A NOVEL METHOD TO PREDICT THE ELIMINATION HALF-LIVES AND THE RENAL EXCRETION MECHANISMS OF CEPHALOSPORINS

IZUMI KOMIYA, MOTOHIRO NISHIO, SHINJIRO MURATA,* FUMIKO CHIBA, TAKASHI SAKURAI, SACHIHIKO SHINKAI AND MASATAKA FUJITA**

Pharmacology and Toxicology Laboratories, Meiji Seika Kaisha, Ltd.,* Morooka-cho, Kohoku-ku, Yokohama, 222, Japan and Pharmaceutical Development Laboratories, Meiji Seika Kaisha, Ltd.,** Horikawa-cho, Saiwai-ku, Kawasaki, 210, Japan

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A novel method was proposed to predict the elimination half-lives of cephalosporins from plasma protein binding (unbound fraction, f) and fraction of the dose excreted into urine (f*) on the basis of the following four assumptions. 1) The drug is only distributed to the extracellular fluid, 2) the bound fraction of the drug in plasma is independent of the plasma drug concentration, 3) the binding protein of the drug is albumin, 4) the unbound drug in plasma is excreted by the glomerular filtration and the contribution of active secretion and reabsorption is negligible.

The V_{SS}'s and t_{1/2}s of MT-141, one of cephalosporins, in rabbits, dogs and healthy human subjects were well predicted, whereas in rats, the prediction of the both values was failed. The t_{1/2}'s of various cephalosporins in healthy subjects were calculated from f and f*, in reasonably good agreement with the observed ones, except for some cephalosporins which have been reported to be secreted actively in the renal tubules. Thus, the comparison of the calculated t_{1/2}'s with the observed ones makes it possible to presume the renal excretion mechanism. Moreover, this method will be applicable to other drugs which satisfy the above four assumptions.

Keywords — cephalosporin; elimination half-life; distribution volume; renal excretion mechanism; glomerular filtration rate; protein binding

INTRODUCTION

The correlutive relationship between pharmacokinetic parameters such as serum clearance and volume of distribution with body weight over a wide range of animal species has made it possible to extrapolate animal pharmacokinetic data to humans.1 The correlation of physiological properties such as organ weights, renal function and hepatic function has also been used to develop interspecies correlations of drug pharmacokinetics.1 Furthermore, interspecies scalability and the precise prediction of drug distribution in specific organs have been possible on the basis of the physiologically based pharmacokinetics.2,3 Biological half-lives of cephalosporins including MT-141 (Fig. 1), a novel cephamycin, vary remarkably from one animal species to others.4-7 Moreover, when compared within one species, they are different among the antibiotics.4-7 The major factors to determine the pharmacokinetics of cephalosporins are 1) the binding to the plasma protein, 2) the ratios of renal clearance and hepatic clearance (metabolism

![Chemical Structure of MT-141](attachment:image.png)

FIG. 1. Chemical Structure of MT-141
and/or biliary excretion) to the total body clearance and 3) the renal excretion mechanism
(whether tubular secretion or reabsorption exists or not).

Recently Niewoehner and Tozer put forth an equation concerning the apparent volume of distribution, where the effect of the linear plasma protein binding of drugs was incorporated. McNamara, et al. also developed the similar equation, which is applicable to the nonlinear plasma protein binding.

In this study, Niewoehner’s equation is further developed and a novel method is proposed to predict the elimination half-lives of cephalosporins quantitatively from in vitro plasma protein binding data and the cumulative urinary excretion data. Furthermore, the assumption of the renal excretion mechanism is possible, when the half-lives predicted by our method is compared with the experimental values.

THEORETICAL

According to Niewoehner and Tozer, the apparent volume of distribution is expressed by Eq. 1, when a drug is only distributed to the extracellular fluid and cannot enter the cells.

\[ V_{SS} = V_p (1 + R_{E/I}) + f V_p \left( V_e / V_p - R_{E/I} \right) \]  

\[ V_{SS} \text{: apparent volume of distribution at steady state} \]
\[ V_p \text{: plasma volume} \]
\[ V_e \text{: extracellular space minus plasma volume} \]
\[ R_{E/I} \text{: ratio of the total number of binding sites or the amount of protein in extracellular fluids outside the plasma to that in the plasma} \]
\[ f \text{: unbound fraction in plasma} \]

When the plasma proteins to which the drug binds are assumed to be albumin itself or to be distributed like albumin, \( R_{E/I} \) in man is estimated to be about 1.4. Furthermore, \( V_p \) and \( V_e \) in man are 0.043 and 0.171 l/kg, respectively. With these normal values, Eq. 1 becomes:

\[ V_{SS} = 0.103 + 0.111 f \]  

The unit of \( V_{SS} \) in Eq. 2 is l/kg.

The relationship between the total body clearance, \( C_{l_{tot}} \), and the renal clearance, \( C_{l_r} \), of the drug can be expressed by Eq. 3.

\[ C_{l_r} = f^* \cdot C_{l_{tot}} \]  

where \( f^* \) is the fraction of dose excreted into urine until infinite time after the administration.

When the two-compartment open model is considered to the serum or plasma concentration versus time curves, the total body clearance is expressed as:

\[ C_{l_{tot}} = \beta \cdot V_{d\beta} \]  

where \( \beta \): hybrid rate constant at pseudo-distribution equilibrium (\( \beta \)-phase)  
\[ V_{d\beta} \text{: apparent volume of distribution at} \ \beta \text{-phase} \]

When the unbound drug in plasma is excreted by the glomerular filtration and the contribution of the active secretion and the reabsorption in the renal tubules is negligible, Eq. 5 expresses the relation of the renal clearance of the drug to the glomerular filtration rate, GFR.

\[ C_{l_r} = f \cdot GFR \]  

From Eqs. 3, 4 and 5, the elimination half-life, \( t_{1/2\beta} \), can be calculated by Eq. 6.

\[ t_{1/2\beta} = \frac{0.693 \cdot f^* \cdot V_{d\beta}}{f \cdot GFR} \]  

Although \( V_{d\beta} \) is greater than \( V_{SS} \) theoretically, the difference between the two volumes of distribution is small. Hence, instead of \( V_{d\beta} \) in Eq. 6, \( V_{SS} \) in Eq. 2 is replaced, then Eq. 6 gives:

\[ t_{1/2\beta} = \frac{0.693 \cdot f^* (0.103 + 0.111 f)}{f \cdot GFR} \]  

By Eq. 7, the elimination half-life of the drug, \( t_{1/2\beta} \) in an hour, is obtained from in vitro plasma protein binding \( f \), renal excretion ratio \( f^* \) and glomerular filtration rate \( GFR \) in l/h/kg. Assumptions used in Eq. 7 are as follows: (1) A drug is only distributed to the extracellular fluid and cannot enter the cells. (2) The binding protein of a drug is mainly albumin, or the binding protein is distributed like albumin. (3) The unbound fraction of a drug in plasma is independent of plasma drug concentration. (4) The unbound drug in plasma is excreted by the glomerular filtration and the contribution of active secretion and reabsorption is negligible.
MATERIALS AND METHODS

Drugs — MT-141 produced by Meiji Seika Kaisha, Ltd. was used. Other reagents were of analytical grade.

Animals — Male Sprague-Dawley rats weighing 270—370 g, male and female albino rabbits weighing 3.0—4.2 kg and female beagle dogs weighing 9.5—12.5 kg were used.

Administration Methods — MT-141 was dissolved in normal saline for injection. One ml of MT-141 solution per kg was injected into the femoral vein of rats and 0.4 ml per kg was injected within 10—15 s into the ear vein of rabbits or the cutaneous vein of forearm of dogs.

Methods for Collection of Blood, Urine and Bile Specimens — In the rat experiments, the blood samples were collected through a polyethylene cannula (PE-50) implanted into the right femoral artery. The urine and bile samples were collected through polyethylene cannulae implanted into the bladder (PE-100 with PE-200) and the bile duct (PE-50), respectively. The surgery for the cannulation was carried out under anesthesia by pentobarbital (40 mg/kg). In the rabbit and dog experiments, the blood samples were collected from the ear artery of rabbits or from the cutaneous vein of forearm of dogs. The urine samples were collected through a rubber catheter from rabbits and through a metallic catheter from dogs. The bile samples of rabbits and dogs were collected through polyethylene cannulae implanted into the bile duct under pentobarbital anesthesia. The plasma, urine and bile samples from rats were adequately diluted with distilled water and were determined by high performance liquid chromatography (HPLC) method. The serum, urine and bile samples from rabbits and dogs were adequately diluted with 0.05 M phosphate buffer (pH 7.0) and were determined by bioassay method.

In Vivo Serum Protein Binding in Human — The blood samples were taken at appropriate time after the bolus intravenous injection or intravenous constant infusion of MT-141 of 1 or 2 g/man to healthy subjects. Serum was obtained and the concentration of MT-141 in the serum was determined by HPLC method. The serum was subjected to centrifugal ultrafiltration using Centriflo® CF 25 (Amicon Corp., U.S.A.). The MT-141 concentration in the filtrate was determined by HPLC method. The free fraction was expressed as the ratio of the MT-141 concentration in the filtrate to that in the serum. Although the nonspecific adsorption of the drug to the membrane was small (1—3%), the correction for the nonspecific adsorption was made.

In Vitro Serum Protein Binding — Consena® (Nissui) was used as human serum. Other sera were obtained from rats, rabbits and dogs. Serum protein binding was measured with the same method as in vivo protein binding.

Analytical Method — Bioassay: The concentrations of MT-141 in the diluted serum, urine and bile samples from rabbits and dogs were assayed by a cup method, using Vibrio percolans ATCC 8461 as the test organism. The accuracy of the microbiological assay was ±5%.

HPLC: The concentrations of MT-141 in the diluted plasma or serum from rats and humans were determined using solvent I after the precipitation of proteins in the samples with 6% trichlooroacetic acid. Trimellitic acid was used as an internal standard for the determination of MT-141 concentration in serum or plasma. The concentrations of MT-141 in the diluted urine and bile from rats and humans were determined using solvent II and III, respectively. The accuracy of the HPLC assay was ±1%. The HPLC conditions were as follows:

Separation column: TSK-gel ODS-120A, 5 μm (TOYOSSODA), 4 i.d. x 250 mm, pre-column: TSK-gel ODS-120A, 5 μm, 4 i.d. x 50 mm, flow rate: 1 ml/min, detection: 270 nm, mobile phase: solvent I: 2% CH₃COOH : CH₃OH : CH₃CN = 92 : 5 : 3, solvent II: 2% CH₃COOH : CH₃OH : CH₃CN = 98 : 1 : 1, solvent III: 2% CH₃COOH : CH₃OH : CH₃CN = 90 : 7 : 3.

Pharmacokinetic Analysis — A two-compartment open model where elimination occurs from the central compartment was used to describe the serum or plasma concentration-time
curves. The pharmacokinetic parameters of the model were obtained by a nonlinear regression using Gauss–Newton method. The same weighting values were used for the nonlinear regression.

RESULTS

Figures 2 and 3 represent the serum or plasma levels of MT-141 after the bolus intravenous ad-

![Graph of Plasma Level of MT-141 over time](image1)

**FIG. 2.** Plasma Level of MT-141 after Bolus Intravenous Administration of 40 mg/kg of MT-141 in Rats

Values represent the mean ± standard deviation (n=6).

![Graph of Serum Level of MT-141 over time](image2)

**FIG. 3.** Serum Level of MT-141 after Bolus Intravenous Administration of 20 mg/kg of MT-141 in Rabbits and Dogs

▲: rabbit (n=3), □: dog (n=6).

Values represent the mean ± standard deviation.

<table>
<thead>
<tr>
<th>Animal species</th>
<th>$\alpha$ (h$^{-1}$)</th>
<th>$\beta$ (h$^{-1}$)</th>
<th>$V_1$ (l/kg)</th>
<th>$V_2$ (l/kg)</th>
<th>$V_{ss}$ (l/kg)</th>
<th>$Cl_{tot}$ (l/h/kg)</th>
<th>$t_{1/2\beta}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (n=6)</td>
<td>16.4</td>
<td>1.57</td>
<td>0.147</td>
<td>0.144</td>
<td>0.291</td>
<td>0.520</td>
<td>0.454</td>
</tr>
<tr>
<td></td>
<td>± 6.18</td>
<td>±0.278</td>
<td>±0.0376</td>
<td>±0.00922</td>
<td>±0.0423</td>
<td>±0.0461</td>
<td>±0.0820</td>
</tr>
<tr>
<td>Rabbit (n=3)</td>
<td>15.5</td>
<td>1.33</td>
<td>0.135</td>
<td>0.0325</td>
<td>0.167</td>
<td>0.224</td>
<td>0.541</td>
</tr>
<tr>
<td></td>
<td>± 2.39</td>
<td>±0.317</td>
<td>±0.0269</td>
<td>±0.0120</td>
<td>±0.0209</td>
<td>±0.0300</td>
<td>±0.119</td>
</tr>
<tr>
<td>Dog (n=6)</td>
<td>8.78</td>
<td>1.06</td>
<td>0.125</td>
<td>0.0786</td>
<td>0.201</td>
<td>0.244</td>
<td>0.665</td>
</tr>
<tr>
<td></td>
<td>± 5.46</td>
<td>±0.148</td>
<td>±0.0236</td>
<td>±0.00581</td>
<td>±0.0242</td>
<td>±0.0106</td>
<td>±0.0801</td>
</tr>
</tbody>
</table>

Mean ± S.D.

TABLE I. Pharmacokinetic Parameters of MT-141 in Rats (40 mg/kg), Rabbits (20 mg/kg) and Dogs (20 mg/kg) after Bolus Intravenous Administration of MT-141
ministration in rats (40 mg/kg), rabbits (20 mg/kg) and dogs (20 mg/kg). These concentration-time curves were well expressed by biexponential equations. The pharmacokinetic parameters according to the two-compartment model are shown in Table I. The total body clearances (Cl\text{tot}) and the volumes of distribution at steady state (V\text{SS}) were 0.520 l/h/kg, 0.291 l/kg in rats, 0.224 l/h/kg, 0.167 l/kg in rabbits and 0.244 l/h/kg, 0.201 l/kg in dogs, respectively. The elimination half-lives (t\text{1/2}\beta) in rats, rabbits and dogs were 0.454, 0.541 and 0.665 h, respectively. Figures 4 and 5 represent the urinary and biliary excretion of MT-141 after the bolus intravenous administration of MT-141 in rats (40 mg/kg), rabbits (20 mg/kg) and dogs (20 mg/kg). The urinary recoveries of MT-141 were more than 80% of the dose in rabbits and dogs, whereas only 37% of the dose was excreted in the rat urine. On the other hand, the cumulative biliary excretions of MT-141 were 9.6% of the dose in rats, 0.5% in rabbits and 1.2% in dogs.

Table II represents the in vitro serum protein binding of MT-141 in various animal species. The fraction bound of MT-141 to human serum proteins was almost constant and the value was about 0.61, when the serum concentration of MT-141 was less than 100 μg/ml. In vivo serum protein binding of MT-141 in healthy subjects after the bolus intravenous administration or constant rate infusion is shown in Table III. The fraction bound of MT-141 in healthy subjects was 0.68 on the average, being comparable with the in vitro binding data. Table III demonstrates the volumes of distribution at steady state of MT-141 calculated using Eq. 2 and those obtained by the two-compartment analysis of the serum MT-141 concentration-time curves in man. The average V\text{SS} value calculated using Eq. 2 was 0.139 l/kg and coincided with the observed one which was 0.146 l/kg. Table IV shows the prediction of V\text{SS} and t\text{1/2}\beta of MT-141 in rats, rabbits, and dogs from f/f* (Table II, Fig. 4) and GFR obtained from Adolph's equation,\textsuperscript{13} i.e. GFR in ml/h/body = 1.74 × (body weight in

**FIG. 4. Cumulative Urinary Excretion of MT-141 in Rats (40 mg/kg), Rabbits (20 mg/kg) and Dogs (20 mg/kg) after Bolus Intravenous Administration of MT-141**

●: rat (n = 8), ▲: rabbit (n = 3), □: dog (n = 6).

Values represent the mean ± standard deviation.

**FIG. 5. Cumulative Biliary Excretion of MT-141 in Rats (40 mg/kg), Rabbits (20 mg/kg) and Dogs (20 mg/kg) after Bolus Intravenous Administration of MT-141**

●: rat (n = 9), ▲: rabbit (n = 5), □: dog (n = 6).

Values represent the mean ± standard deviation.
The fractions excreted until at least 4—5 times as long as half-lives were used as \( f^* \). Both \( V_{\text{SS}} \) and \( t_{1/2\beta} \) were predicted precisely in rabbits and dogs. In rats, however, \( V_{\text{SS}} \) and \( t_{1/2\beta} \) were both underestimated, even when \( t_{1/2\beta} \) was calculated using observed \( V_{\text{SS}} \) value instead of calculated one.

The unbound fractions \( (f) \), the urinary recoveries \( (f^*) \) and the elimination half-lives \( (t'_{1/2\beta}) \) in man of various cephalosporins recently developed are listed in Table V from references.\(^{4,5,7,12,14-28}\) The elimination half-lives were calculated using Eq. 7 and \( GFR = 0.139 \) l/h/kg (based on 60 kg-man) obtained from the Adolph's equation,\(^{13}\) and are compared with the observed ones.

**TABLE II.** Serum Protein Binding of MT-141

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Drug concn. (µg/ml)</th>
<th>Percent bound (^{a)}) Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat serum</td>
<td>20</td>
<td>24.7</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>24.9 ± 0.667</td>
</tr>
<tr>
<td>Rabbit serum</td>
<td>100</td>
<td>30.9 ± 0.391</td>
</tr>
<tr>
<td>Dog serum</td>
<td>100</td>
<td>11.1 ± 2.79</td>
</tr>
<tr>
<td>4% bovine serum albumin</td>
<td>100</td>
<td>13.4 ± 0.91</td>
</tr>
<tr>
<td>Human serum</td>
<td>5</td>
<td>56.7</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>60.3</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>63.5 ± 0.535</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>47.0 ± 1.37</td>
</tr>
</tbody>
</table>

\(^{a)}\) Centrifugal ultrafiltration method.

**TABLE III.** Prediction of the Volume of Distribution \( (V_{\text{SS}}) \) of MT-141 in Healthy Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Body weight (kg)</th>
<th>( f^{a)} )</th>
<th>( V_{\text{SS}} ) (obs) ( \text{(l/kg)} )</th>
<th>( V_{\text{SS}} ) (calc) ( \text{(l/kg)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>0.359</td>
<td>0.153</td>
<td>0.143</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>0.328</td>
<td>0.144</td>
<td>0.139</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>0.305</td>
<td>0.149</td>
<td>0.137</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>0.383</td>
<td>0.175</td>
<td>0.146</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>0.336</td>
<td>0.161</td>
<td>0.140</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>0.318</td>
<td>0.167</td>
<td>0.138</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>0.253</td>
<td>0.125</td>
<td>0.131</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>0.260</td>
<td>0.121</td>
<td>0.132</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>0.264</td>
<td>0.123</td>
<td>0.132</td>
</tr>
<tr>
<td>10</td>
<td>86</td>
<td>0.348</td>
<td>0.119</td>
<td>0.142</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>0.360</td>
<td>0.137</td>
<td>0.143</td>
</tr>
<tr>
<td>12</td>
<td>76</td>
<td>0.346</td>
<td>0.177</td>
<td>0.141</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>65.9 ± 8.41</td>
<td>0.322 ± 0.0429</td>
<td>0.146 ± 0.0212</td>
<td>0.139 ± 0.00487</td>
</tr>
</tbody>
</table>

\(^{a)}\) Fraction unbound determined by centrifugal ultrafiltration method.

\(^{b)}\) Observed \( V_{\text{SS}} \) values.\(^{12}\)

\(^{c)}\) \( V_{\text{SS}} \) values calculated according to Eq. 2.
DISCUSSION

It is reported that β-lactam antibiotics usually poorly penetrate into the cells, hence the first assumption in Theoretical can be permitted in organs other than the liver and kidneys. Fisher and Jardetzky have demonstrated that penicillin G binds to serum albumin but does not bind to γ-globulin. And generally β-lactam antibiotics are considered to bind to albumin in plasma and extracellular fluid. Furthermore, the bound fraction of MT-141 to human serum was independent of concentration in the usual therapeutic or experimental concentration range (<100 μg/ml) as shown in Table II, and lata-moxef (LMOX) was also demonstrated to bind linearly to human plasma under 100 μg/ml.

TABLE IV. Prediction of the Volume of Distribution (V<sub>ss</sub>) and the Elimination Half-life (t<sub>1/2β</sub>) of MT-141 in Rats, Rabbits and Dogs

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Body weight (kg)</th>
<th>GFR&lt;sup&gt;a)&lt;/sup&gt; (l/h/kg)</th>
<th>f</th>
<th>f*</th>
<th>V&lt;sub&gt;ss&lt;/sub&gt; (obs) (l/kg)</th>
<th>V&lt;sub&gt;ss&lt;/sub&gt; (calc)&lt;sup&gt;b) &lt;/sup&gt;(l/kg)</th>
<th>t&lt;sub&gt;1/2β&lt;/sub&gt; (obs) (h)</th>
<th>t&lt;sub&gt;1/2β&lt;/sub&gt; (calc)&lt;sup&gt;c) &lt;/sup&gt;(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>0.3</td>
<td>0.469</td>
<td>0.752</td>
<td>0.367</td>
<td>0.291</td>
<td>0.186</td>
<td>0.454</td>
<td>0.134</td>
</tr>
<tr>
<td>Rabbit</td>
<td>3</td>
<td>0.276</td>
<td>0.691</td>
<td>0.962</td>
<td>0.167</td>
<td>0.180</td>
<td>0.541</td>
<td>0.629</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>0.209</td>
<td>0.889</td>
<td>0.816</td>
<td>0.201</td>
<td>0.202</td>
<td>0.665</td>
<td>0.615</td>
</tr>
</tbody>
</table>

<sup>a) Obtained from Adolph's equation.</sup><br><sup>b) V<sub>ss</sub> calculated according to Eq. 2.</sup><br><sup>c) t<sub>1/2β</sub> calculated according to Eq. 7.</sup><br><sup>d) t<sub>1/2β</sub> calculated using V<sub>ss</sub> (obs) instead of V<sub>ss</sub> (calc) in Eq. 7.</sup>

TABLE V. Prediction of the Elimination Half-life (t<sub>1/2β</sub>) of Various Cephalosporins in Healthy Subjects

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>f</th>
<th>f*</th>
<th>t&lt;sub&gt;1/2β&lt;/sub&gt; (obs) (h)</th>
<th>t&lt;sub&gt;1/2β&lt;/sub&gt; (calc)&lt;sup&gt;a) &lt;/sup&gt;(h)</th>
<th>References&lt;sup&gt;b) &lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT-141</td>
<td>0.365</td>
<td>0.920</td>
<td>2.13</td>
<td>1.80</td>
<td>12</td>
</tr>
<tr>
<td>Cefoperazone (CPZ)</td>
<td>0.132</td>
<td>0.400</td>
<td>1.40, 2.15</td>
<td>1.78</td>
<td>5, 15</td>
</tr>
<tr>
<td>Cefotetan (CTT)</td>
<td>0.090</td>
<td>0.821</td>
<td>2.92</td>
<td>5.14</td>
<td>4, 16</td>
</tr>
<tr>
<td>Latamoxef (LMOX)</td>
<td>0.400</td>
<td>0.983</td>
<td>1.92</td>
<td>1.81</td>
<td>14, 17</td>
</tr>
<tr>
<td>Cefmenoxime (CMX)</td>
<td>0.310</td>
<td>0.830</td>
<td>1.00</td>
<td>1.83</td>
<td>18</td>
</tr>
<tr>
<td>Ceftrizoxime (CZK)</td>
<td>0.690</td>
<td>0.952</td>
<td>1.48</td>
<td>1.24</td>
<td>19</td>
</tr>
<tr>
<td>Cefotaxime (CTX)</td>
<td>0.299</td>
<td>0.475</td>
<td>0.74</td>
<td>1.08</td>
<td>20</td>
</tr>
<tr>
<td>Cefsulodin (CFS)</td>
<td>0.930</td>
<td>0.750</td>
<td>1.70</td>
<td>0.83</td>
<td>21</td>
</tr>
<tr>
<td>Cefotiam (CTM)</td>
<td>0.920</td>
<td>0.750</td>
<td>0.79</td>
<td>0.83</td>
<td>22</td>
</tr>
<tr>
<td>Cefamandole (CMD)</td>
<td>0.340</td>
<td>0.967</td>
<td>0.45</td>
<td>2.00</td>
<td>23</td>
</tr>
<tr>
<td>Cefuroxime (CXM)</td>
<td>0.590</td>
<td>0.814</td>
<td>1.26</td>
<td>1.16</td>
<td>24</td>
</tr>
<tr>
<td>Cefmetazole (CMZ)</td>
<td>0.158</td>
<td>0.693</td>
<td>0.81</td>
<td>2.64</td>
<td>25</td>
</tr>
<tr>
<td>Cefpiramide (CPM)</td>
<td>0.037</td>
<td>0.252</td>
<td>4.44</td>
<td>3.64</td>
<td>7, 26</td>
</tr>
<tr>
<td>Ceftriaxone (CTR)</td>
<td>0.06</td>
<td>0.8</td>
<td>7.0—7.5</td>
<td>7.29</td>
<td>27</td>
</tr>
<tr>
<td>Cefbuperazone (CBPS)</td>
<td>0.451</td>
<td>0.768</td>
<td>1.58</td>
<td>1.30</td>
<td>28</td>
</tr>
</tbody>
</table>

<sup>a) t<sub>1/2β</sub> calculated using Eq. 7 and GFR (0.139 l/h/kg) obtained from Adolph's equation.</sup><br><sup>b) References where f, f* and t<sub>1/2β</sub> (obs) values were obtained.</sup>
Although the protein binding of cefazolin is reported to be expressed by Langmuir-type equation, the binding can be assumed to be linear when the total drug concentration is under 100 μg/ml. However ceftriaxone shows capacity-limited plasma protein binding. Accordingly, the second and third assumptions in Theoretical can be permitted with regard to cephalosporins, except for some exceptions. In fact, the values of $V_{SS}$ of MT-141 in man calculated on the basis of the first three assumptions were in good agreement with those obtained from the serum concentration-time data (Table III), and this verified the usefulness of Eq. 2. More recently, Eq. 2 and its modified equation have been demonstrated to be applicable in the case of ceftriaxone.

Some of β-lactam antibiotics have been reported to be secreted actively in the renal tubules of various animals. When the contribution of the tubular secretion is not negligible, $t_{1/2B}$ predicted on the basis of the 4th assumption will be overestimated. On the contrary, when the contribution of the tubular reabsorption is not negligible, the reverse will occur. Therefore, it will be possible to presume the contribution of the tubular secretion or the reabsorption. The accurate prediction of $V_{SS}$'s and $t_{1/2B}$'s of MT-141 in rabbits and dogs (Table IV) as well as humans (Table III, V) implies that the tubular secretion and reabsorption of MT-141 are negligible in rabbits and dogs, which was verified in our previous experiment coadministered probenecid with MT-141 in dogs. This also shows that Eqs. 2 and 7 are valid even in experimental animals. On the other hand, in rats $V_{SS}$ and $t_{1/2B}$ were both underestimated. The underestimation of $V_{SS}$ will be explained by the difference of the extracellular volume and the difference of the albumin distribution in the body i.e. $R_{El}$ in rats from other animal species and extensive distribution of MT-141 to rat kidneys. Generally the first and second assumptions in Theoretical can not be applied to the liver and kidneys even about cephalosporins. If the tissue-to-plasma ratios ($K_P$) in the liver and kidneys are large, i.e., a drug is highly distributed to the liver and kidneys, $V_{SS}$ is underestimated. Komiya, et al. suggested the possibility of the existence of the reabsorption and/or metabolism in the rat renal tubules, which may contribute toward the underestimation of $t_{1/2B}$ in rats.

In Fig. 6, $t_{1/2B}$'s calculated were plotted versus those observed. CMD and CMX, being obviously underestimated in the $t_{1/2B}$ prediction (Fig. 6), are reported to be actively secreted in humans. Yamaka, et al. suggested capacity-limited excretion of CMZ in rats, which implies the possibility of the active secretion in the tubules. On the contrary, in the case of LMOX, being well predicted in the $t_{1/2B}$ calculation, the contribution of the tubular secretion and reabsorption were negligible in rats, dogs and man. The tubular secretion would exist in the case of cefotetan and the tubular reabsorption

**FIG. 6. Comparison of Predicted and Observed $t_{1/2B}$'s of Various Cephalosporins in Healthy Subjects**

would exist in the case of cefsulodin. However, the appropriateness of the four assumptions mentioned above are not clearly certified with these two antibiotics. Moreover, since the free fractions of cefotetan, cefpiramide and ceftriaxone are small (Table V), small errors caused by methodologically or nonlinear binding are directly reflected in the error of the $t_{1/2B}$ calculation. Therefore, further studies will be needed to conclude the existence of the tubular secretion or reabsorption in the case of cefotetan and cefsulodin. Since the predicted $t_{1/2B}$ of MT-141 was agreed with the observed one, the tubular secretion and reabsorption of MT-141 in man will be negligible as well as the results in rabbits and dogs. Consequently, the renal excretion mechanism of cephalosporins can be presumed from this calculation.

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