Inter- and intra-individual variability in gastro-intestinal physiology has significant effects on the prediction of the fraction of dose absorbed (f_a)

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Introduction

Drug absorption is a complex process affected by physicochemical properties of the compound such as solubility, permeability, formulation factors, and physiological variables including regional permeability differences, pH, luminal and mucosal enzymology, and gastric and intestinal motility (Burton *et al*., 2002). These physiological variables significantly contribute to inter- and intra-subject variability of observed f_a in *in vivo* studies.

In order to obtain reliable estimates of oral bioavailability for drug candidates, predictive physiologically-based (PB) PK models are being applied increasingly in drug development. However, the application of such models without consideration of inter- and intra-individual variability of the physiological parameters in the target population may lead to flawed conclusions. The aim of this communication was to study the extent of the influence of physiological parameters on the predicted f_a.

Results and Discussion

The simulation results for four compounds (fluvastatin, metoprolol, terbutaline, and enalaprilat) are shown in Figure 1, in which the median, 5th and 95th percentiles of f_a for each trial and the population are given. Table 1 provides the population statistics which demonstrate the significance of physiological parameters variability on the predicted f_a for each compound.

Table 1 – The range of variation for the predicted f_a

f_a	Enalaprilat	Terbutaline	Metoprolol	Flovastatin
Minimum	0.05	0.24	0.39	0.47
Median	0.29	0.51	0.88	0.97
Maximum	0.46	0.73	0.97	1
Observed	0.10	0.44	0.88	0.95

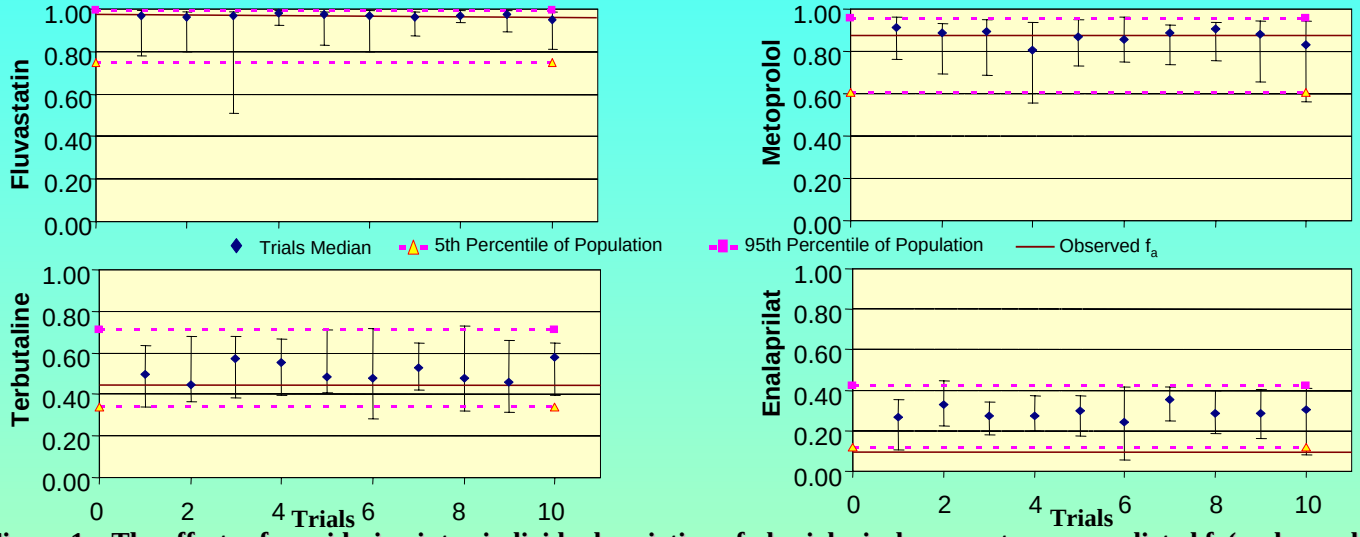

Figure 1 – The effects of considering inter-individual variation of physiological parameters on predicted f_a (each graph shows the results from 10 trials with a group of 10 randomly selected individuals; see methods for further details)

Methods

The Compartmental Transit and Absorption (CAT) model (Yu & Amidon 1999) and literature values defining the variability of relevant aspects of gastrointestinal physiology (Argenyi *et al*., 1995) were implemented in Simcyp®. The parameters were: gastric emptying time, Ts, small intestinal transit time, Tsi, and the radius and length of the small intestine, R and L, respectively. Model drugs with a wide range of permeability characteristics were studied, including enalaprilat (a poorly permeable compound; Peff= 0.079 cm/h) and antipyrine (a highly permeable compound; Peff= 2.02 cm/h) (Lennernas et al. 1994).

Simulations were carried-out using a virtual North-European Caucasian population of 100 subjects (age 20-50 years and 50% female) repeated for 10 separate trials. In each trial, a group of 10 subjects were randomly selected and their physiological characteristics were determined according to the population demographic specifications provided in Simcyp®. Then, based on the drug and physiological data f_a was predicted for each individual.

The predicted values of f_a for fluvastatin were less susceptible to variability in physiological parameters, and the predicted medians for trials and the population were very close. These results suggest that sensitivity to inter-individual differences would be more significant for less permeable compounds, and support the claim that the prediction sensitivity to physiological parameters diminishes as permeability exceeds 1 cm/h (Jamei *et al.*, 2004).

Conclusions

The outcome of this study confirmed the assertion that inter- and intra-variability of the parameters should be considered in any predictive PB modelling studies, particularly when less permeable drugs are investigated. Inconsistency between point estimates of f_a and observed values from small clinical studies may be expected if inter- and intra-individual variability is not considered.

References

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