A Saturable Tissue–Angiotensin I Converting Enzyme (ACE) Binding Model for the Pharmacokinetic Analysis of Imidapril, a New ACE Inhibitor, and Its Active Metabolite in Human

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In order to obtain a rational explanation and analytical method of the unique pharmacokinetic behaviors of imidapril and imidaprilat in human, a new pharmacokinetic model was designed by introducing a saturable-reversible angiotensin I converting enzyme (ACE)-imidaprilat binding process and a linear imidapril-imidaprilat conversion process. According to the new model, six differential equations were given which considered the mass balance of both compounds in each component. Various pharmacokinetic parameters were estimated by the simultaneous curve fitting method using the plasma concentration data and the urinary excretion data of imidapril and imidaprilat in a multiple dosing study of healthy human volunteers. To validate the value of each parameter, this pharmacokinetic model was also applied to analyze the various plasma concentration data of both compounds in the single dosing studies with four different dosages, 2.5, 5, 10, and 20 mg. Excellent curve fitting was obtained in every case, suggesting that the proposed pharmacokinetic model is applicable for predicting the plasma concentrations of imidapril and imidaprilat under various dosage conditions of clinical use.

Keywords imidapril; imidaprilat; ACE inhibitor; saturable tissue binding; nonlinear pharmacokinetics; human

Imidapril hydrochloride (imidapril), (4S)-1-methyl-3-((2S)-2-N-(1S)-1-ethoxycarbonyl-3-phenylpropyl)amino)propionyl)-2-oxo-imidazolidine-4-carboxylic acid hydrochloride, is an orally applicable angiotensin I converting enzyme (ACE) inhibitor, which has recently been developed by Tanabe Seiyaku Co.1) The chemical structures of imidapril and its active metabolite, imidaprilat, are shown in Fig. 1. In preclinical toxicity studies,2,3) it was confirmed that imidapril was well tolerated with a low incidence of adverse effects.

In previous phase I studies,4,5) it has been clarified that after oral administration, imidapril was readily biotransformed into an active metabolite, imidaprilat, which appeared gradually and declined slowly in plasma, exerting a prolonged blood pressure reducing effect by a once-a-day dosing regimen.6) Imidapril and imidaprilat have been reported to bind to human plasma protein at about 85% and 50%, respectively.7) The plasma concentration profile of imidapril was found to behave in a pharmacokinetically linear manner over a wide range of dosing in human.

However, the pharmacokinetic behavior of imidaprilat was found to be considerably different from that of imidapril, which was characterized by a prolongation of elimination half-life and a delay of the T_{max} at a lower dose. These unique pharmacokinetic behaviors of both compounds were also observed in dog9) and in rat.9)

The most likely reason for the observed nonlinear behavior of imidaprilat could be its binding ability to the ACE widely distributed in various tissues, which is intimately related to the pharmacological effect of this drug. Previously, through a series of rat studies,9) it was confirmed that imidaprilat could dominantly bind to ACE in various tissues in a saturable and reversible manner, and that prolongation of the elimination half-life of imidaprilat occurred in an inverse correlation with the binding amount of imidaprilat in the lungs. It was also reported that other ACE inhibitors exhibited specific and saturable binding to ACE in tissues.10,11)

The objectives of the present study are to obtain more detailed information on the pharmacokinetic behaviors of imidapril and imidaprilat in human and thereby to establish a rational pharmacokinetic model to analyze the pharmacokinetic behaviors of those drug compounds, which are important not only for understanding the drug property in connection with its pharmacological effect but also for developing a more reasonable dosing regimen for this new drug. In this paper, a new pharmacokinetic model was designed by introducing the saturable-reversible ACE-imidaprilat binding process on the basis of previous findings. The applicability and the rationality of the proposed pharmacokinetic model will be discussed through various test calculations.

MATERIALS AND METHODS

Data Used for Analysis The data used for this investigation were the plasma concentrations and urinary
excretions of imidapril and imidaprilat obtained from the phase I studies. In the studies, six healthy Japanese males received imidapril (2.5, 5, 10 or 20 mg) in a single administration and 10 mg once a day for 7 successive days as a multiple oral administration. Each subject voluntarily gave informed consent for the study as described in previous papers.

**Pharmacokinetic Model with Saturable Tissue-ACE Binding** The previous findings in rat studies implied that imidaprilat exists as two different forms in the body, a non-binding form and the form which binds to ACE; the observed nonlinear pharmacokinetic behavior of imidaprilat should be caused by the saturable binding to ACE in tissues obeying the Langmuir complexation mechanism. To describe the behaviors of imidapril and imidaprilat in the body, the pharmacokinetic model shown in Fig.2 was designed. This model was comprised of six compartments, including the saturable tissue-ACE binding process of imidaprilat, and was set under the following assumptions: the absorption of imidapril from the gastrointestinal tract; the bioconversion from imidapril to imidaprilat; the urinary excretion of imidapril and imidaprilat obey the first-order kinetics, and imidaprilat can rapidly bind to ACE in tissues in a saturable and reversible manner. Then, the mass balances of imidapril and imidaprilat in each process were given as the six differential equations from Eq. 1 to Eq. 6.

$$\frac{dX_1}{dt} = -k_1 \cdot X_1$$  
$$\frac{dC_i}{dt} = \frac{F \cdot k_1 \cdot X_i}{V_1} - (k_1 + k_3) \cdot C_i$$

**Analytical Method** All the pharmacokinetic parameters were estimated from the plasma concentrations and the urinary excretions of imidapril and imidaprilat after multiple dosing by the simultaneous curve fitting method. The nonlinear least squares regression program based on a simplex method, Olson’s program, was used with modification. The computations were carried out on an Apollo DN-4000 computer (Hewlett Packard, U.S.A.). The weighing condition was 1 for all calculations.

Prior to the nonlinear least squares regression, the initial value of each parameter was determined according to the following steps: $k_{11}$, $(k_3 + k_4)$ and $V_1/F$ were estimated by the curve fitting of the plasma concentration data of imidapril on the 1st day by the linear one compartment model; $k_4$ and $V_2/F$ were estimated by the curve fitting of the plasma concentration data of imidaprilat on the 7th day based on the same linear model; $F$ was given as the total percent of 24 h urinary excretion ($E_{24}$) of imidapril and imidaprilat on the 7th day; $k_2$ and $k_5$ were given as the proportionally divided value of $(k_3 + k_2)$ by $E_{24}$ of imidapril and imidaprilat on the 7th day; $B_{\text{max}}$ and $k_{30}$ were estimated by the rat data; $k_5$ was used as large value as $10 \text{ h}^{-1}$ so as to be no rate limiting in terms of the previous finding that the concentration of imidaprilat was rapidly equilibrated between lung and plasma after administration in rat.

The linear pharmacokinetic parameters were calculated from the plasma concentration data set by a nonlinear least squares regression based on the integrated equations of one-compartment open model (program: MULTI algorithm: simplex, computer: PC-9801 NEC microcomputer).

The maximum plasma concentration ($C_{\text{max}}$), the time to reach the $C_{\text{max}}$ ($T_{\text{max}}$), the area under plasma concentration ($AUC$) and the elimination half life ($t_{1/2}$) were also obtained from the actual plasma concentration data of imidapril and imidaprilat. The $AUC$ was calculated by the trapezoidal rule up to 24 h and expressed as $AUC_{24}$. The value of $t_{1/2}$ was calculated by log-linear regression for the declining plasma concentrations against time after administration.

**RESULTS AND DISCUSSION**

**Pharmacokinetic Profiles of Imidapril and Imidaprilat in Human** Figure 3 shows the mean plasma concentrations of imidapril and imidaprilat versus time curves after a single oral administration of imidapril in varying doses (2.5, 5, 10 and 20 mg), each of which was obtained from the phase I study conducted using six healthy Japanese males.
male volunteers. The scale of the vertical axis in each figure is altered in proportion to the dose for the convenience of direct comparison. The plasma concentration profiles of imidapril seemed similar to each other, irrespective of the dosing size; that is, the plasma concentration increased in proportion to the dose and reached a maximum level after 1—2 h in every dose, and then it declined with an elimination half-life of about 2 h. On the other hand, the plasma concentration profiles of imidaprilat were different from those of imidapril, each of which was characterized by a considerably delayed profile; it was also noticeable that the profile was extremely lowered at the lowest dose (2.5 mg) when compared with other doses.

Figure 4 shows the plasma concentration profiles of imidapril and imidaprilat obtained from the previous multiple dosing study. All the plasma concentration data of imidapril agreed with the fitting curve calculated using the conventional linear one-compartment open model from the first dosing data (Fig. 4A), suggesting that the pharmacokinetic behavior of imidapril was essentially linear. However, as shown in Fig. 4B, the plasma concentration of imidaprilat seemed to behave in a different manner; that is, the imidaprilat level after first dosing was relatively low, but increased by repetitive administration over the fitting curve calculated from the first dosing data. It was also found that the steady state of the imidaprilat level could be attained by only a few repetition of administration.

The $C_{\text{max}}$, $T_{\text{max}}$, $t_{1/2}$, and $AUC_{24}$ of both compounds in human are listed in Table I, which were calculated from the plasma concentration data of the 1st day and 7th day in the multiple dosing study. There was no large difference in each pharmacokinetic parameter of imidapril between the two different observation days. However, as for imidaprilat, the $C_{\text{max}}$ and $AUC_{24}$ on the 7th day increased about 2.5 times compared with those on the 1st day, the
TABLE I. Comparison of Bioavailability Parameters of Imidapril and Imidaprilat between Observed Values (OBS) and Simulated Values (SIM1cont) by a Linear 1 Compartment Model after Multiple Oral Administrations of Imidapril Once a Day to Healthy Male Human Volunteers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Parameter</th>
<th>OBS</th>
<th>SIM1cont</th>
<th>OBS</th>
<th>SIM1cont</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidapril</td>
<td>$C_{max}$ (ng/ml)</td>
<td>28.9 ± 3.3</td>
<td>28.9 ± 3.4</td>
<td>27.1 ± 2.5</td>
<td>28.9 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>$T_{max}$ (h)</td>
<td>2.0 ± 0.0</td>
<td>2.0 ± 0.0</td>
<td>2.3 ± 0.3</td>
<td>2.0 ± 0.0</td>
</tr>
<tr>
<td></td>
<td>$t_{1/2}$ (h)</td>
<td>1.7 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.6 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>$AUC_{24}$ (ng · h/ml)</td>
<td>113.3 ± 10.0</td>
<td>104.3 ± 8.6</td>
<td>113.0 ± 15.8</td>
<td>104.4 ± 8.6</td>
</tr>
<tr>
<td>Imidaprilat</td>
<td>$C_{max}$ (ng/ml)</td>
<td>7.8 ± 1.7</td>
<td>7.5 ± 1.3</td>
<td>20.3 ± 3.0</td>
<td>9.2 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>$T_{max}$ (h)</td>
<td>9.3 ± 0.8</td>
<td>9.8 ± 0.6</td>
<td>7.0 ± 0.4</td>
<td>8.8 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>$t_{1/2}$ (h)</td>
<td>14.8 ± 3.6</td>
<td>12.4 ± 3.7</td>
<td>7.6 ± 0.4</td>
<td>12.4 ± 3.7</td>
</tr>
<tr>
<td></td>
<td>$AUC_{24}$ (ng · h/ml)</td>
<td>107.8 ± 17.9</td>
<td>107.6 ± 19.8</td>
<td>246.6 ± 38.0</td>
<td>157.1 ± 26.3</td>
</tr>
</tbody>
</table>

$C_{max}$: maximum plasma concentration, $T_{max}$: time to reach $C_{max}$, $t_{1/2}$: elimination half-life in plasma, $AUC_{24}$: area under the plasma concentration-time curve from 0h to 24h. Each value represents the mean ± S.E. of 6 subjects.

Fig. 5. Simulated Plasma Concentration Curves and Cumulative Urinary Excretion Curves Based on a Saturable Tissue-ACE Binding Model after Multiple Oral Administrations of 10 mg of Imidapril Once a Day to Healthy Male Human Volunteers

Observed data: imidapril (○), imidaprilat (●), simulated curves: imidapril (-----), imidaprilat (-----).

$T_{max}$ was somewhat shortened, and $t_{1/2}$ on the 7th day decreased to one half of that on the 1st day. From these results, it can be considered that the pharmacokinetic behavior of imidapril in human is essentially linear whereas that of imidaprilat is nonlinear. These findings coincide qualitatively with the previous findings in dog8) and in rat5,9).

Estimation of Pharmacokinetic Parameters The pharmacokinetic parameters of the above equations for the saturable tissue-ACE binding model were estimated by the simultaneous curve fitting method using the mean plasma concentration data and urinary excretion data of imidapril and imidaprilat obtained from the multiple dosing study in human.

The calculation was done successfully and excellent fitted curves were obtained as shown in Fig. 5. The convergent value of each pharmacokinetic parameter by nonlinear least squares analysis was summarized in Table II.

Four convergent rate constants, $k_1$, $k_2$, $k_3$ and $k_4$, were all close to the initial values. The estimated value of $k_1$ suggests that the absorption rate of imidapril from the gastrointestinal tract was fairly rapid. The similarity of the $k_2$ and $k_3$ values suggests that imidapril was eliminated from the systemic circulation at a rate almost equal to urinary excretion and the bioconversion to imidaprilat. The estimated value of $k_4$ suggests that the intrinsic elimination rate of imidaprilat was considerably faster than the apparent elimination rate, because the intrinsic elimination half-life calculated from $k_4$ was about 5h whereas the apparent value was 7.6—14.8 h (see Table I). The estimated value of $k_4$ was one third of the initial value, which was estimated from the rat study, suggesting that the affinity of imidaprilat to ACE might be stronger in human than in rat. From the values of $B_{max}$ and $k_4$, it can be estimated that ACE in all tissues of human could be saturated with about 1 mg of imidaprilat in systemic circulation, and that 50% of ACE would be inhibited by
binding with imidaprilat at the concentration of about 3 ng/ml in plasma.

**Application to Single Administration Study** To examine whether the above-mentioned saturable tissue–ACE binding model was also applicable for the pharmacokinetic analysis of single administration data, the plasma concentration and urinary excretion data of imidapril and imidaprilat obtained in the single dosing study (2.5, 5, 10 and 20 mg) were attempted to be simulated by the saturable tissue–ACE model using the parameters listed in Table II. In this study, $F$ values were recalculated to give the most suitable value for each single dosing data by the curve fitting method. As can be seen in Fig. 6, all the plasma concentration and urinary excretion data of imidapril and imidaprilat coincided well with the individual simulation curve. It was remarkable that the extremely low and lasting plasma concentration profile of imidaprilat observed at the 2.5 mg dose was completely reproduced by this simulation analysis. All these results indicate that the proposed pharmacokinetic model is rationally applicable to describe the pharmacokinetic behaviors of imidapril and imidaprilat in human.

**Rationality of the Saturable Tissue–ACE Binding Model** On the basis of the above pharmacokinetic analysis, the behaviors of imidapril and imidaprilat in the human body can be explained. Imidapril is absorbed from the gastrointestinal tract in proportion to the dose and is quickly converted to imidaprilat depending on the absorbed amount of imidapril. Thereafter, imidaprilat binds to ACE in tissues, which causes the slow appearance and disappearance of imidaprilat in plasma. The binding probably occurs according to the Langmuir-type complexation mechanism involving saturable and reversible binding processes, so that the ratio of the binding amount against the total amount in the body increases with a decreasing dose. Consequently, the plasma concentration of imidaprilat became remarkably lowered at the low dose (2.5 mg) in human. Since the ACE-imidaprilat binding can be readily saturated by such an extremely small amount as 1 mg in the body, the plasma concentration of imidaprilat proportionally increases with doses in the range of more than 5 mg. On the other hand, under the condition where the plasma concentration of imidaprilat is quite low, some part of bound imidaprilat could be dissociated to compensate for the eliminated imidaprilat from plasma, resulting in the more lasting plasma profile of imidaprilat.

When imidapril was administered repetitively, the plasma concentration level of imidapril hardly changed because of its essentially linear pharmacokinetic behavior. However, the plasma concentration and urinary excretion of imidaprilat after the 2nd dose increased about 2.5-fold of that observed at the 1st dosing, and then remained at the same level. This phenomena can be explained by the saturable tissue–ACE binding model. After the first dosing of repetitive administration, part of the imidaprilat binds to ACE in tissues and hence the plasma concentration level can be relatively lowered as mentioned above, whereas since the binding to ACE is almost saturated at

### Table II. Pharmacokinetic Parameters Estimated by Curve Fittings Based on a Saturable Tissue–ACE Binding Model after Multiple Oral Administrations of 10 mg of Imidapril Once a Day to Healthy Male Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$ ($h^{-1}$)</td>
<td>0.975</td>
<td>0.724 ± 0.145</td>
</tr>
<tr>
<td>$k_2$ ($h^{-1}$)</td>
<td>0.287</td>
<td>0.334 ± 0.004</td>
</tr>
<tr>
<td>$k_3$ ($h^{-1}$)</td>
<td>0.305</td>
<td>0.368 ± 0.006</td>
</tr>
<tr>
<td>$k_4$ ($h^{-1}$)</td>
<td>0.089</td>
<td>0.202 ± 0.007</td>
</tr>
<tr>
<td>$F$</td>
<td>0.152</td>
<td>0.144 ± 0.013</td>
</tr>
<tr>
<td>$k_{d1}$ (mg/ml)</td>
<td>9.0</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>$B_{max}$ (mg/body)</td>
<td>0.850</td>
<td>0.790 ± 0.030</td>
</tr>
<tr>
<td>$V_1$ (liter)</td>
<td>24.2</td>
<td>18.8 ± 0.7</td>
</tr>
<tr>
<td>$V_2$ (liter)</td>
<td>31.4</td>
<td>16.9 ± 0.6</td>
</tr>
</tbody>
</table>

$k_3$ was used as the constant value; $k_4 = 10 h^{-1}$. Each value of final parameter represents the mean ± S.E. of 6 subjects.

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**Fig. 6.** Simulated Plasma Concentration Curves and Cumulative Urinary Excretion Curves Based on a Saturable Tissue–ACE Binding Model after the Single Oral Administration of 2.5 (A), 5 (B), 10 (C), 20 (D) mg of Imidapril to Healthy Male Human Volunteers

Observed data: imidapril (○), imidaprilat (●), simulated curves: imidapril (-----), imidaprilat (—).
the 2nd dosing, the plasma concentration of imidaprilat increases, and it behaves linearly thereafter.

CONCLUSION

In order to obtain a rational explanation of and an analytical method for the unique pharmacokinetic behaviors of imidapril and imidaprilat in human, a pharmacokinetic model was designed introducing the saturable-reversible ACE-imidaprilat binding process. Through various test calculations, the proposed model was proven valid for describing the behaviors of imidapril and imidaprilat. This model can be applicable to predict the plasma concentrations of imidapril and imidaprilat in various dosage conditions for clinical use.

REFERENCES


