Pharmacokinetic Model of Oral Levodopa and Role of Carbidopa in Parkinsonian Patients

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A pharmacokinetic model of oral levodopa is proposed to elucidate the effects of carbidopa on the pharmacokinetics of levodopa. The propriety of the model was evaluated by simultaneous computer Multi-Line fitting for the plasma concentration–time data of levodopa and dopamine-3-O-sulfate (DA-S), a major metabolite of levodopa, after oral administration of three different levodopa doses to parkinsonian patients. Plasma profiles of levodopa and DA-S were also determined in 12 parkinsonian patients during daily oral administration of Neodopaston®, a levodopa preparation containing carbidopa in tablet form. We investigated the role of carbidopa by comparing the populational mean parameters calculated in the levodopa alone model with those obtained in patients coadministered levodopa and carbidopa. The results indicated that the pharmacokinetics of levodopa coadministered with carbidopa were dose-independent and that carbidopa reduces the first-pass metabolism of levodopa in the gut wall to less than 10% of the dose absorbed, and decreases the systemic clearance of levodopa by 35–39%.

The proposed pharmacokinetic model and the evaluation of carbidopa in this study will provide useful information for the development of drug delivery systems for levodopa or catechol-O-methyltransferase inhibitors, for further stabilization of plasma concentrations of levodopa in parkinsonian patients.

Key words levodopa; carbidopa; dopamine-3-O-sulfate; pharmacokinetic model; first-pass metabolism; parkinsonian patient

Levodopa is one of the most widely-used drugs for the treatment of Parkinson’s disease. A relationship between plasma levodopa concentration and pharmacological response has been demonstrated.1) Sasahara et al. reported that levodopa shows dose-independent pharmacokinetic properties when administered intravenously, while a non-linear relationship was observed between the oral dose and area under the plasma concentration–time curve (AUC) of levodopa in parkinsonian patients during chronic levodopa therapy,2) indicating that the systemic bioavailability of this drug is affected by the dose administered. It was concluded that dose-dependent bioavailability is caused by the saturable first-pass metabolism due to levodopa decarboxylase (LDC) located in the gut wall during the absorption process.3

Levodopa is generally used in combination with carbidopa, a reversible inhibitor of LDC. The mechanism of this inhibition is known to be by “scavenging” of the enzyme’s pyridoxal phosphate cofactor. It has been reported that coadministration of carbidopa significantly increases the AUC of levodopa without prolongation of its half-life.4) On the other hand, Nutt et al.5) reported that plasma clearance of levodopa following intravenous administration was reduced by 43% when coadministered with carbidopa. There was, however, no explanation of these observations. Furthermore, to our knowledge, studies concerning the pharmacokinetic model of orally administered levodopa and the role of carbidopa on its pharmacokinetic behavior have been limited.

In the present study, we propose a pharmacokinetic model of oral levodopa including first-pass metabolism and metabolic pathway to dopamine-3-O-sulfate (DA-S), a major metabolite of levodopa, to elucidate the effects of carbidopa on the pharmacokinetics of levodopa. By simultaneous computer Multi-Line fitting for plasma profiles of levodopa and DA-S after oral administration of three different levodopa doses to parkinsonian patients reported previously,2) the propriety of this model was evaluated and the populational mean parameters were calculated.

We also determined the plasma concentrations of levodopa and DA-S in 12 parkinsonian patients during daily oral administration of Neodopaston®, a levodopa preparation containing carbidopa in tablet form, and estimated the values of mean parameters as in the group coadministered carbidopa. We attempted to elucidate the role of carbidopa by comparing the populational mean parameters calculated in a levodopa alone model with those obtained in our 12 patients coadministered levodopa and carbidopa, assuming that these different population groups were comparable.

THEORETICAL

Proposed Model of Oral Levodopa When the absorption of levodopa was estimated by its intact form and metabolites, the absolute bioavailability of the orally administered drug was essentially constant regardless of the dose administered.2) After intravenous administration, the plasma profile of levodopa appeared to fit to a two-compartment model while the plasma level of DA-S declined mono-exponentially.2,6) Since intact dopamine (DA) scarcely exists in plasma during levodopa therapy,7) levodopa can be considered to be decarboxylated to DA.

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and is metabolized rapidly to DA-S, 3,4-dihydroxyphenylacetic acid (DOPAC) or homovanillic acid (HVA) at both the absorption site and peripheral metabolic sites. Rutledge and Hoehn\(^9\) showed that the metabolic process from DA to DA-S at the absorption site is rate-limiting. It is also known that DA-S is excreted only into the urine and is not susceptible to further metabolism in dogs.\(^9\)

Based on these observations, the following assumptions were made for the pharmacokinetic model of oral levodopa:

1. Plasma profile of levodopa follows two-compartment model characteristics.
2. Both the steps of levodopa to DA and DA to DA-S in the gut wall can be described by Michaelis–Menten kinetics.
3. Plasma profiles of DA-S can be described as a one-compartment model and metabolism or elimination from this compartment other than excretion into the urine is negligible.

According to these assumptions, we proposed a pharmacokinetic model of oral levodopa including first-pass metabolism and plasma compartment of DA-S (Fig. 1). After oral administration, levodopa is distributed to the gastrointestinal tract, the absorption compartment (D\(_D\)), and is absorbed into the first-pass metabolism compartment (D\(_f\)) by a first-order process in the gut wall tissue with an absorption fraction (F). The drug then enters the central compartment (D\(_c\)) including the blood. In the gut wall tissue (compartment D\(_c\)), levodopa is decarboxylated to DA and DA is further conjugated with sulfate at compartment D\(_a\), with Michaelis–Menten kinetics. The Michaelis–Menten constants (\(K_{m_1}\), \(K_{m_2}\) (mg/kg)) and maximum velocity (\(V_{m_1}\), \(V_{m_2}\) (mg h\(^{-1}\)/kg)) are described here in mass rate terms. The peripheral compartment for levodopa is D\(_3\), and the plasma compartment of DA-S is D\(_S\). The first-order rate constants are represented by \(k_1-k_4\) (h\(^{-1}\)), and distribution volumes (l/kg) of D\(_2\) and D\(_3\) are \(V_{D_2}\) and \(V_{D_3}\), respectively.

MATERIALS AND METHODS

Pharmacokinetic Analysis of Oral Levodopa Administered Alone Using the proposed model, simultaneous computer Multi-Line fitting of the plasma concentration–time data of levodopa and DA-S after oral levodopa administration of 3.8, 7.7 and 15.4 mg/kg in a cross-over fashion was performed. The average values of all patient plasma concentrations reported previously by Sasahara et al.\(^3\) were used in this fitting, and \(F, k_1, k_4, k_5, k_6, V_{D_2}\) and renal clearance of DA-S (C\(_{DA-S}=V_{D_2}k_7\)) were fixed with the mean values of the population pharmacokinetic parameters (indicated in Table 1) obtained following intravenous and oral administration; this was based on the assumption that these different population groups in the three different oral dose studies and the intravenous study were comparable. Other parameters were fitted with the different equations using the computer program MULTI-RUNGE.\(^{10}\) under conditions of 1/C weighting, by the Damping–Gauss–Newton method. To obtain minimal sums of squares, a lag-time of 0.25 h and DT of 0.05 h were adopted from empirical observations in this fitting. The respective equations are as follows:

\[
dA_1/dt = -k_1A_0
\]
\[
dA_2/dt = k_1A_0 - V_{m_1}A_1/(K_{m_1} + A_1) - k_2A_1
\]
\[
dC_1/dt = k_2A_1/V_{D_2} + k_5C_3 - (k_3 + k_5 + k_6)C_2
\]
\[
dC_2/dt = k_6C_2 - C_3
\]
\[
dA_3/dt = V_{m_2}A_2/(K_{m_2} + A_2) - V_{m_2}A_2/(K_{m_2} + A_2) - k_4A_4
\]
\[
dC_3/dt = (k_6C_2/V_{D_3} + V_{m_2}A_2/(K_{m_2} + A_2))/V_{D_3} - k_7C_5
\]

Table 1. Estimated Pharmacokinetic Parameters

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(k_1)</td>
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</tr>
<tr>
<td>(k_2)</td>
<td>0.878 ± 0.07</td>
</tr>
<tr>
<td>(k_3)</td>
<td>0.724 ± 0.075</td>
</tr>
<tr>
<td>(k_4)</td>
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<tr>
<td>(k_5)</td>
<td>0.724 ± 0.075</td>
</tr>
<tr>
<td>(k_6)</td>
<td>0.724 ± 0.075</td>
</tr>
<tr>
<td>(k_7)</td>
<td>0.724 ± 0.075</td>
</tr>
<tr>
<td>(k_8)</td>
<td>0.724 ± 0.075</td>
</tr>
</tbody>
</table>

The values show mean ± S.D. \(a\) Cited from Sasahara's data.\(^a\) \(b\) Renal (assumed total) clearance of DA-S (C\(_{DA-S}\)).
where \( A_0 - A_4 \) are amounts in compartments \( D_0 - D_4 \), respectively, and \( C_2 - C_5 \) are concentrations in compartments \( D_2 - D_5 \). The data of dose and plasma concentration of levodopa, DA, and DA-S were all input to a computer in terms of levodopa.

**Coadministration Study with Carbidopa in Patients**

Drug and Chemicals: A levodopa preparation in tablet form, Neodopaslon® (100 mg levodopa and 10 mg carbidopa per tablet), was obtained from Sankyo Co., Ltd., Tokyo, Japan. Levodopa and DA were purchased from Sigma Chemical Company (St. Louis, MO, U.S.A.). All other chemicals were obtained from commercial sources and were used without further purification.

Patients: Twelve parkinsonian patients, 7 females and 5 males, aged 44—79 years and weighing 36—60 kg, who had received chronic therapy with levodopa for more than one month participated in the present study. None of the patients had any liver or renal impairment. Informed consent was obtained from each patient after a full explanation of the procedures.

Study Design: Administration of levodopa was withdrawn 24 h before the clinical study. The patients were permitted to have usual meals and therapeutic drugs throughout the study; however, none of these drugs had been reported to alter the kinetics of levodopa. Each patient received the levodopa preparation at 7:00 a.m., 12:00 p.m. and 4:00 p.m. (2—6 tablets/d); these were given 1 h before meals. Venous blood samples (about 5 ml) were collected hourly from 7:00 a.m. to 9:00 p.m. One hundred ml of 10% sodium metabisulfite solution was added to the blood samples, and the plasma samples obtained by centrifugation were stored at \(-20^\circ\) C until analysis. Urine was also collected from 7:00 a.m. for 24 h in bottles containing 5 ml of 6 N HCl and 3 ml of 0.2 M EDTA-2Na. The collected urine was adjusted to pH 2.0 with 6 N HCl and stored at \(-20^\circ\) C until the assay.

Analytical Procedure: Urinary concentration of DA-S and plasma concentrations of levodopa and DA-S were determined by high-performance liquid chromatography (HPLC) with an electrochemical detector according to the method described by Regin et al. The MIC is intact DA was found in plasma, total DA obtained by acid hydrolysis was defined as DA-S in this study.

Pharmacokinetic Analysis: \( AUC_{\text{levodopa}} = AUC_{\text{DA-S}} \) were calculated by the linear trapezoidal integration with extrapolation to infinite time. The apparent elimination rate constant (\( k_{\text{app}} \)) was estimated by least-squares regression analysis of the terminal concentration—time curve corresponding to the evening administration. The apparent systemic clearance of levodopa (\( CL_{\text{CD,app}} \)) when coadministered with carbidopa and the renal (assumed total) clearance of DA-S (\( CL_{\text{DA-S}} \)) were calculated by the following equations:

\[
CL_{\text{CD,app}} = \frac{\text{oral dose of levodopa (mg)}}{AUC_{\text{CD}}}
\]

\[
CL_{\text{DA-S}} = \frac{\text{urinary amount of DA-S (mg)}}{AUC_{\text{DA-S}}}
\]

where \( AUC_{\text{CD}} \) and \( AUC_{\text{DA-S}} \) are \( AUC \) of levodopa and that of DA-S when coadministered with carbidopa. In this study, amount and concentration of DA-S are represented as those of DA.

**Evaluation of Role of Carbidopa** As shown later, we found that the pharmacokinetics of levodopa coadministered with carbidopa were dose-independent, and that the relationship between dose of levodopa and \( AUC_{\text{DA-S}} \) was also linear regardless of the dose of carbidopa. Accordingly, carbidopa was assumed to linearize all kinetic processes described by the Michaelis—Menten equation in the proposed model due to an apparent increase in \( K_{\text{m1,CD}} \) and reductions in \( k_3 \) and \( k_6 \), without any changes in maximum velocity, distribution of levodopa or other kinetic parameters of each compound.

Based on these assumptions, a linear pharmacokinetic model of oral levodopa coadministered with carbidopa was derived (Fig. 2) from the proposed pharmacokinetic model. In this model, \( f_p \) is the fraction of metabolism from levodopa to DA in the gut wall, and is described by the following equation under the conditions \( f_1 = f_4 \), where \( f_1 \) is the amount of levodopa in \( D_1 \), and \( K_{\text{m1,CD}} \) (mg/kg) is the Michaelis—Menten constant (in mass rate terms) increased from \( K_{\text{m1}} \) by carbidopa:

\[
f_{1} = \frac{V_{m1}/K_{m1,\text{CD}}}{V_{m1}/K_{m1,\text{CD}} + k_2}
\]

where \( k_2 \) is defined in Fig. 1. As compared with \( K_{\text{m2}} \) (mg/kg), the amount of DA (\( A_4 \)) in \( D_4 \) seemed extremely small when coadministered with carbidopa. Therefore, the fraction of sulfation (\( f_{s1} \)) in \( D_2 \) is represented similarly by the following equation:

\[
f_{s1} = \frac{V_{m2}/K_{m2}}{V_{m2}/K_{m2} + k_8}
\]

where \( V_{m2} \), \( K_{m2} \) and \( k_8 \) are defined in Fig. 1. When levodopa is administered alone, \( k_{DA} \) is the apparent rate constant of metabolism from levodopa to DA and \( k_{DA} \) is the apparent rate constant of other elimination in \( D_2 \).

**Fig. 2. Linear Pharmacokinetic Model of Oral Levodopa Coadministered with Carbidopa**

Abbreviations are the same as in Fig. 1.
DA-S, DOPAC and HVA appear rapidly in plasma following oral and intravenous administration of levodopa, whereas there is little DA in plasma. As shown later, the plasma profile of DA-S was well fitted by the proposed pharmacokinetic model in which the process of metabolism from D₂ to D₃ was described by one first-order rate constant (k₅). Therefore, it seems that DA is an intermediate and is further metabolized rapidly to DA-S at the same peripheral metabolic site. k₆ is thus represented as k₆ = k₅+ k₆, where fₛ₂ is the fraction of metabolism from DA to DA-S. These rate constants are described as follows:

\[ k_{DA} + k_{OT} = k_5 + k_6 \]  
\[ k_{DA} f_{22} = k_6 \]  

where k₅ and k₆ are defined in Fig. 1. The fraction of metabolism from levodopa to DA in D₂ (fₛ₃) is represented as:

\[ f_{2} = \frac{k_6}{k_{DA} + k_{OT}} \]  

When coadministered with carbidopa, the reduced value of k₆ is represented by Rk₆, where R is the coefficient of k₆ and R = 1 without carbidopa. The ratio of plasma clearance of levodopa coadministered with carbidopa (CL₁,CD) to that of levodopa alone (CL₁) gives, using Eq. 13:

\[ \frac{CL_{1,CD}}{CL_1} = \frac{Rk_D + k_{OT}}{k_{DA} + k_{OT}} = Rf_{2} + (1 - f_{2}) \]  

and the relationship between CL₁,CD and CL₁,CD,app is:

\[ \frac{CL_{1,CD}}{f(1-f_{2})} = CL_{1,CD,app} \]  

Thus, the fraction of metabolism from levodopa to DA in D₂ when coadministered with carbidopa (fₛ₃,CD) is also represented, using Eqs. 13 and 14, as:

\[ f_{3,CD} = \frac{Rk_D + k_{OT}}{Rk_D + k_{OT}} = \frac{Rf_{2}}{Rf_{2} + (1 - f_{2})} \]  

The values of R, fₛ₃, Kₘ₁,CD and the theoretical elimination rate constant (βₑₘₑₐ) of plasma levodopa were also calculated by the following equations using the mean values of the pharmacokinetic parameters (CL₁,CD,app and AUC₁,DA-S/AUC₁,CD are shown in Table 2, others are listed in Table 1), according to optional fₛ₃ (see Appendix).

\[ R = \frac{CL_{1,CD,app} AUC_{1,DA-S} / AUC_{1,CD}}{f_{3,CD} CL_{1,CD,app} V_{m2} / K_{m2}} \]  

where \( r (0.777) \) is the ratio of molecular weight of DA to levodopa.

\[ f_{3} = \frac{CL_{1,CD,app}(1-f_{2}) - CL_{1} CL_{1}(R-1)}{CL_{1}(R-1)} \]  

\[ f_{3} = \frac{k_6}{k_{DA} k_5 + k_6} \]  

\[ K_{m1,CD} = \frac{V_{m1}(1-f_{2})}{k_l f_{2}} \]  

\[ \beta_{e,m} = \frac{(k_3 + k_4 + Rk_D + k_{OT}) - \sqrt{(k_3 + k_4 + Rk_D + k_{OT})^2 - 4k_4(Rk_D + k_{OT})}}{2} \]  

where \( Rk_D + k_{OT} = [Rf_{2} + (1 - f_{2})](k_5 + k_6) \)

RESULTS

Computer-Fitting for the Data of Oral Levodopa Alone

The computer-fitting curves for levodopa and DA-S data after oral administration of levodopa alone were well fitted and are illustrated in Fig. 3. The estimated pharmacokinetic parameters as populational mean values are shown in Table 1. This model for levodopa seems to represent a Flip-Flop type, since the apparent absorption rate constant \( k_1 = 0.724 \text{ h}^{-1} \) was smaller than the elimination rate constant \( \beta_{e,m} = 1.061 \text{ h}^{-1} \) calculated by Eq. 21 with \( R = 1 \)

<table>
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<th>No.</th>
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<th>Sex</th>
<th>Weight (kg)</th>
<th>Dose/d</th>
<th>CL₁,CD,app (h⁻¹)</th>
<th>CL₁,DA-S (h⁻¹)</th>
<th>AUC₁</th>
<th>AUC₁,DA-S (µg h/ml)</th>
<th>AUC₁,DA-S/AUC₁,CD</th>
<th>βₑₘₑₐ (h⁻¹)</th>
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<td>F</td>
<td>36</td>
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<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>52.5</td>
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</table>
(without carbidopa).

**Plasma Profiles of Levodopa and DA-S in Patients Coadministered Carbidopa** Plasma concentrations of levodopa and DA-S following morning administration of Neodopaston® in 12 patients are illustrated in Fig. 4. The corresponding pharmacokinetic data for levodopa and DA-S are summarized in Table 2. The typical plasma profiles of levodopa and DA-S during daily administra-

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**Fig. 3.** Fitted (——) and Observed* (Symbols) Plasma Levels of Levodopa (A) and DA-S (B) Following Oral Administration of Levodopa in Patients

▲, 3.8 mg/kg; ○, 7.7 mg/kg; ●, 15.4 mg/kg. Each point represents the mean ± S.E. of three patients. a) Cited from Sasahara's data.²

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**Fig. 4.** Plasma Concentrations of Levodopa (A) and DA-S (B) Following Morning Administration of Neodopaston® in 12 Patients

▲, 100 mg (n=3); ○, 150 mg (n=3); ●, 200 mg (n=6). Each point represents the mean ± S.E.

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**Fig. 5.** Typical Plasma Concentration–Time Curves of Levodopa and DA-S during Daily Administration of Neodopaston® in Patient No. 1 ○, levodopa; ●, DA-S.
tion of Neodopaston® in patient No. 1 are also shown in Fig. 5. Plasma concentrations of both levodopa and DA-S at 7:00 a.m. were negligible (less than 0.01 μg/ml) in all patients. The values (mean ± S.D.) for $CL_{L,CD,app}$, $CL_{DA-S}$ and $\beta_{app}$ were $1.03 ± 0.1441$ h$^{-1}$/kg, $0.156 ± 0.0154$ h$^{-1}$/kg and $0.710 ± 0.0868$ h$^{-1}$, respectively. The renal clearance of DA-S ($CL_{DA-S}$) in each patient was virtually constant regardless of dose administered. The $AUC$ of levodopa and that of DA-S increased proportionally with increases in dose ($r = 0.899; p < 0.01$, and $r = 0.719; p < 0.01$, respectively). The mean ratio of $AUC$ (DA-S/levodopa) was $0.42 ± 0.096$. These results indicate that the pharmacokinetics of oral levodopa coadministered with carbidopa were dose-independent.

**Evaluation of Role of Carbidopa** According to optimal $f_p$, the value of $R$, $\beta_{the}$, $f_s$, $f_{s2}$, $CL_{L,CD}/CL_L$ and $K_{m1,CD}$ were calculated and are summarized in Table 3. These calculations were performed within $\beta_{app}$ (obtained from the slope of plasma concentration) $< \beta_{the}$ (calculated from theoretical microscopic rate constants), because the

<table>
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<tr>
<th>$f_p$</th>
<th>$R$</th>
<th>$\beta_{app}$ (h$^{-1}$)</th>
<th>$f_s$</th>
<th>$CL_{L,CD}/CL_L$</th>
<th>$f_{s2}$</th>
<th>$K_{m1,CD}$ (mg/kg)</th>
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<td>0.646</td>
<td>0.184</td>
<td>8.20</td>
</tr>
<tr>
<td>0.1</td>
<td>0.328</td>
<td>0.722</td>
<td>0.577</td>
<td>0.614</td>
<td>0.192</td>
<td>3.88</td>
</tr>
</tbody>
</table>

Calculations were performed within $\beta_{app}$ (0.71 h$^{-1}$) $< \beta_{the}$. $f_p$: fraction of first-pass metabolism. Abbreviations are explained in the text and glossary.

**DISCUSSION**

It is difficult to evaluate the non-linear kinetics of levodopa after oral administration from its plasma concentration profiles. Levodopa is known to metabolize to DA, which further undergoes sulfation. In addition, DA-S is known to be excreted into the urine while its endogenous excretion is negligible. In the present study, therefore, we calculated the pharmacokinetic parameters of levodopa using both plasma concentration data of levodopa and DA-S.

There has been no previous study reported on the effects of carbidopa on the distribution or absorption of levodopa in humans. In rats pretreatment with carbidopa (25 mg/kg) caused a reduction in the distribution volume of levodopa, but had no effect on the fraction of oral dose absorbed. However, the dose used in that study is about 100-fold higher than that in clinical use. On the other hand, the plasma levodopa concentrations producing an optimal clinical response in each patient were the same when levodopa was coadministered with or without carbidopa, indicating that clinical dose of carbidopa does not affect the distribution of levodopa to the brain. Therefore, we assumed that carbidopa inhibits only the metabolic process from levodopa to DA in both the absorption and peripheral metabolic sites at a constant degree, without causing any changes in the absorption and distribution of levodopa and other kinetic parameters of each compound.

The estimated parameters for oral levodopa alone showed that the absorption rate constant ($k_1 = 0.724$ h$^{-1}$) was smaller than the elimination rate constant ($\beta_{the} = 1.06$ h$^{-1}$). The estimated absorption rate constant can be supported by the evidence that parkinsonian patients show a much slower gastric emptying rate than younger healthy subjects, probably due to age-related differences. Therefore, it is believed that the apparent half-life (ln 2/$\beta_{app}$) obtained from the slope of plasma concentration...
Fig. 7. Predicted Relationship between Single Dose of Oral Levodopa (Alone) and Bioavailability at Optional Absorption Rate Constant \((k_{i})\) Curves were simulated by five different optional absorption rate constants \((k_{i})\) based on the proposed model (Fig. 1) and other parameter values shown in Table 1.

does not reflect the elimination rate constant \((\beta_{hm})\) when levodopa is administered alone. Fahn\(^4\) reported no prolongation of the half-life of levodopa when coadministered with carbidopa. A possible explanation for this phenomenon is that the determinant of the slope of plasma concentration of levodopa is not \(\beta_{hm}\) but a small absorption rate constant when coadministered with or without carbidopa.

As shown in Fig. 7, the computer simulations using the mean parameters shown in Table 1 demonstrated that the bioavailability of levodopa changed with increase in the absorption rate constant \((k_{i})\) as well as in dose. The bioavailability of 26% at the dose of 10 mg/kg improved to 46% when the value of \(k_{i}\) shifted from the mean value \((0.724\text{ h}^{-1})\) obtained in this study to \(2.0\text{ h}^{-1}\). It can, therefore, be considered that the absorption rate of levodopa is a determinant of its bioavailability, and that its low bioavailability results in poor clinical response after oral administration.

In the analysis of the role of carbidopa on the pharmacokinetics of levodopa after oral administration based on the linear pharmacokinetic model (Fig. 2), the value of \(R\) (coefficient of the rate constant \((k_{DA})\) for the metabolism from levodopa to DA in the plasma compartment of levodopa) was estimated to be 0.33—0.41; this indicates that carbidopa reduces the metabolic rate of plasma levodopa to DA by 59—67% as compared with that administered without carbidopa. The ratio \((0.61—0.65)\) of the plasma clearance of levodopa with carbidopa to that without carbidopa \((\text{CL}_{DA,0}/\text{CL}_{DA})\) obtained in this study indicates that carbidopa reduces the plasma clearance of levodopa by 35—39%. This result was in good agreement with the reduction (43%) estimated by the change in the infusion rate required to achieve a constant plasma level of levodopa when coadministered orally with and without carbidopa.\(^5\) The value of \(f_{u}\) estimated as 0.58—0.60 indicated that 58—60% of plasma levodopa was metabolized to DA when administered alone. This value is in near accordance with that in a previous report\(^6\) in which 69% of levodopa metabolites recovered in the urine of humans were found to be comprised of DA and its metabolites following intravenous injection of radiolabeled levodopa.

The computer simulation showed that the bioavailability of about 20% at the normal clinical dose of levodopa \((2\text{ mg/kg})\) increased to about 80%, while the plasma clearance of levodopa was reduced by about 40% when coadministered with carbidopa. Therefore, it was suggested that carbidopa acts to improve plasma level of levodopa mainly by reducing the first-pass metabolism of oral levodopa. This hypothesis is consistent with the previous report\(^6\) that daily carbidopa doses of more than 75 mg caused no further reduction of effective levodopa dose, indicating that the clinical dose of carbidopa had already inhibited the activity of LDC in the gut wall almost completely.

It is difficult to perform a cross-over trial or a loading regimen in parkinsonian patients because of their serious clinical condition. We therefore attempted to determine the role of carbidopa by comparing the populational mean parameters calculated in a levodopa alone model with those obtained in our 12 patients coadministered levodopa and carbidopa, based on the assumption that these different population groups were comparable. The mean value of the renal clearance \((\text{CL}_{DA,0})\) observed in patients with carbidopa \((0.1561\text{ h}^{-1}/\text{kg})\) was nearly equivalent to that cited as the mean parameter following intravenous injection\(^6\) \((0.144\text{ h}^{-1}/\text{kg})\), suggesting not only that \(\text{CL}_{DA,0}\) was not affected by carbidopa but also that these different population groups were comparable, probably due to their similarity in that the patients had started levodopa therapy and all were Japanese.

In conclusion, the present study demonstrated that the non-linearity in the pharmacokinetics of oral levodopa and the reason no prolongation was found in its half-life with carbidopa can both be explained by the proposed model which seems to be a Flip-Flop type, and that the pharmacokinetics of oral levodopa coadministered with carbidopa are dose-independent. Furthermore, carbidopa was indicated to reduce the first-pass metabolism of levodopa in the gut wall to less than 10% of the dose absorbed and to decrease the systemic clearance of
levodopa by 32—39%. Therefore, even if the O-methylation of levodopa can be completely inhibited by COMT-inhibitors developed in the near future, carbidopa should be used with these drugs, since it acts mainly by diminishing the first-pass metabolism of oral levodopa. The results of this study will thus provide useful information for the development of drug delivery systems for levodopa or COMT-inhibitors, aimed at further stabilization of plasma concentrations of levodopa in parkinsonian patients.

APPENDIX

The total amount of levodopa transported into compartment $D_2$ is represented as $DF(1-f_p)$ and corresponds to $(\text{CL}_{A,\text{CD}}AUC_C)$:

$$DF(1-f_p) = \text{CL}_{A,\text{CD}}AUC_C$$

where $D$ is oral dose (mg/kg) of levodopa, $F$ is fraction of absorption, and $AUC_C$ (µg h/ml) is the $AUC$ of levodopa, respectively. In compartment $D_3$, the amount of DA-S (mg as DA) produced from $D_2$ is represented as $A_{2-3}$ by Eq. A2:

$$A_{2-3} = DF(f_p f_{cd} f_{st})$$

and that from $D_4$ is described as $A_{4-5}$ by Eq. A3:

$$A_{4-5} = DF f_{st}$$

where $r$ (0.777) is the ratio of molecular weight of DA to levodopa. The total amounts transported into compartment $D_3$ can be determined by adding Eqs. A2 and A3, and corresponds to $(\text{CL}_{DA,S} AUC_{DA,S})$:

$$A_{2-3} + A_{4-5} = DF(f_{st} f_{cd} (1-f_p)f_{cd} f_{st} + f_p f_{st})$$

$$= \text{CL}_{DA,S} AUC_{DA,S}$$

where $\text{CL}_{DA,S}$ is renal (assumed total) clearance (1h$^{-1}$/kg) of DA-S and $AUC_{DA,S}$ (µg h/ml) is $AUC$ of DA-S. Equation A4 is divided by Eq. A1 and the solution of $R$ can be expressed using Eqs. 10—16 as follows:

$$R = \frac{r}{k_s k_f} \frac{V_{m2} / k_m2 + k_s}{k_s k_f}$$

$$= \frac{\text{CL}_{DA,S} AUC_{DA,S} - \text{CL}_{DA,S} AUC_C}{\text{CL}_{A,\text{CD}}}$$

This may be rearranged to:

$$f_a = \frac{\text{CL}_{A,\text{CD,app}} (1-f_p) - \text{CL}_{A}}{\text{CL}_{A} (R-1)}$$

From Eqs. 11—13, $f_{a2}$ is expressed as:

$$f_{a2} = \frac{k_s}{f_d (k_s + k_a)}$$

From Eq. 9, $K_{m1,\text{CD}}$ represents:

$$K_{m1,\text{CD}} = \frac{V_{m1} (1-f_p)}{k_2 f_p}$$

When coadministered with carbidopa, the decreased value of the sum of elimination constants from $D_2$ is described as $(R_{ka} + k_{OT})$, and can be expressed using Eqs. 11 and 14 as follows:

$$R_{KA} + k_{OT} = [R_{f_d} + (1-f_p) (k_a + k_s)]$$

(A6)

whereas the relationship between $x$ and $\beta$ in the two-compartment model can be described as follows:

$$x + \beta = k_s + k_a + R_{ka} + k_{OT}$$

(A7)

$$x = k_d (R_{ka} + k_{OT})$$

(A8)

Then, the solution for $\beta$ is:

$$\beta = \frac{(k_s + k_a + R_{ka} + k_{OT}) - \sqrt{(k_s + k_a + R_{ka} + k_{OT})^2 - 4k_d (R_{ka} + k_{OT})}}{2}$$

(G2)

GLOSSARY

- $A_x$: amount of drug in compartment $D_x$ (mg)
- $A_{DA,S}$: total amount of drug transported from $D_1$ to $D_2$ (mg/kg)
- $AUC_C$: area under the plasma concentration-time curve (µg h/ml)
- $AUC_{DA,S}$: $AUC$ of DA-S
- $AUC_{CAR,\text{CD}}$: $AUC$ of levodopa with carbidopa
- $AUC_{CAR,\text{DA},S}$: $AUC$ of DA-S
- $\beta$: elimination rate constant (h$^{-1}$)
- $\beta_{app}$: apparent $\beta$ obtained from the slope of plasma concentration
- $\beta_{th}$: theoretical $\beta$ calculated by theoretical microscopic rate constants
- $C_v$: concentration in $D_4$ (µg/ml)
- $CL$: clearance (h$^{-1}$/kg)
- $CL_{DA,S}$: $CL$ of levodopa
- $CL_{CAR,\text{CD}}$: apparent $CL$ of levodopa with carbidopa
- $CL_{CAR,\text{DA},S}$: $CL$ of DA-S
- $D_1$: dose (mg)
- $D_2$: pharmacokinetic compartment of levodopa and its metabolites
- $F$: fraction for the absorption of levodopa
- $f_a$: fraction for metabolism from levodopa to DA in $D_2$
- $f_{ac,\text{CD}}$: fraction for metabolism from levodopa to DA in $D_2$ when coadministered with carbidopa
- $f_{st}$: fraction for first-pass metabolism in $D_1$
- $f_{st}$: fraction for conjugation of DA in $D_2$
- $F$: first-order rate constant (h$^{-1}$)
- $k_{DA}$: rate constant of metabolism from levodopa to DA in $D_2$
- $k_{OT}$: rate constant of elimination other than $k_{DA}$ in $D_2$
- $K_m$: Michaelis–Menten constant (mg/kg) represented in mass rate terms
- $K_{m1,\text{CD}}$: increased $K_m$ with carbidopa
- $K_{m2,\text{CD}}$: $K_m$ in $D_4$
- $K_{m2,\text{CAR,DA},S}$: $K_m$ in $D_4$
- $R$: coefficient of $k_{DA}$ when coadministered with carbidopa
- $r$: ratio of molecular weight of DA to levodopa (0.777)
- $V_d$: distribution volume of $D_1$ (l/kg)
- $V_{m1}$: maximum velocity (mg h$^{-1}$/kg) represented in mass rate terms
- $V_{m1}$: $V_m$ in $D_1$
- $V_{m2}$: $V_m$ in $D_2$

REFERENCES