Quantitative Evaluation of Effect of Renal Failure on the Pharmacokinetics of Panipenem in Rats

Naoyuki TAJIMA,*a Masako SOMA,b Hitoshi ISHIZUKA,a and Hideo NAGANUMAb

a Clinical Pharmacology and Biostatistics Department, Sankyo Co., Ltd.; and b Drug Metabolism and Pharmacokinetics Research Laboratories, Sankyo Co., Ltd.; 1–2–58, Hiromachi, Shinagawa-ku, Tokyo 140–8710, Japan.

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The pharmacokinetics of panipenem in experimental renal failure animal models was investigated in order to identify the appropriate covariates affecting the pharmacokinetic behavior. Panipenem and betamipron were administered intravenously to rats with a variety of renal failures, such as nephritis induced by glycerol, gentamicin, uranium and antisera against glomerular basement membrane as well as 5/6 subtotal nephrectomy. Panipenem in plasma and urine was determined and pharmacokinetic analysis was performed using a one-compartment open model. The elimination half-life prolonged and total body clearance, renal clearance ($CL_R$) and renal excretion ratio were decreased according to the renal function, i.e., control > glycerol > anti-GBM = gentamicin > nephrectomy = uranium in order. However, distribution volume was consistent in all models. $CL_R$ showed strong positive correlation with the glomerular filtration rate in spite of a weak correlation with the reciprocal of blood urea nitrogen. However, no obvious correlation was observed with secretory clearance of N-1-methylnicotinamide. This preliminary information based on animal model might be useful for designing pharmacokinetic studies in special population at early stage of new drug development.

Key words panipenem; pharmacokinetics; renal failure; experimental animal model; rat

Panipenem is a parenteral carbapenem antibiotic agent which has a broad antibacterial spectrum against Gram-positive and Gram-negative bacteria.1,2) In healthy volunteers, 30% of the panipenem administered was excreted in urine as an unchanged form.3,4) On the other hand, in the patients with severe renal malfunction (creatinine clearance < 30 ml/min), AUC and elimination half-life were tripped compared with normal subjects.5,6) Betamipron, 3-benzoylamino-3-propionic acid, is formulated with panipenem in order to reduce the risk of nephrotoxicity of panipenem. The action mechanism of betamipron has so far been elucidated through a series of non-clinical experiments to be one of specific inhibitors of organic anion transporters.7—9) Previous clinical and non-clinical studies proved betamipron was low toxic and had not influenced pharmacokinetic of panipenem.3,10,11)

Although carbapenems are generally well tolerated, typical adverse events including gastrointestinal disturbances and convulsions due to inhibition of the GABA receptor are occasionally reported.12—14) Therefore, for the patients with renal malfunction suspecting higher systemic exposure, an appropriate optimization of individual dose regimen might be effective to prevent these adverse events. Generally population pharmacokinetic approach provides a useful solution to find out several key covariates, i.e., individual demography and endogenous laboratory parameters, which predominate pharmacokinetic property of the drugs interest. Prior to this statistical approach in human, the definite pharmacokinetic properties in the experimentally disease animals are also informative to forecast the significant covariates and their relative contribution.

In our previous study, the elimination of panipenem was predominately occurred from the glomerular route, and renal tubular secretion in part.15) Therefore the glomerular filtration rate ($GFR$), blood urea nitrogen (BUN) and secretory clearance of N-1-methylnicotinamide ($CL_{sec,NMN}$); later two are practical indices of the renal tubal secretion,16,17) might be permissible candidate for covariates, however it still remains unclear under nephritic state because of heterogenetic characteristics of kidney.

The aim of this study was to investigate the pharmacokinetics of panipenem in various kinds of experimental renal failure animals in order to find the biochemical covariates, which describe the alteration of pharmacokinetics of panipenem appropriately.

MATERIALS AND METHODS

Chemicals Panipenem was synthesized at Sankyo Co., Ltd. Betamipron and N-1-methylnicotinamide (NMN) chloride were purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan) and Sigma-Aldrich Corporation (St. Louis, MO, U.S.A.), respectively. All other reagents used were of guaranteed reagent grade or HPLC grade (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Animals Wistar-Imamichi rats weighing 200—300 g were obtained from the Institute for Animal Reproduction (Ibaraki, Japan). Before the experiments, the rats were housed in a temperature- and humidity-controlled room with free access to water and standard chow. Rats were handled in accordance with the Guidance of the Ethics Review Committee for Animal Experimentation of Sankyo Co., Ltd.

Pharmacokinetic Study Glycol-induced nephritic rats were used for experiments a day after an intraperitoneal injection of 5 ml/kg of 50% glycerol.18) Gentamicin-induced nephritic rats were used a day after seven intraperitoneal injections of 100 mg/kg/d of gentamicin.18) Uranium-induced nephritic rats were used a day after an intravenous injection of 5 mg/kg of uranyl nitrate.18) Anti-glomerular basement membrane (anti-GBM) nephritic rats were used a week after intravenous injection of 5 ml/kg of rabbit antisera against rat glomerular basement membrane.19) Nephrectomized rats were prepared by surgically removing entire right kidney and following deletion of 2/3 of left branch. The animals were used two weeks after surgery.20)
The animals were catheterized with polyethylene tubing at the left jugular artery, vein and urinary bladder, under light ether anesthesia. After recovery from anesthesia, panipenem and betamipron at 50 mg/kg each were administered intravenously. NMN chloride was simultaneously administered at a dose of 8 mg/kg. Inulin was administered at a loading dose of 10 mg/kg and followed by a constant rate infusion at 0.3 mg/min to determine GFR. Mannitol was also administered to maintain a sufficient and constant urine flow at a constant rate of 3 mg/min during experiment. Blood was collected at pre-dosing, 5, 15, 25, 35, 45, 55, 65 and 80 min after dosing and plasma was obtained by centrifugation. Urine was periodically collected until 90 min. An aliquot of 3-(N-morpholino)propanesulfonic acid (MOPS) buffer was added to plasma and urine as a stabilizer of panipenem.

Analytical Methods Panipenem in plasma and urine was determined by the HPLC-UV method.\(^{21}\) The quantification range was between 0.2 and 50 mg/ml and the intra-assay precisions were within 3.5%. NMN was assayed by fluorometry, and BUN and inulin was assayed spectrophotometrically.\(^{22,23}\)

Pharmacokinetic Analysis The pharmacokinetic parameters were obtained by one-compartment open model parameterized by the distribution volume (V) and clearance (CL) with fitting of the plasma concentrations using WinNonlin (version 4.1, Pharsight Corporation, Mountain View, CA, U.S.A.). Renal excretion ratio (Xi) was obtained from urinary concentration and volume, and renal clearance (CLR) was calculated by multiplying CL and Xi.

CLsec,NMN was calculated by subtracting GFR from renal clearance of NMN, which was obtained from AUC and renal excretion ratio of NMN.

Statistical Analysis All data are expressed as means± standard deviations. The differences between the control and renal failure model animals were analyzed by an unpaired t-test.

RESULTS

The biochemical parameters of experimental renal failure rats are shown in Table 1. The GFR of all renal failure models was significantly reduced while the BUN was significantly increased except for anti-GBM nephritis rats. Although the orders for BUN and GFR were different in a part, the renal function was arbitrarily classified into four groups; control group, slight renal failure group including glycerol-induced nephritis, moderate renal failure group including gentamicin-induced and anti-GBM nephritis, and severe renal failure group including uranium-induced nephritis and nephrectomized models. The secretory clearance of NMN (CLsec,NMN) was also reduced according to this order.

The pharmacokinetic parameters of panipenem are shown in Table 2. The AUC and t_{1/2} increased contrary to decrease of CL, CLR, and Xi as a function of biochemical parameters. However, V was almost consistent in all models. The relationships of CLR to GFR, a reciprocal of BUN (1/BUN) and CLsec,NMN are illustrated in Fig. 1. CLR showed a strong positive correlation with the GFR in spite of a weak correlation with 1/BUN. However, no obvious correlation was observed between CLR and CLsec,NMN.

DISCUSSION

An investigation of the relationship between renal function and excretory mechanism of the cationic drugs such as tetrothylammonium and N-acetylprocainamide using NMN as an endogenous marker has been reported.\(^{16,17}\) However, no one has reported whether the CLR of NMN could also be applied as a covariate for peptides or zwiterionic drugs such as panipenem. In order to find out appropriate covariates for panipenem, we first examined the influence of renal function on the pharmacokinetics of panipenem using five animal models with different degrees of experimentally induced renal failure in either or both glomerular filtration and tubular secretion. A concomitant administration of betamipron, an organic anion transport inhibitor, would not affect on the renal function such as the CLR of NMN because NMN is a cationic compound. Thus, we explored the possibility as a covariate based on correlation analysis.

### Table 1. Biochemical Parameters Related to Renal Function and Secretory Clearance of N-1-Methylnicotinamide (CLsec,NMN) in Experimental Renal Failure Rats

<table>
<thead>
<tr>
<th>Renal failure</th>
<th>n</th>
<th>GFR (ml/min/kg)</th>
<th>BUN (mg/dl)</th>
<th>CLsec,NMN (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5</td>
<td>8.15±1.56</td>
<td>25.1±6.3</td>
<td>97.1±43.9</td>
</tr>
<tr>
<td>Glycerol</td>
<td>6</td>
<td>5.08±2.17</td>
<td>32.4±12.8*</td>
<td>87.5±34.2</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5</td>
<td>2.96±1.44</td>
<td>56.9±32.8*</td>
<td>59.1±12.3*</td>
</tr>
<tr>
<td>Anti-GBM</td>
<td>4</td>
<td>3.27±0.97</td>
<td>31.0±9.05</td>
<td>68.3±6.4*</td>
</tr>
<tr>
<td>Uranium</td>
<td>4</td>
<td>0.23±0.20</td>
<td>147.0±33.7*</td>
<td>25.3±7.0*</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>5</td>
<td>0.96±0.87</td>
<td>103.2±42.6*</td>
<td>18.8±5.6*</td>
</tr>
</tbody>
</table>

Control: normal Wistar-Iamamichi rats, glycerol: glycerol-induced nephritis rats subcutaneously administered 5 ml of 50% glycerol, gentamicin: gentamicin-induced nephritis rats subcutaneously administered 100 mg of gentamicin, anti-GBM: nephritis rats induced by intravenous administration of rabbit antiserum to glomerular basement membrane, uranium: uranium-induced nephritis rats intravenously administered 5 mg of uranium nitrate, nephrectomy: nephritis rats surgically removed 5/6 parts of kidney. CLsec,NMN was calculated by subtracting GFR from renal clearance of NMN. Data represent mean±S.D. of each model, and values significantly different from control represent * (p<0.05) and ** (p<0.01).

### Table 2. Pharmacokinetic Parameters of Panipenem after Intravenous Administration in Experimental Renal Failure Rats

<table>
<thead>
<tr>
<th>Renal failure</th>
<th>CL (ml/min)</th>
<th>V (ml)</th>
<th>AUC (mg·h/ml)</th>
<th>t_{1/2} (min)</th>
<th>Xi (%)</th>
<th>CLR (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>41.6±16.82</td>
<td>291.5±107.1</td>
<td>22.47±7.79</td>
<td>4.9±1.0</td>
<td>36.0±8.0</td>
<td>13.96±2.46</td>
</tr>
<tr>
<td>Glycerol</td>
<td>36.7±3.37</td>
<td>310.9±36.0</td>
<td>22.84±2.18</td>
<td>5.9±0.5</td>
<td>16.3±10.4</td>
<td>6.25±4.33</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>25.92±5.94</td>
<td>251.3±35.2</td>
<td>33.85±9.43</td>
<td>7.1±2.6</td>
<td>12.9±9.0</td>
<td>3.58±2.81</td>
</tr>
<tr>
<td>Anti-GBM</td>
<td>27.74±2.58</td>
<td>386.3±95.0</td>
<td>30.23±2.73</td>
<td>9.6±1.6</td>
<td>6.3±2.3</td>
<td>1.75±0.68</td>
</tr>
<tr>
<td>Uranium nitrate</td>
<td>13.52±3.32</td>
<td>195.4±18.8</td>
<td>65.09±18.94</td>
<td>10.7±3.8</td>
<td>0.9±1.0</td>
<td>0.15±0.16</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>17.17±4.71</td>
<td>250.5±9.9</td>
<td>51.83±15.30</td>
<td>10.8±3.1</td>
<td>7.4±2.4</td>
<td>1.38±1.00</td>
</tr>
</tbody>
</table>

Panipenem and betamipron of 50 mg/kg each were each administered intravenously to control, gentamicin-induced nephritis, glycerol-induced nephritis, anti-GBM nephritis, uranium-induced nephritis, and 5/6 nephrectomized rats. Data represent mean±S.D. of each model (n=4—6).
Acute renal failure models were the most convenient and reliable, as short-term treatments with some chemical substances or antibodies against renal cortical tissue to normal animals could stably induce renal dysfunctions with different pathophysiological property.\(^{9\)}} \(\text{GFR}\) was significantly reduced while BUN was consistent in anti-GBM nephritis rats because the glomerulus might be selectively damaged by the antibody.\(^{10\)}} Although the surgically nephrectomized model might not seem clinical reality, it has been favorably used as chronic model of renal hypertension.\(^{11\)}} These five acute models suggested to range widely enough to investigate the influence of renal function on the pharmacokinetics of panipenem and imply the clinical relevant nephritis.

As shown in Table 2, \(CL\) and \(CL_R\) were altered correspondingy, therefore, \(CL_R\) was considered to be most sensitively influenced by renal function.

The slope of the regression line directly reflecting the clearance ratio of \(CL_R\) of panipenem to \(GFR\) was 1.45, indicating that panipenem would be mainly excreted by glomerular filtration and tubular secretion in part. This clearance ratio coincided well with the observations found in vivo clearance study using normal rabbits.\(^{13\)}}

In our previous investigation regarding population pharmacokinetics of panipenem, the creatinine clearance of patients, a reliable alternate of \(GFR\), was one of the significant covariates to determine its pharmacokinetics.\(^{14\)}} This suggests that an investigation using various kinds of renal failure animal models and subsequent covariate analysis would be available as prior information to build a population pharmacokinetic model of renal excretory drugs like panipenem in human.

In conclusion, the renal clearance of panipenem was correlated with the \(GFR\) in the renal failure models of rats and the \(GFR\) was an appropriate index of renal function to describe pharmacokinetics of panipenem.

REFERENCES


