Modelling Time Varying PK Using Concentration Dependent Feedback Control on Clearance

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INTRODUCTION

A compound which is currently under clinical development for a psychiatric indication has exhibited dose and time dependent pharmacokinetics (PK), showing less than expected accumulation at steady state. Although the reason for the time varying PK is not clearly understood at the moment, a possible autoinduction phenomena has been postulated. Due to the time-varying PK it is difficult to predict the exposure of this compound under different dose regimens. Therefore, a better understanding of the time course of the autoinduction could help in optimizing the dosing regimens. A mechanistic model using enzyme turnover was selected in this case to model the time-varying PK.

OBJECTIVES

a) to model the time-varying PK of the compound using a mechanistic approach

b) to understand the impact of the enzyme turnover on the PK of the compound

METHODS

Data

Pharmacokinetic data from three repeat dose Phase I studies conducted in healthy volunteers (n= 65) were included in the analysis. The compound was administered as 25, 50, 100 and 150 mg BID doses for 28 days (in two studies) and 14 days (in one study). Full PK profile was obtained on days 1, 14 and 28.

Modelling

A two compartment model with first order absorption was used to characterize the compound disposition. The analysis was conducted using the NONMEM program, version V, with FO method. The interindividual variability was expressed using an exponential relationship. A proportional error model was used to model residual variability.

A change in the enzyme turnover was used as a mechanistic model to characterize the autoinduction. The enzyme production is stimulated by the drug plasma concentration in a non-linear fashion and the enzyme level regulates the drug clearance (Fig. 1). Linear dependence of the stimulation of the enzyme production and linear and nonlinear dependence inhibition of the enzyme degradation were also tested. The baseline enzyme level was set to 1. Equations below describe the final selected model:

$$\frac{dA_1}{dt} = -k_a \cdot A_1$$

$$\frac{dA_2}{dt} = k_a \cdot A_1 - \left(\frac{Cl}{V}\right) \cdot A_{enz} \cdot A_2 - k_{12} \cdot A_2 + k_{21} \cdot A_3$$

$$\frac{dA_3}{dt} = k_{12} \cdot A_2 - k_{21} \cdot A_3 \qquad C_p = A_2 / V$$

$$\frac{dA_{enz}}{dt} = k_{enz} \cdot \left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) - k_{enz} \cdot A_{enz}$$

where k_a is the first order absorption rate, Cl is clearance, V is volume of distribution, V_2 is the volume of distribution of the peripheral compartment, Cl_{inter} is the intercompartmental clearance, A_{enz} is the amount of enzyme in the enzyme pool, k_{enz} in the first order rate constant for degradation of the enzyme, SC_{50} is the drug concentration producing 50% of stimulation and S_{max} is the maximum stimulatory capacity. The half-life of the enzyme turnover was calculated as ln2 divided by k_{enz}.

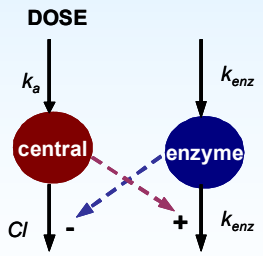

Figure 1. Schematic representation of the PK model

RESULTS

The data were best described using a model in which the drug plasma concentration stimulates the enzyme production. Goodness of fit plots are shown in Figure 2. Model parameter estimates are listed in Table 1.

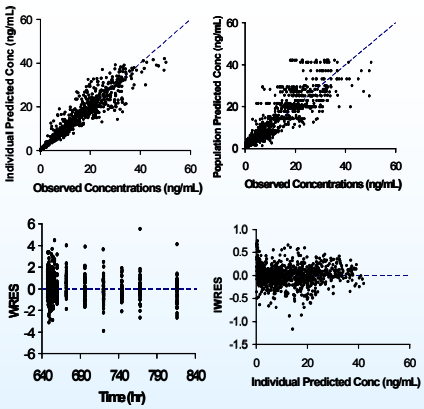

Figure 3. Goodness of fit plots on Day 28

Table 1: Estimated model parameters

Parameter	Estimate (RSE)[a]	Inter-individual Variability (RSE)[b]
k_a (hr^{-1})	1.38 (9.6)	100 (22)
V_c (L)	17.3 (6.4)	33 (45)
Cl ($L.hr^{-1}$)	0.282 (74)	18 (63)
V_2 (L)	46.3 (15)	63 (54)
Cl_{inter} ($L.hr^{-1}$)	2.35 (19)	56 (41)
k_{enz} (hr^{-1})	0.0095 (18)	130 (43)
S_{max}	6.09 (92)	n.e.
SC_{50} (ng/mL)	5.21 (80)	87 (62)
Residual error		
proportional [b]	19 (7.9)	-

n.e. not estimated
[a] Population estimate (relative standard error in percent)
[b] % CV (relative standard error in percent)

Figure 3 shows, for a typical subject, the observed and predicted plasma concentration on the three days in which PK was measured including the washout after the last dose on Day 28.

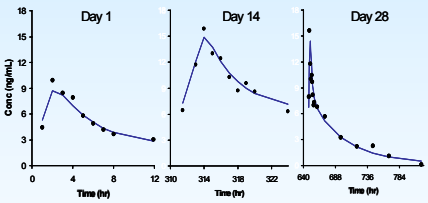

Figure 3. Observed and predicted concentrations in a typical subject

Figure 4 shows the temporal change in clearance for the different dose levels. As the drug enters in the central compartment, stimulates the enzyme pool which in turn increases the Cl. At the steady state, there is a 4-fold increase in Cl for the low dose and a 5.5-fold increase for the top dose. Therefore, the drug plasma concentration achieved at the top dose is almost producing the maximum possible stimulation of 6-fold according to the estimated S_{max} value of 6.09.

The rate constant for the first order degradation of the enzyme was 0.228 day-1, which corresponds to a half-life of 3 days. This means that it would take about 15 days to achieve the steady state enzyme autoinduction, as reflected in Figure 4.

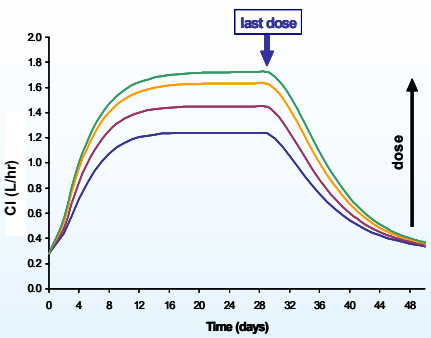

Figure 4. Temporal change in clearance for the different dose levels

CONCLUSIONS

- The proposed enzyme turnover model was appropriate to describe the time varying pharmacokinetics of the compound.
- This mechanistic autoinduction model will be useful to determine the most suitable dosing regimen to achieve the target exposure.

REFERENCES

- Hassan M, Sevensson USH, Bjorkstrand B *et al*. A mechanism-based pharmacokinetic-enzyme model for cyclophosphamide autoinduction in breast cancer patients. Br J Clin Pharmacol 1999; 48:669-677.
- Kerbusch T, Mathot RAA, Keizer HJ *et al*. Influence of dose and infusion duration on pharmacokinetics of ifosfamide and metabolites. Drug Metab Dispos 2001; 29: 967-975.