Levodopa (L-Dopa) is currently the most widely accepted drug for treating Parkinson’s Disease. Improving our understanding of the pharmacokinetics of L-Dopa and factors that influence these dynamics is important for improving treatment efficacy. Murata and Kanazawa (1997) conducted a cohort study to assess the effect of chronic L-Dopa therapy pharmacokinetics. It was concluded that the maximum blood concentration ($C_{max}$) was higher in the long-term than after acute exposure. Furthermore, it was observed that the half-life of L-Dopa ($T_{1/2}$) and the time to maximum concentration ($T_{max}$) were lower in patients who have been receiving L-Dopa therapy for a prolonged period of time. Murata and Kanazawa then hypothesized that this was due to an increase in the rate of drug absorption ($k_a$). The aim of this study is to test this hypothesis by applying a mathematical model of $C_{max}$ and $T_{max}$ to test the outcome of varying values of $k_a$ across a 15 year span. The collection of $k_a$ values serve as a translational equivalent to the deviation in biological rates from patient to patient. This analysis ultimately supports that an increase $k_a$ over time correlates with a reduction in $T_{max}$, especially when the increase in $k_a$ is incremental. However, the increasing $k_a$ does not offer an explanation for the higher $C_{max}$ observed in Murata and Kanazawa’s model.

### Methods and Parameters

Key parameters for this model were based on values obtained from Murata and Kanazawa’s 1997 cohort study that examined the effects of long-term levodopa treatment.

Variables:
- $x_{b0}$ = current concentration level in the gastrointestinal tract
- $k_a$ = rate of absorption into the blood = 1.155/hr as baseline
- $k_e$ = rate of elimination from the blood = 0.546/hr
- $C_{max}$ = current concentration level in the blood plasma
- $C_{max}$ = peak levels of drug concentration in the blood
- $T_{max}$ = time to peak concentration level
- $T_{1/2}$ = Half-life of the drug
- $V_d$ = volume of distribution = 99.7 liters

Summary of Calculations of Key Parameter Values

Given $T_{1/2}$ and $T_{max}$ from Murata and Kanazawa (1997), $k_a$ and $k_e$ values were determined:

$T_{1/2} = 78.2$ min $= 1 h/0.60 = 1 h/27.2$ hr

$T_{max} = 75.8$ min $= 1 h/0.60 = 1 h/22$ hr

Using $T_{1/2}$ and $T_{max}$, the $k_a$ and $k_e$ values can be computed:

$k_a = \frac{0.693}{T_{1/2}} = \frac{0.693}{27.2} = 0.046/hr

k_e = \frac{0.693}{T_{max}} = \frac{0.693}{22} = 0.032/hr

such that $k_a = 1.155

V_d = 99.7 liters was determined as the average of four different studies.

Incremental increases in $k_a$ were computed as sequential additions of a fixed rate ($r$)

Exponential increase in $k_a$ were computed as $k_a(t+1) = r k_a(t)$ year of treatment.

### Results

#### Table 1. Summary of the Different Rates of $k_a$ Over 15 Years for the Seven Pseudo-patients in this model

<table>
<thead>
<tr>
<th>Patient</th>
<th>$k_a$</th>
<th>Simulated trend of $k_a$ over 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>$k_a$</td>
<td>No change (values in 5-year steps)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>$k_a$</td>
<td>No change (values in 5-year steps)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>$k_a$</td>
<td>Incremental increase ($r=0.05$ per year) for all 15 years</td>
</tr>
<tr>
<td>Patient 4</td>
<td>$k_a$</td>
<td>Incremental increase ($r=0.05$ per year) for all 15 years</td>
</tr>
<tr>
<td>Patient 5</td>
<td>$k_a$</td>
<td>Incremental increase ($r=0.02$ per year) for all 15 years</td>
</tr>
<tr>
<td>Patient 6</td>
<td>$k_a$</td>
<td>Incremental increase ($r=0.01$ per year) for all 15 years</td>
</tr>
<tr>
<td>Patient 7</td>
<td>$k_a$</td>
<td>Incremental increase ($r=0.00$ per year) for all 15 years</td>
</tr>
</tbody>
</table>

The resulting $T_{max}$ for each $k_a$ was then computed using the following equation:

$T_{max} = \frac{\ln(ka)}{-\ln(C_{max})}

C_{max}$ can be computed from $k_a$ in the two-compartment model via a system of two differential equations:

$$\begin{align*}
X &= C_a + C_b \\
C_b' &= -k_a C_b + k_e C_a
\end{align*}$$

Where $C_b$ is when $C=0

#### Figure 2. Different Rates of Increase of $k_a$ Over 15 Years

#### Figures 3 and 4. Resultant Effect on $T_{max}$ and $C_{max}$

#### Figure 5. Correlation of log-transformed $k_a$ to $T_{max}$

- Increases in $k_a$ yield the expected decrease in $T_{max}$ but a decrease in $C_{max}$
- Incremental increase in $k_a$ better predict $T_{max}$

### Conclusion

Murata and Kanazawa (1997) hypothesized that the observed increase in the $C_{max}$ and decrease in $T_{max}$ and $T_{1/2}$ of early-onset patients (i.e., patients on long-term L-Dopa therapy) were a result of changes in the absorption of L-Dopa ($k_a$); specifically, an acceleration of the drug absorption rate into the blood from the gut.

In testing this hypothesis, the computational runs performed on a pseudo-cohort of one control pseudo patient with a baseline $k_a$ and six other pseudo patients with elevated $k_a$ values (Fig. 2) demonstrated that an increased $k_a$ does significantly correlate with a lowered $T_{max}$ (Fig. 3 and 5) but does not produce an increased $C_{max}$ except for with extremely high $k_a$ (Fig. 4).

By experimenting with a variation in $k_a$ values and recording the output peripheral pharmacokinetics of L-Dopa, this research contributes to the ongoing conversation about how chronic or long-term L-Dopa therapy affects symptom severity in human patients. This mathematical model serves as a baseline framework for comparing $k_a$, $C_{max}$, $T_{max}$ and $T_{1/2}$ values in human cohorts.

### Significance

This study will help to improve symptomatic treatment of idiopathic PD with Levodopa by providing a mathematical framework to supplement future patient cohort studies. The hope is that a better understanding of the effects of long-term Levodopa treatment on the pharmacokinetics of the drug will allow for personalization of treatment as medical professionals will know to monitor how a patient’s rate of the drug absorption will progress over time and adjust their treatment regime accordingly.