

The Use of Population Approach to Characterize PK Time-course with Erratic Absorption

Stefano Zamuner PhD and Roberto Gomeni PhD

Clinical Pharmacokinetics Modelling & Simulation – CPDM, GlaxoSmithKline, Verona, Italy

INTRODUCTION

The majority of drugs are given orally, and it is well known that intra- and inter-individual variations in the gastro-intestinal process may lead to large variability in the rate and extent of drug absorption. Usually PH-dependent absorption of weakly acid or basic drugs in the unionized lipid-soluble is an important reason of intra- and inter-individual variations.

The rate of gastric emptying is another important factor. Drug are usually very rapidly absorbed in the small intestine because of the much greater surface area compared with stomach. Thus, the rate of drug absorption is directly related to the rate of gastric emptying^{1,2}. Gastric emptying may account for much of the observed individual variation in drug absorption since is influenced by many factor such as emotional state, posture, food, PH, viscosity and temperature, surface active agents.

OBJECTIVES

Develop a population pharmacokinetics model describing the high variable absorption of a new CNS compound explored in neurological and psychiatric disorder accounting for intra and inter-subjects variability from a single ascending dose study.

Simulate the impact of variability in absorption (inter- and intra-subject) on a steady state levels expected after repeat dosing administration.

METHODS

Twenty subjects received a single dose from 10 to 250 mg. Each subject received up to four ascending doses on separate occasions. High intra-subjects variability (40-60%) likely due to PH-dependent absorption and/or gastric emptying time was observed. Concentration-time data were analyzed using nonlinear mixed-effect modeling (NONMEM) assuming a variable rate and extent of absorption from occasion-to-occasion.

Model

A first order-absorption with two-compartmental model has been used.

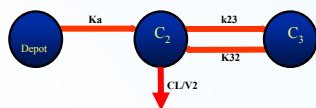


Figure 1. Schematic representation of the two-compartment model with first order absorption

Initially, a two compartmental model with first order absorption accounting only for inter-individual variability (IIV) has been used. Then, the same structural model including inter-occasions variability (IOV) in both ka (rate of absorption) and extent of absorption (F) was developed. Different models including IOV on absorption rate and/or extent of absorption were tested. The model selection has been done using diagnostic plots and statistical criteria (log-likelihood and posterior predictive check).

Model for IIV and IOV

The following exponential models were evaluated to describe IIV and IOV variability:

$$P_{ij} = P^* \cdot e^{(\eta_i + k_{ij})}$$

$$\eta_i \approx N(0, \omega^2)$$

$$k_{ij} \approx N(0, \pi^2)$$

where P^* is a typical value of P in the population and η_i and k_{ij} are assumed to be independently, normally distributed parameters both with zero mean and variance ω^2 and π^2 , respectively.

The η_i represents the between individual difference (IIV) and the k_{ij} the between occasion difference within an individual (IOV).

The residual error on PK data was modelled using both proportional (σ_1) and additive (σ_2) model.

RESULTS: MODELLING

The comparison between all the different models led to select the one accounting for IOV in both rate and extent of absorption (Table 1).

- Model A represents the model without IOV
- Model B applied the IOV on the F parameter (extent of absorption)
- Model C applied the IOV on both F and Ka parameters

Moreover, the highest source of variability has been identified in the inter-occasion variability for the extent of absorption suggesting the critical role of inter-occasion variability for the future development of this compound.

Table 1 Non-linear mixed effects modelling: fixed and random effects parameter values (The IIV, IOV and proportional residual error variability are expressed as CV%). Model A: IIV, Model B: IIV + IOV on F, Model C: IIV + IOV on F and Ka

Parameters	Model A	Model B	Model C
CL (L/h)	9.18	7.25	7.33
k_{23} (h ⁻¹)	0.106	0.165	0.192
k_{32} (h ⁻¹)	0.197	0.227	0.251
V (L)	134	107	101
Ka (h ⁻¹)	2.19	2.39	2.02
ω_{CL}	30	19	20
$\omega_{k_{23}}$	85	70	56
$\omega_{k_{32}}$	< 1	8	23
ω_V	22	8	< 1
ω_{Ka}	80	70	63
π_F	-	120	120
π_{Ka}	-	-	69
σ_1 (proportional)	25	13	8
σ_2 (additive)	44	13	13
OF	9955	8965	8384
ΔOF		990	1607

The best model, selected according to the log-likelihood criteria, is model C (typical fitting reported in Figure 2)

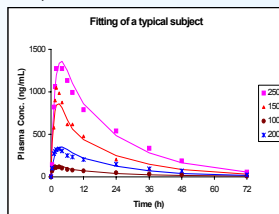


Figure 2. Typical subject profile and fitting

The overall evaluation of the fit obtained with Model C is illustrated by a good agreement between individual predictions vs. observed values with the unitary slope reference line (Figure 3).

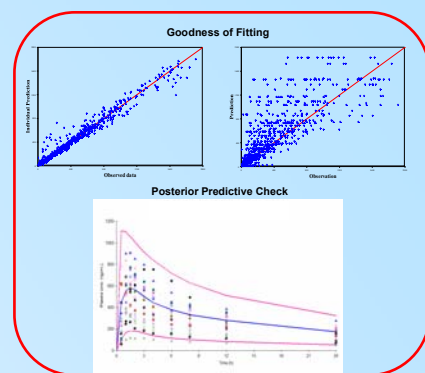


Figure 3. Predicted versus observed plots (upper panels) and posterior predictive check (obtained from Monte Carlo simulation approach, N=1000)

SIMULATION

The current PK model developed from the single ascending dose study data has been used to simulated repeated dose profiles.

The following assumptions have been made:

- time independent kinetic over the time
- erratic, random absorption as observed in the single dose study

The simulation approach has provided guidelines to design the next repeat study in human volunteers (Figure 4). The aims of the simulation were to predict the degree of individual variability after chronic treatment and to establish confidence interval (5th and 95th percentiles) of exposures (AUC and Cmax) at certain dose preventing to exceed safety margin set by the toxicological preclinical data.

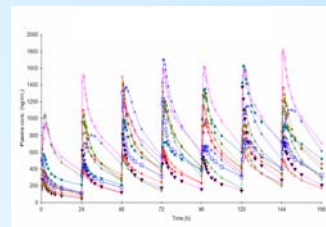


Figure 4. Simulated PK profile after repeat dose administration (7 days, N=10)

CONCLUSIONS

An appropriate population PK model was successfully developed to characterize plasma concentration-time data of the drug after oral administration. Based on the results, the influence of the erratic absorption profiles on the PK after repeat dose has been predicted using a simulation approach assuming time independent behaviour.