cdot e^{-\beta t} \]  

(Eq. 4)

\[ V_1 = D/(P + Q) \]  

(Eq. 5)

\[ k_{21PD} = (P \cdot \delta + Q \cdot \gamma)/(P + Q) \]  

(Eq. 6)

\[ P = D \cdot (k_{21PD} - \gamma)/(V_1 \cdot (\delta - \gamma)) \]  

(Eq. 7)

\[ Q = D \cdot (k_{21PD} - \delta)/V_1 \cdot (\gamma - \delta) \]  

(Eq. 8)

\[ \gamma + \delta = k_{12} + k_{21PD} + k_d \]  

(Eq. 9)

\[ \gamma \cdot \delta = k_{21PD} \cdot k_d \]  

(Eq. 10)

\[ V_{2PD} = k_{12} \cdot V_1/k_{21PD} \]  

(Eq. 11)

where \( D \) represents the dose. The parameters with subscript PD are the deductive parameters related to PD. In the dedPD-PK model, no change in \( V_1, k_{12} \) and \( k_d \), which were estimated inductively in non-PD rats by a conventional 2-compartment model,21) is assumed. Once the value for \( V_{2PD} \) is fixed according to Eq. 2, \( k_{21PD} \) will be estimated based on Eq. 11, followed by the estimation of other deductive parameters. The calculated dedPD-PK parameters for tolbutamide, propranolol and cefazolin are listed in Table 3.

Evaluation of prediction by dedPD-PK model: Incorporating \( V_{2PD} \) and \( k_{21PD} \) to Eqs. 5–11, deductively predicted concentration profiles in the peripheral compartment (\( C_{2ded}(t) \)) in PD-undergoing rat can be expressed as follows:

\[ C_{2ded}(t) = (D \cdot k_{12}/(V_{2PD} \cdot (\delta - \gamma))) \cdot e^{-\gamma t} \]  

\[ + (D \cdot k_{12}/(V_{2PD} \cdot (\gamma - \delta))) \cdot e^{-\delta t} \]  

(Eq. 12)

\[ C_{PDded}(t) = C_{2ded}(t) \cdot (1 - f_b) \]  

(Eq. 13)

Then \( C_{PDded}(t) \) is expressed as Eq. 14 by substituting \( C_{2ded}(t) \) in Eq. 13 using Eq. 12.

\[ C_{PDded}(t) = ((D \cdot k_{12}/(V_{2PD} \cdot (\delta - \gamma))) \cdot e^{-\gamma t} \]  

\[ + (D \cdot k_{12}/(V_{2PD} \cdot (\gamma - \delta))) \cdot e^{-\delta t}) \cdot (1 - f_b) \]  

(Eq. 14)

Finally, deductively the estimated values of the deductive parameters, \( V_{2PD}, \delta \) and \( \gamma \), were plugged into Eqs. 4 and 14 to simulate the concentration profiles in plasma and in peritoneal fluid, respectively.

Data analysis: Data are shown as the mean ± S.D. unless indicated otherwise. Significant differences were evaluated by Student’s t-test, and \( p < 0.05 \) was considered significant.

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Results

The establishment of acute renal failure was assessed by measuring Ccr and BUN. Ccr was significantly increased from 0.98 ± 0.03 to 5.00 ± 0.88 mg/dL (p < 0.05). BUN was significantly increased from 16.6 ± 1.4 to 118.2 ± 26.0 mg/dL (p < 0.05). Induction of ARF rats was regarded as successful by the increase of Ccr and BUN values compared with those reported previously.22)

The plasma protein binding of the model drugs was examined in normal and ARF rats (Table 1). Plasma unbound fractions of all three model drugs increased in ARF rats. Protein binding of tolbutamide and cefazolin sodium in ARF rats was significantly decreased in ARF rats.

The plasma concentration-time profiles under the non-PD condition in normal and ARF rats are summarized in Figure 2. The inductive parameters calculated by each plasma concentration-time profile are summarized in Table 2. The deductive pharmacokinetic parameters characterizing the pharmacokinetics of drugs under PD conditions were then calculated according to the PD-PK model (Fig. 1) and the related equation (Eq. 2). The deductive parameters in normal and ARF rats are summarized in Table 3.

Concentration-time profiles in plasma and abdominal fluid are predicted by the dedPD-PK model applying these deductive parameters. As the relative osmotic ratio of the introduced peritoneal dialysate to the plasma was approximately 1.2,20) the apparent solvent movement factor, F, defined in Eq. 3 was considered to be between 1.0 and 1.2. In the predicted profiles shown in Figures 3–5, two simulation lines generated by applying the F values as 1.0 and 1.2 are presented as a solid line and a dotted line, respectively. However, the effect of solvent movement, which might be generated by the introduced hypertonic peritoneal dialysate, on the pharmacokinetics of drugs was insignificant.

Discussion

In accord with the progression of renal dysfunction, several unusual metabolites, so-called uremic toxins, indoxyl sulfate, indole-3-acetic acid, hippuric acid, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) and so on, are accumulated in the body.23) Inhibition of the plasma protein binding of drugs has been argued against increased uremic toxins in plasma in renal dysfunction24,25) Displacement of drug molecules from their binding site on albumin by increased uremic toxins in plasma is the most convincing explanation of this phenomenon.

Table 1. Plasma protein binding (fub) of model drugs in Normal and ARF rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal rats</th>
<th>ARF rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide (TB)</td>
<td>0.933 ± 0.004</td>
<td>0.857 ± 0.048*</td>
</tr>
<tr>
<td>Propranolol (PPL)</td>
<td>0.876 ± 0.018</td>
<td>0.830 ± 0.085</td>
</tr>
<tr>
<td>Cefazolin (CEZ)</td>
<td>0.891 ± 0.010</td>
<td>0.780 ± 0.107*</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± S.D. of 3–6 experiments. *p < 0.05; compared with Normal rats.

Table 2. Inductive pharmacokinetic parameters of TB, PPL and CEZ based on 2-compartment model after i.v. bolus injection under non-PD conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TB (10 mg/kg)</th>
<th>PPL (2 mg/kg)</th>
<th>CEZ (5 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (µg/mL)</td>
<td>Normal rats</td>
<td>ARF rats</td>
<td>Normal rats</td>
</tr>
<tr>
<td>B (µg/mL)</td>
<td>43.4</td>
<td>27.3</td>
<td>0.454</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>1.02</td>
<td>1.25</td>
<td>7.26</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>6.82 × 10⁻³</td>
<td>1.03 × 10⁻²</td>
<td>0.78</td>
</tr>
<tr>
<td>k12 (h⁻¹)</td>
<td>5.86 × 10⁻¹</td>
<td>7.86 × 10⁻¹</td>
<td>3.12</td>
</tr>
<tr>
<td>k21 (h⁻¹)</td>
<td>4.28 × 10⁻¹</td>
<td>4.50 × 10⁻¹</td>
<td>3.06</td>
</tr>
<tr>
<td>k4 (h⁻¹)</td>
<td>1.63 × 10⁻²</td>
<td>2.87 × 10⁻²</td>
<td>1.80</td>
</tr>
<tr>
<td>V1 (L/kg)</td>
<td>0.096</td>
<td>0.129</td>
<td>2.21</td>
</tr>
<tr>
<td>V2 (L/kg)</td>
<td>0.131</td>
<td>0.226</td>
<td>2.34</td>
</tr>
</tbody>
</table>

Doses of the drugs are presented in parentheses.

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As shown in Table 1, plasma protein binding of the three model drugs decreased in ARF rats. Tolbutamide binds primarily to site I (warfarin site) on human serum albumin. There is no significant species difference in site I on serum albumin in humans and rats. It was reported that the plasma CMPF concentration correlated to BUN in renal dysfunction patients. As CMPF also bound to site I, competitive inhibition of the protein binding of tolbutamide to this site by accumulated uremic toxins in ARF rats is expected. Increase of the plasma unbound fraction of propranolol has been reported in renal failure patients. However, propranolol is reported not to bind to site I or site II on human serum albumin. The binding site of propranolol is assumed to be another site on human serum albumin. Cefazolin binds to the bilirubin site on human serum albumin. As several uremic toxins, including CMPF, bind to this site, competitive inhibition of protein binding at this site between cefazolin and uremic toxins probably occurred.

Thus, the accumulation of uremic toxins in patients with renal failure will cause changes in the pharmacokinetics of drugs in individual patients. In addition, the pharmacokinetics of drugs varies more in renal failure patients undergoing PD. If the concentration-time profiles of drugs under PD conditions could be

Table 3. Calculated deductive pharmacokinetic parameters for simulation by PD-PK model under PD conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal rats</th>
<th>ARF rats</th>
<th>Normal rats</th>
<th>ARF rats</th>
<th>Normal rats</th>
<th>ARF rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P$ (µg/mL)</td>
<td>62.5</td>
<td>51.2</td>
<td>0.85</td>
<td>0.48</td>
<td>55.4</td>
<td>68.6</td>
</tr>
<tr>
<td>$Q$ (µg/mL)</td>
<td>42.1</td>
<td>26.1</td>
<td>0.28</td>
<td>0.16</td>
<td>20.6</td>
<td>31.3</td>
</tr>
<tr>
<td>$\gamma$ (h$^{-1}$)</td>
<td>1.00</td>
<td>1.22</td>
<td>1.68</td>
<td>2.12</td>
<td>1.84</td>
<td>3.47</td>
</tr>
<tr>
<td>$\delta$ (h$^{-1}$)</td>
<td>$6.62 \times 10^{-3}$</td>
<td>$9.85 \times 10^{-3}$</td>
<td>0.99</td>
<td>0.35</td>
<td>$1.52 \times 10^{-1}$</td>
<td>$3.82 \times 10^{-2}$</td>
</tr>
<tr>
<td>$k_{21PD}$ (h$^{-1}$)</td>
<td>$4.08 \times 10^{-1}$</td>
<td>$4.20 \times 10^{-1}$</td>
<td>2.98</td>
<td>0.64</td>
<td>$9.05 \times 10^{-1}$</td>
<td>1.42</td>
</tr>
<tr>
<td>$V_{2PD}$ (L/kg)</td>
<td>0.138</td>
<td>0.243</td>
<td>2.38</td>
<td>9.45</td>
<td>0.067</td>
<td>0.080</td>
</tr>
</tbody>
</table>

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Transfer kinetics of drugs between systemic plasma and peritoneal dialysate is attributable to both the physicochemical characteristics of drugs and their biological characteristics. We have reported that the plasma concentration profile of tolbutamide, a highly protein-bound compound, in normal rats was not changed by PD, whereas that in ARF rats decreased significantly by PD. Under PD conditions, the plasma clearance of tolbutamide in ARF rats increased, whereas its concentration profile in the peritoneal dialysate of ARF rats was equivalent to that in normal rats. These findings suggest that the protein binding of drugs is the primary factor altering the plasma elimination kinetics of drugs by PD treatment.

Tolbutamide and propranolol are occasionally prescribed for peritoneal dialysis patients. As shown in Figures 3 and 4, the predicted concentration profiles of these model drugs both in plasma and peritoneal fluid by the dedPD-PK model correspond to the observed profile under PD conditions in both normal and ARF rats. On the other hand, the prediction accuracy of the dedPD-PK model for cefazolin (Fig. 5) was inferior to those for tolbutamide and propranolol. It is well known that organic anion transporters (OATs) expressed on the basolateral membrane of the proximal tubules of the kidneys play a major role in the renal clearance of both endogenous and exogenous anionic substances. Dysfunctional regulation of mRNA levels of OATs in renal failures was investigated, the less accurate prediction of cefazolin, especially in peritoneal fluid, in the dedPD-PK model would be related in part to the dysfunctional regulation of the expression of OATs. Even in an experimentally induced disease-state model, the progression of renal failure differs in individual rats. To discuss the usefulness of the dedPD-PK model for predicting the peritoneal concentration of drugs exhibiting relatively small V<sub>z</sub>, cefazolin in this study, application of individual deductive parameters derived from the protein binding data obtained individually will be required.

Deterioration of the permeability function of the peritoneum during repeated PD treatment is one of the major problems in PD patients. We can introduce an additional parameter, K, in Eq. 14 as an apparent observed/predicted coefficient of peritoneal concentration as follows:

\[ C_{PD_{\text{obs}}}(t)^* = K \cdot C_{PD_{\text{pred}}}(t) = K \cdot C_{z_{\text{obs}}}(t) \cdot (1 - \Gamma_b) \]  (Eq. 15)

where \( C_{PD_{\text{obs}}}(t)^* \) represents the observed drug concentration in the peritoneal fluid in deteriorated peritoneum permeability function. Although we used 1.0 as the K value in Eq. 15 in the simulation study shown in Figures 3-5, the parameter K in Eq. 15 will be applicable as the peritoneum-function linked variables in cases that the simulated peritoneal concentration profile exhibits homothetic curve to the observed data.

The proposal of a rational dosage regimen is based on the plasma concentration-time profile predicted by a pharmacokinetic information set, a model and the parameters. Recommended dosage regimens designed by inductively estimated pharmacokinetic parameters are generally for an “average” patient. This “one size fits all” approach involves inter-patient variability, especially in renal failure patients undergoing PD.

There are a variety of modeling approaches to realize individualized medication. The physiologically based pharma-
kinetic (PBPK) model is composed of several primarily rate-determining pharmacokinetic processes of the drug in the body. Thus, PBPK modeling is also deductive PK modeling. Each component in the PBPK model is expressed usually by a well-stirred model. PBPK was considered in order to convert non-clinical data to the dose in humans. Although the PBPK model is useful for applying to preclinical fundamental research, clinical application is difficult. When parameters such as protein binding of a drug, blood flow rate in the major eliminating organ, and the tissue-to-plasma partition coefficient are meaningfully determined, the PBPK model incorporating these parameters draws a plasma concentration-time profile and profiles in several tissues effectively. The PBPK model approach is clinically helpful for understanding the pharmacokinetic changes of drugs in drug-drug interactions and for rationalization of cytoxic drug therapies.

Population pharmacokinetics (PPK) is a method that evaluates pharmacokinetic parameters quantitatively in a fictitious patient population with contributions from a huge scale clinical study, and the rational dose-regimen for individual patients is recommended by the statistical population parameters and individual one-point data. However, each PPK model uses fixed effects that depend on the attention of the developers, even when the same drug is administered for the same disease. The usefulness of PPK analysis is that prediction is available while lacking individual PK parameters.

We have proposed a new concept, deductive PK modeling, in this study. The aim of the deductive PK modeling is to obtain substantially meaningful prediction of drug concentration-time profiles in both the plasma and the peritoneal fluid. In discussing the prediction accuracy, model drugs which are occasionally administered in renal failure patients were used. Generally, these uremic toxins bind to plasma proteins. Protein binding of administered drug in ARF rats would be competitively inhibited by the accumulated uremic toxins. In the dedPD-PK model, \( V_{PD} \), a fundamental parameter describing distribution under the PD, is deductively expressed as indexed by the plasma unbound fraction of the drug, \( f_u = 1 - f_b \) (Eq. 2). Accordingly, drugs exhibiting remarkable changes in \( f_u = 1 - f_b \) in ARF rats were considered to be preferable for the model drugs to discuss the dedPD-PK model. As shown in Table 1, \( f_u \) for toltubatide, propanolol and cefazolin were 2.43, 1.37 and 2.02, respectively. Deductive PK modeling includes both the estimation of deductively modified PK parameters in the PD rats and the application of these parameters to the Non-PD PK model. As the deductive PK modeling aimed at predicting profiles from variables obtained in a small population, the deductive modification should be expressed by minimal variables. The deductively introduced modifiers in this study were the volume of distribution in the peripheral compartment, plasma protein binding, and solvent movement factor to the peritoneal fluid. However, the effect of solvent movement generated by the introduced hypertonic peritoneal dialysate on the pharmacokinetics of drugs was insignificant.

In this study, we applied the dedPD-PK model under PD conditions in which the infused peritoneal dialysate was not replaced during the experiment. In PD patients, dialysate exchange was repeated once daily or more frequently, and drug administration was also repeated in parallel. Modification of the present dedPD-PK model to such repeated replacement will match the clinical needs more closely. We can add other pathological parameters of individual patients, such as serum creatinine and body weight, which represent renal function and an index for the distribution volume, respectively, together with individual protein binding data to improve the prediction accuracy.

The complications of renal failure are various. A variety of therapeutics administered to patients undergoing PD. As pharmacokinetic information about drugs in patients undergoing PD is limited, medical staff have no efficient tools to alter therapeutic efficacy in PD patients. In addition, in the case of emergent drug intoxication, the dedPD-PK model approach will be a valuable tool for predicting rational intoxication even in normal renal-function patients. The prediction of drug concentration profiles in plasma and peritoneal fluid of individual PD patients from the profiles of renal failure patients not undergoing PD will be meaningful for clinical demand. Our present finding that the dedPD-PK model approach provides effective prediction of PK changes in both ARF and normal rats undergoing PD will lead to successive studies.

References