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 Hofold [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.

<table>
<thead>
<tr>
<th>Score</th>
<th>Patient</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total UPDRS</td>
<td></td>
<td>29</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>Hoon &amp; Yahr</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Schwab &amp; England</td>
<td></td>
<td>90</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

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 Hofold [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:

\[
\begin{align*}
\frac{dC}{dt} &= -k_1 a_i \\
\frac{dC}{dt} &= \text{BIO} \cdot k_2 b_i - (k_3 + k_4) b_i + k_5 a_i + R_{\text{in}} \\
\frac{dC}{dt} &= k_6 b_i + k_7 a_i \\
\frac{dC}{dt} &= k_8 a_i / V_i = a_i / \langle I \rangle
\end{align*}
\]

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

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 intradividual 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.

Discussion

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

\[
E = \text{BASE} \cdot \frac{E_{\text{max}} \cdot \text{ABS}}{a_1 + E \cdot C_{\text{in}}} \]

References

