Modeling the Pharmacokinetic Effects of Chronic Levodopa in Treatment of Idiopathic Parkinson's Disease

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Abstract

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) conduct 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_{GI}** = current concentration level in the gastrointestinal tract
- **k_a** = rate of absorption into the blood = 1.155/hr as baseline
- **k_{el}** = rate of elimination from the blood = 0.546/hr
- **C_{blood}** = 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_{dl}** = volume of distribution = 99.7 liters

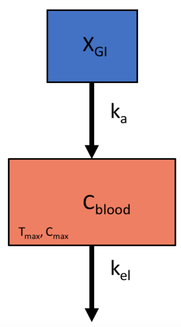
Summary of Calculations of Key Parameter Values

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

$T_{1/2}$ = 76.2 min × 1 hr.60 min.=1.27 hr.
T_{max} = 73.8 min × 1 hr.60 min.=1.23 hr.

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

$k_{el} = \ln 2/T_{1/2} = 0.693/1.27$ hr.$= 0.546$/hr
$T_{max} = \ln(ka) - \ln(k_{el})/ka - k_e| = 1.23 = \ln(ka) - \ln(0.546)/ka - 0.546$
such that $k_a = 1.155$



V_{dl} = 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 $k_a(1+r)^t$ were t=year of treatment.

Research Question

Does an increase in k_a yield the decrease in T_{max} and increase in C_{max} observed in Murata and Kanazawa's 1997 cohort study?

Results

Table 1. – Summary of the Different Rates of Δk_a Over 15 Years for the Seven Pseudo-patients in this model

Patient	Simulated trend of k_a rate over 15 years
Patient 1	No change (stable k_a over 15 years) [Control condition]
Patient 2	No change for 8 years, followed by incremental increase (+0.2 per year) for 7 years
Patient 3	Incremental increase (+0.2 per year) for all 15 years
Patient 4	Incremental increase (+0.5 per year) for all 15 years
Patient 5	Incremental increase (+0.2 per year) for 8 years, then exponential increase (r=0.02) for 7 years
Patient 6	Exponential increase (r=0.05) for all 15 years
Patient 7	Exponential increase (5=0.07) for all 15 years

Fig. 1 - Patient 1 is our constant control:

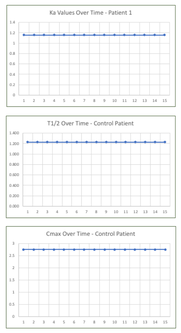
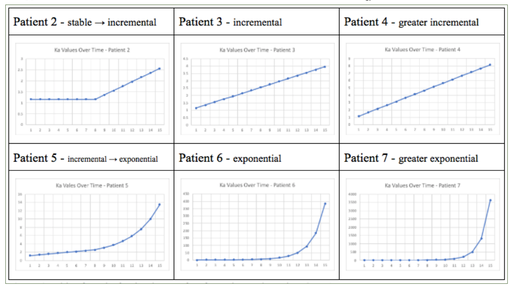


Fig 2. – Different Rates of Increase of k_a Over 15 Years



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

$$T_{max} = ln(\frac{k_a}{k_{el}})(\frac{1}{(k_a - k_{el})})$$

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

$X' = -k_{el}C$
$C' = (k_a/V)X - k_{el}C$

Where C_{max} is when C'=0

Fig 3. – Resultant Effect on T_{max}

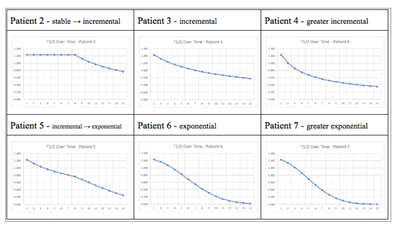


Fig 4. – Resultant Effect on C_{max}

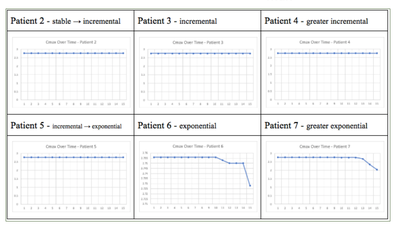
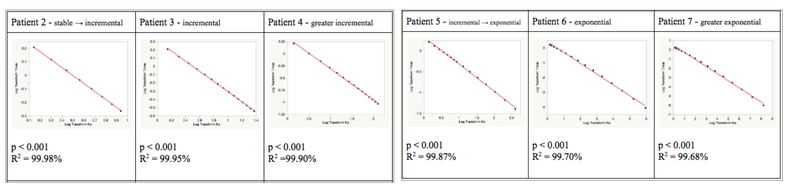


Fig 5. – Correlation of log-transformed k_a to T_{max}



- 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.

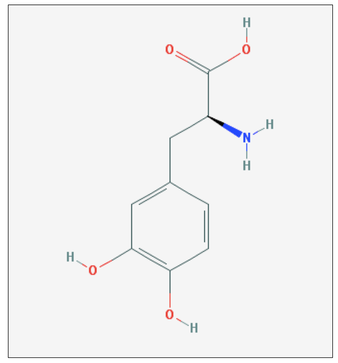


Fig. 6 - Molecular Structure of Levodopa

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.

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