

# A pharmacokinetic-pharmacodynamic model for duodenal levodopa infusion

Jerker Westin<sup>1,3\*</sup>, Thomas Willows<sup>2</sup>, Torgny Groth<sup>1</sup>, Mark Dougherty<sup>3</sup>, Mats Karlsson<sup>4</sup>, Dag Nyholm<sup>5</sup>, Sven Pålhagen<sup>2</sup>

<sup>1</sup> Department of Medical Sciences, Biomedical Informatics and Engineering, Uppsala University, Uppsala, Sweden

<sup>2</sup> Department of Neurology, Karolinska University Hospital Huddinge, Stockholm, Sweden, <sup>3</sup> Department of Economy and Society, Computer Science, Dalarna University, Borlänge, Sweden

<sup>4</sup> Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, <sup>5</sup> Department of Neuroscience, Neurology, Uppsala University Hospital, Uppsala, Sweden

\* jwe@du.se

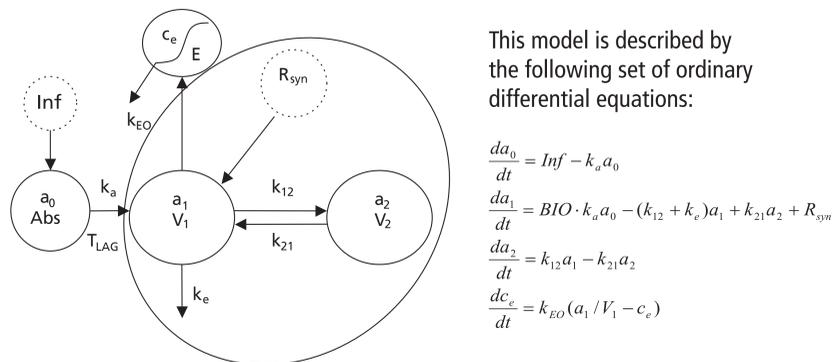
## Objective

Levodopa in presence of decarboxylase inhibitors is following two-compartment kinetics and its effect is typically modelled using sigmoid Emax models. Pharmacokinetic modelling of the absorption phase of oral distributions is problematic because of irregular gastric emptying. The purpose of this work was to identify and estimate characteristic parameters of a population pharmacokinetic-pharmacodynamic model for duodenal infusion of levodopa/carbidopa (Duodopa®) that can be used for *in numero* simulation of treatment strategies.

## Results

Our results indicate that Duodopa absorption can be adequately modelled with an absorption compartment with an added bioavailability fraction and a lag time. The most successful effect model was of sigmoid Emax type with a steep Hill coefficient,  $\gamma$  and an effect compartment delay. The structure of the model is shown in Figure 1. Estimated parameter values are presented in Table 1. Figure 2 illustrates the model's ability to predict actual plasma concentrations as well as motor ratings in one typical patient from the PEDAL study. In Figure 3, simulated responses to 'optimal' and 'non-optimal' settings for flow rate (a.) and morning dose (b.) are shown for the same parameter set that was used in Figure 2. Results from linear regression of morning doses vs. flow rates are presented in Figure 4.

**Figure 1.** Structural pharmacokinetic-pharmacodynamic model. The encircled part is adopted from [1].



This model is described by the following set of ordinary differential equations:

$$\begin{aligned} \frac{da_0}{dt} &= Inf - k_a a_0 \\ \frac{da_1}{dt} &= BIO \cdot k_a a_0 - (k_{12} + k_e) a_1 + k_{21} a_2 + R_{syn} \\ \frac{da_2}{dt} &= k_{12} a_1 - k_{21} a_2 \\ \frac{dc_e}{dt} &= k_{EO} (a_1 / V_1 - c_e) \end{aligned}$$

In addition, there is an initial time delay parameter for the absorption,  $TLAG$ .  $t \mapsto t + TLAG$

where:

- $Inf$  Levodopa infusion (mg/min)
- $RSYN$  Endogenous levodopa synthesis rate (mg/min)
- $a_i$  Amount (mg) in compartment  $i$
- $V_i$  Apparent volume (L) in compartment  $i$
- $k_i$  Fractional rate constant ( $\text{min}^{-1}$ )
- $BIO$  Bioavailability (fraction absorbed)
- $c_e$  Effect compartment concentration (mg/L)

The following derived PK parameters were estimated:

$CL = k_e V_1$  Clearance (L/min)  
 $Q = k_{12} V_1 = k_{21} V_2$  Intercompartmental clearance (L/min)  
 $TABS = 1/k_a$  Absorption time constant (min)  
 $TKEO = 1/k_{EO}$  Effect time constant (min)

The sigmoid E-max effect model is described by the following equation:

$$E = BASE + \frac{EMAX \cdot c_e^\gamma}{c_e^\gamma + EC50^\gamma}$$

The interindividual/interoccasion variability (IIV/IOV) is modelled as described by these equations. WT is an individual's weight in kg. The same weight model as in [1] was used.

$$\begin{aligned} TLAG &= TLAG_{population} \cdot e^{TLAG_{individual}} \\ RSYN &= RSYN_{population} \cdot e^{RSYN_{individual}} \\ V_i &= V_i_{population} \cdot e^{V_i_{individual}} \cdot WT / 70 \\ BIO &= BIO_{population} \cdot e^{BIO_{individual}} \\ CL &= CL_{population} \cdot e^{CL_{individual}} \cdot (WT / 70)^{0.75} \\ Q &= Q_{population} \cdot e^{Q_{individual}} \cdot (WT / 70)^{0.75} \\ BASE &= BASE_{population} + BASE_{individual} \\ EMAX &= EMAX_{population} \cdot e^{EMAX_{individual}} \\ EC50 &= EC50_{population} \cdot e^{EC50_{individual}} \end{aligned}$$

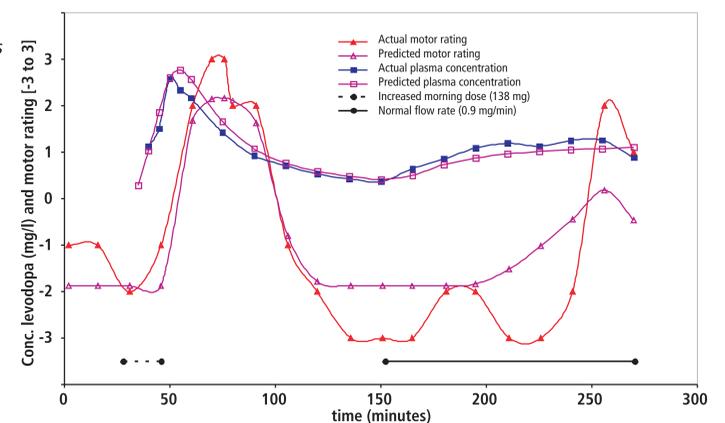
**Table 1.** Estimated model parameters and parameters fixed from the reference [1]. Population mean parameter values, standard error of estimates (SE) and if possible, interindividual/interoccasion variability (IIV/IOV) were estimated.

| Parameter                                  | Population mean | %SE | %IIV/IOV      | %SE of IIV/IOV |
|--|-----------------|-----|---------------|----------------|
| TABS                                       | 21              | 52  | 19            | 340            |
| TLAG                                       | 4.3             | 32  | 69            | 52             |
| BIO  | 0.86            | 5   | 9             | 230            |
| Proportional random error in kinetic model | 0.20            | 17  |               |                |
| $V_1$                                      | 11 [1]          |     | 44 [1]        |                |
| $V_2$                                      | 27 [1]          |     | 25 [1]        |                |
| CL   | 0.52 [1]        |     | 27 [1]        |                |
| Q  | 0.58 [1]        |     | 48 [1]        |                |
| RSYN                                       | 0.010 [1]       |     | 74 [1]        |                |
| BASE                                       | -1.5            | 12  | 56            | 51             |
| EMAX                                       | 2.1             | 10  | 27            | 50             |
| EC50                                       | 2.0             | 5   | 40            | 21             |
| TKEO                                       | 22              | 12  | Not estimated |                |
| GAMMA                                      | 11              | 43  | Not estimated |                |
| Additive random error in effect model      | 1.0             | 7   |               |                |

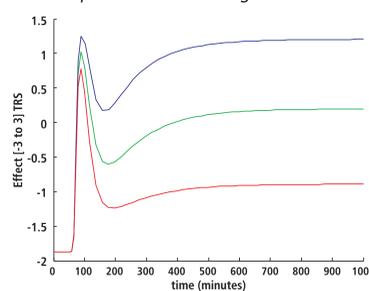
## Methods

The modelling involved pooling data from two studies and fixing some parameters to values found in literature [1]. The first study involved 12 patients on 3 occasions and is described in [2]. The second study, PEDAL, involved 3 patients on 2 occasions. In the PEDAL study, a bolus dose (normal morning dose plus 50%) was given after a washout during night. Plasma samples and motor ratings (clinical assessment of motor function from video recordings on a treatment response scale (TRS) between -3 and 3, where -3 represents severe parkinsonism and 3 represents severe dyskinesia.) were repeatedly collected until the clinical effect was back at baseline (the level before the dose). At this point, the usual infusion rate was started and sampling continued for another two hours. Various structural absorption models and effect models were evaluated using the value of the objective function in the NONMEM package. This objective function is proportional to the likelihood of observing the data given the model. Population mean parameter values, standard error of estimates (SE) and if possible, interindividual/interoccasion variability (IIV/IOV) were estimated. Simulation experiments were performed aiming at finding 'optimal' settings for infusion flow rate and morning bolus dose for one parameter set for each of the 15 patients. The flow rate was adjusted so it would appear stable at zero on the TRS. Thereafter, the morning dose was adjusted so that the target zero would be reached as quickly as possible but minimising any over- and undershoot. In order to find possible shortcuts for predicting an optimal morning dose when an optimal flow rate has been found, linear regression was performed on the morning doses vs. flow rates.

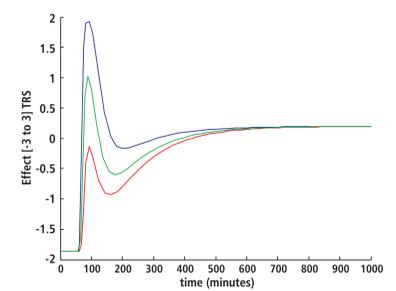
**Figure 2.** Actual and predicted levodopa concentrations and motor ratings for a typical occasion for one patient in the PEDAL study. Smoothened lines connect data points for readability. Missing points indicate levodopa levels under the detection limit (0.2 mg/L). Horizontal lines indicate when infusion was given



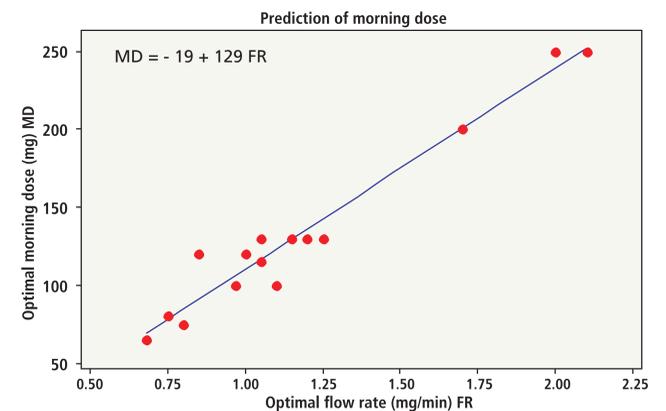
**Figure 3a.** Optimal flow rate (0.8 mg/min) (green), 10% too low (red) and 10% too high (blue). Optimal morning dose was given. Same parameter set as in Figure 2.



**Figure 3b.** Optimal morning dose (75 mg) (green), 20% too low (red) and 20% too high (blue). Optimal flow rate was given.



**Figure 4.** A linear regression shows good ability ( $r^2=0.95$ ) to predict morning dose based on flow rate in the 15 parameter sets, representing one patient each. Note that TRS zero is target for the flow rate and as little overshoot and undershoot as possible, are targets for the morning dose. This may not be desired in practice in all cases. These 'optimal' morning doses assume a zero levodopa level before the dose.



## Conclusions

The absorption and effect models were reasonably successful in fitting observed data and are considered to be useful in simulation experiments. Based on such experiments, the relation between morning dose and flow rate appears to be quite linear. Possibly, a simulation approach can be useful for training clinical staff and/or patients.

## References

- Chan PL, Nutt JG, Holford NH. Importance of within subject variation in levodopa pharmacokinetics: a 4 year cohort study in Parkinson's disease. *J Pharmacokinetic Pharmacodyn.* 2005 Aug;32(3-4):307-31.
- Nyholm D, Askmark H, Gomes-Trolin C, Knutson T, Lennernäs H, Nyström C, Aquilonius SM. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clin Neuropharmacol.* 2003 May-Jun;26(3):156-63.