PEDAL: Identification of Models for Duodenal Administration of Levodopa

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Objectives

The main purpose of the PEDAL study is to identify and estimate sample individual pharmacokinetic-pharmacodynamic (PK-PD) models for duodenal infusion of levodopa/carbidopa (Duodopa®) that can be used for *in numero* simulation of treatment strategies. Other objectives are to study the absorption of Duodopa and to form a basis for a power calculation for a future larger study.

Background

PK-PD modelling based on oral levodopa is problematic because of irregular gastric emptying. Previous work by Chan, Nutt and Holford [1] has found a two-compartment model to be adequate for determination of population PK parameters and their variability for IV infusion.

Methods

The study protocol was accepted by the ethics committee of the Karolinska Institute, Sweden. PEDAL involved three male patients (A, B and C) already on Duodopa who gave informed consent in accordance with the Helsinki declaration. Various baseline scores are presented in Table 1.

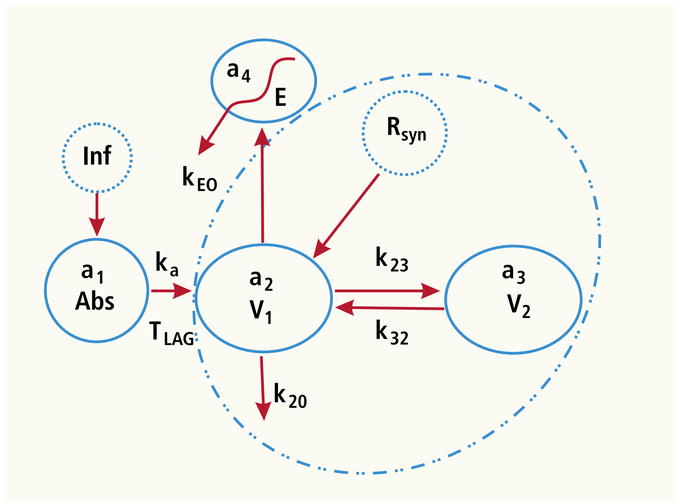
Table 1. *Baseline scores for the patients at the day before the days of measurements.*

Score	Patient:	A		B		C
	Day:	1	2	1	2	1
Total UPDRS		29	33	42	24	61
Hoehn & Yahr		2	2	3	2.5	3
Schwab & England		90	90	80	90	80

A 'bolus' dose (normal morning dose plus 50%) was given with the Duodopa pump after a washout during the night. Patient A was, however, allowed to take levodopa up to 4 hours before the start of measurements. Data collection continued until the clinical effect was back at baseline. At this point, the patient's normal infusion rate was started. This procedure was repeated on two non-consecutive days per patient. Patient C, however, did not complete the second day. Blood samples and effect measurements were collected in 5 to 15 minutes intervals. The main effect variable was 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. Details of this procedure are described in [2].

Modelling was done in the NONMEM package [http://www.globomaxservice.com/nonmem.htm]. We used the same elimination and distribution model with the same parameter values and individual variances as in the paper by Chan, Nutt and Holford [1]. The structure of the model is shown in Figure 1. Different models for absorption and effect were evaluated by minimising the value of NONMEM's objective function, given that parameter estimations were successful.

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



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

$$\frac{da_1}{dt} = -k_a a_1$$

$$\frac{da_2}{dt} = BIO \cdot k_a a_1 - (k_{23} + k_{20}) a_2 + k_{32} a_3 + R_{syn}$$

$$\frac{da_3}{dt} = k_{23} a_2 - k_{32} a_3$$

$$\frac{da_4}{dt} = k_{EO}(a_2 / V_1 - a_4 / 1L)$$

In addition, there is an initial lag-time parameter for the absorption, T_{LAG}.

where:

R_{syn}	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 (min-1)
BIO	Bioavailability (fraction absorbed)

The following derived PK parameters were estimated:

$CL=k_{20}V_1$	Clearance (L/min)
$Q=k_{23}V_1=k_{32}V_2$	Intercomparmental clearance (L/min)
$T_{ABS}=1/k_a$	Absorption time constant (min)
$T_{KEO}=1/k_{EO}$	Effect time constant (min)

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

$$E = BASE + \frac{E_{\max} a_4^{\gamma}}{a_4^{\gamma} + EC_{50}^{\gamma}}$$

References

1. Chan PL, Nutt JG, Holford NH. Importance of within subject variation in levodopa pharmacokinetics: a 4 year cohort study in Parkinson's disease. J Pharmacokinet Pharmacodyn. 2005 Aug;32(3-4):307-31.
2. Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology. 2005 Jan 25;64(2):216-23.

Results

Our preliminary results indicate that the absorption can be modelled with an absorption compartment with an added bioavailability fraction and a lag time. Estimates of parameters are shown in Table 2. The most successful effect model was of sigmoid E-max type with a steep Hill coefficient (Gamma). Actual and predicted levodopa concentrations and motor ratings for the three patients are shown in Figure 2.

Table 2. *Estimated model parameters. The column at right shows population parameters from the reference [1]. These parameters and their estimated between-subject variabilities were fixed in our model. Standard errors of the estimates could not be obtained.*

Parameter	Patient:	A		B		C	"Population" (A,B,C)	Population [1]
	Day:	1	2	1	2	1		
T_{ABS}		28	29	23	14	12	20	
T_{LAG}		3	8	8	13	2	6	
BIO		0.64	0.61	0.60	0.60	0.63	0.61	
V_1		12	12	12	12	11	11	11
V_2		28	26	31	33	30	27	31
CL		0.4	0.5	0.5	0.5	0.5	0.5	0.5
Q		0.3	0.4	0.7	0.7	0.5	0.6	0.6
R_{syn}		0.01	0.19	0.01	0.01	0.01	0.01	0.01
BASE		-2	-1	-1	-1	-2	-1	
E_{max}		2	2	3	4	4	3	
EC_{50}		1	2	1	1	1	1	
T_{KEO}							12	
Gamma							11	

Figure 2(a-c). *Actual and predicted levodopa concentrations and motor ratings for a selected day for each of the three patients. Smoothened lines connect data points for readability. Missing points indicate levodopa levels under the detection limit (0.2 mg/L). Arrows indicate when infusion was given*

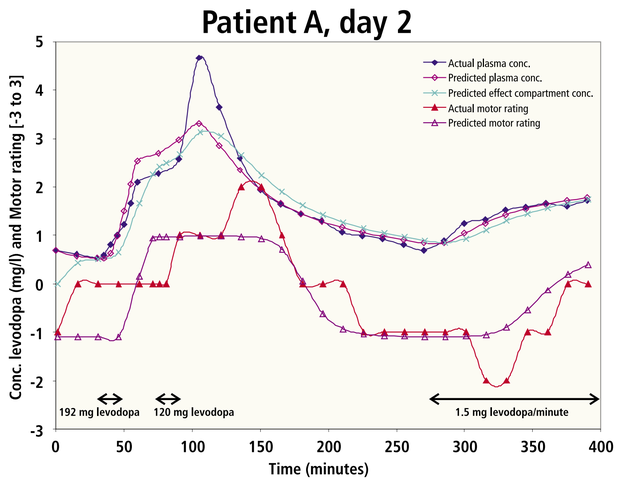


Figure 2a. *Patient A. The pump was stopped for 22 minutes while giving the increased morning dose.*

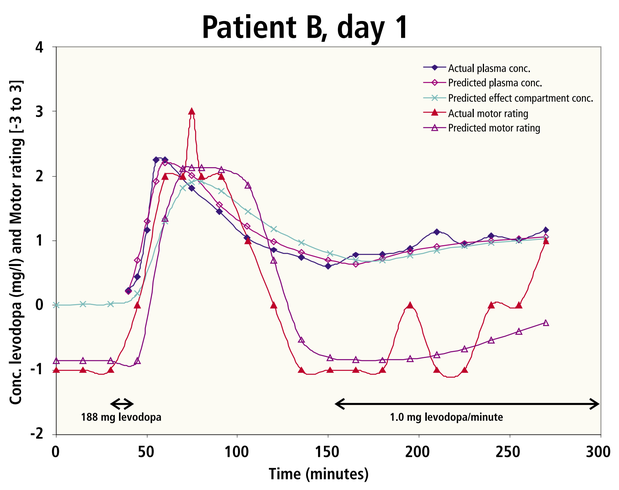


Figure 2b. *Patient B.*

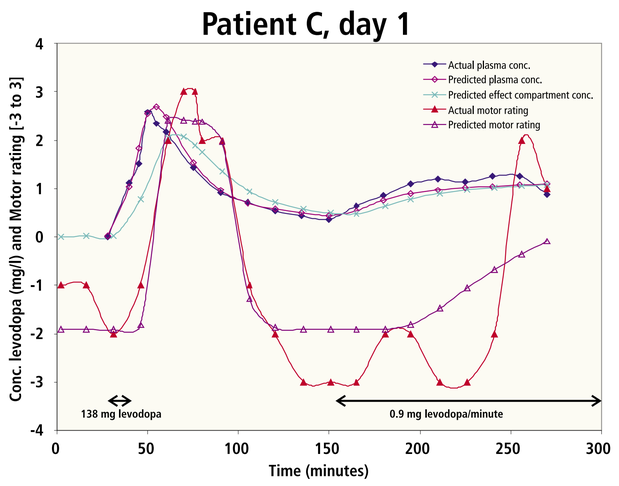


Figure 2c. *Patient C.*

Discussion

These results are from a very small study and data have not yet been fully validated. Differences between days in total UPDRS scores in Table 1 demonstrate the normal intraindividual clinical variability. The figures 2 a, b and c demonstrate the ability to predict plasma concentration as well as effect compartment concentration, although it is to a lesser extent possible to predict motor rating. Given the discrete steps in the motor rating scale and the fact that psychological and other levodopa-unrelated factors may influence the patient state, we still find the fit of the model to data reasonably good.