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Modeling the heterogeneous intestinal absorption of propiverine extended-release

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ABSTRACT

Propiverine is a widely used antimuscarinic drug with bioavailability that is limited by intestinal first-pass extraction. To study the apparent heterogeneity in intestinal first-pass extraction, we performed a population analysis of oral concentration–time data measured after administration of an extended-release formulation of propiverine in ten healthy subjects. Using an inverse Gaussian function as input model, the assumption that the systemically available fraction increases as a sigmoidal function of time considerably improved the fit. The step-like increase in this fraction at time $t = 3.7$ h predicted by the model suggests that propiverine is predominantly absorbed in colon. A nearly perfect correlation was found between the estimates of bioavailability and mean dissolution time.

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1. Introduction

Propiverine is a widely used muscarine receptor blocking drug for the treatment of patients suffering from hyperactive bladder syndrome. From a pharmacokinetic point of view, it is an interesting and unique property of propiverine that the extended-release formulation (ER) has a higher bioavailability than immediate-release tablets (May et al., 2008). The authors suggested a lower first-pass metabolism (CYP3A4) and efflux transport (P-glycoprotein and MRP2) of propiverine in the distal small intestine and colon. This was supported by a positive correlation between bioavailability and mean absorption time. However, no modeling of the absorption process was carried out. Therefore, the objective of the present study was first to reanalyze the ER data using a parametric absorption model. The selection of the inverse Gaussian function as input model (Weiss, 1996; Wang et al., 2008) was was also motivated by the fact that in a pilot study this model well described the in vitro dissolution data of propiverine ER. Second, we tried to improve the model by incorporating a systemically available fraction (absorption and intestinal first-pass availability) that increases with intestinal transit time. Despite its simplicity, the novel input model considerably improved the fit and the results are in line with the reported expression of relevant CYP enzymes and transporters along the gastrointestinal tract (Berggren et al., 2007; Zimmermann et al., 2005). The model may be used as a first indicator of regional differences in intestinal drug uptake.

2. Material and methods

2.1. Data and study protocol

The experimental protocol of the bioavailability study in healthy volunteers has been described before (May et al., 2008). Here we refer only to the data obtained after intravenous injection (IV) and administration of extended-release capsules (propiverine ER containing 45 mg propiverine hydrochloride; Mictonorm®, APOGEPHA, Dresden, Germany). In brief, in a randomized, controlled, crossover study with a washout period of at least 7 days, ten healthy German white subjects (six males, four females; age 22–26 years) received 15 mg propiverine hydrochloride by IV bolus injection (5 min) and 10, 15, 30 and 45 mg propiverine ER swallowed using 200 ml table water. Blood samples were taken before the IV injections and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48 and 72 h thereafter. For propiverine ER, the sampling times were before administration and after 1, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 72 and 96 h. The serum concentrations of propiverine were measured using liquid chromatography–tandem mass spectrometry (LC–MS/MS) after solid phase extraction with a lower limit of quantification of 0.78 ng/ml and a within-day precision <10%.

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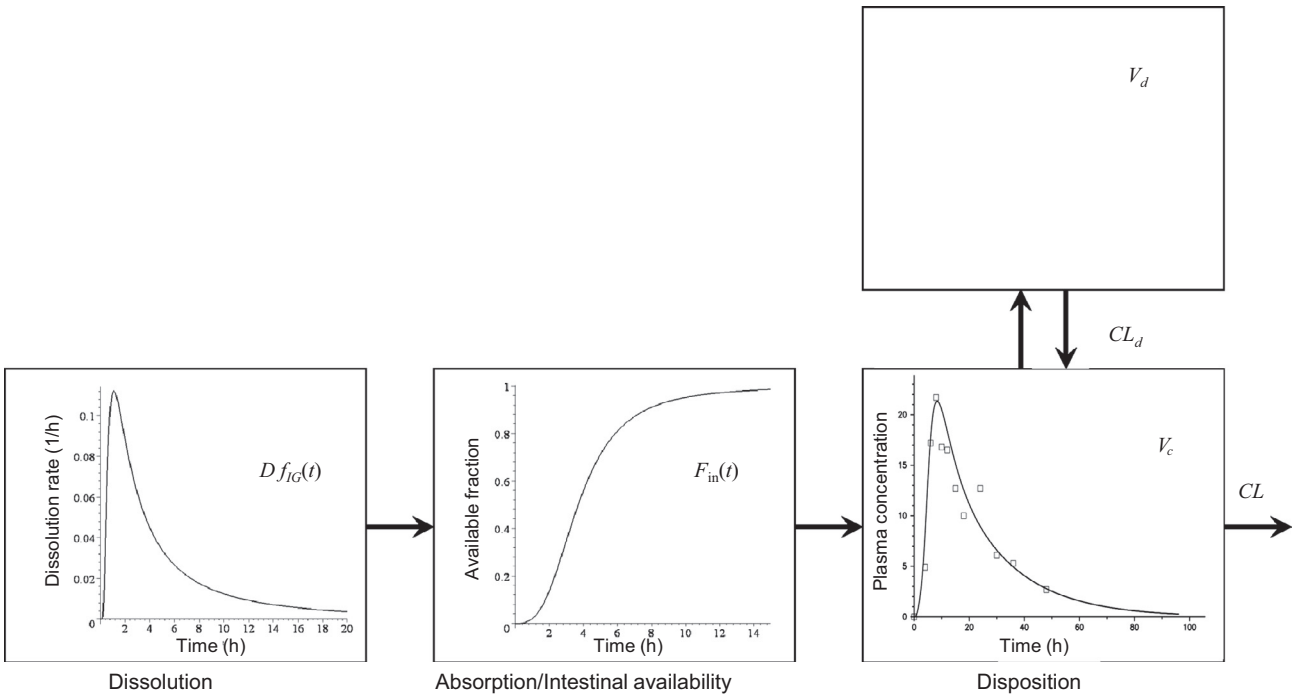

Fig. 1. Two-compartment disposition model with an input function consisting of an in vivo dissolution rate (inverse Gaussian density) and a fraction absorbed as function of time (IG-$F_{in}(t)$ model).

Table 1
Population mean values and interindividual variability (% coefficient of variation in brackets) estimated from data obtained following intravenous administration.

Parameter	Values (% CV)	Description
CL (l/h)	12.9 (35)	Clearance
V_c (l)	89.2 (31)	Central volume
CL_d (l/h)	10.1 (28)	Distribution clearance
V_p (l)	79.3 (15)	Peripheral volume

2.2. Pharmacokinetic model

The plasma concentration–time curve of a drug after oral administration is the result of two independent processes, drug input into and elimination from the systemic circulation. To define the input function $I(t)$, it was assumed that the rate of propiverine release from propiverine ER is the rate-limiting step of the input process. We used the inverse Gaussian density function, $f_{IG}(t)$, to model the dissolution time distribution of slow release formulations in vivo and in vitro (Wang et al., 2008; Weiss, 1996)

$$f_{IG}(t) = \sqrt{\frac{MDT}{2\pi RD^2 t^3}} \exp\left[-\frac{(t-MDT)^2}{2RD^2 MDT\, t}\right] \quad (1)$$

MDT and RD^2 denote the mean and the relative dispersion (normalized variance) of dissolution time, respectively. The input function is then given by (IG-F model)

$$I(t) = DF f_{IG}(t) \quad (2)$$

The factor F is the bioavailability of the orally administered dose D. Based on a two-compartment model for propiverine disposition kinetics, the drug amounts in the central (x_c) and peripheral compartments (x_p) are described by the differential equations:

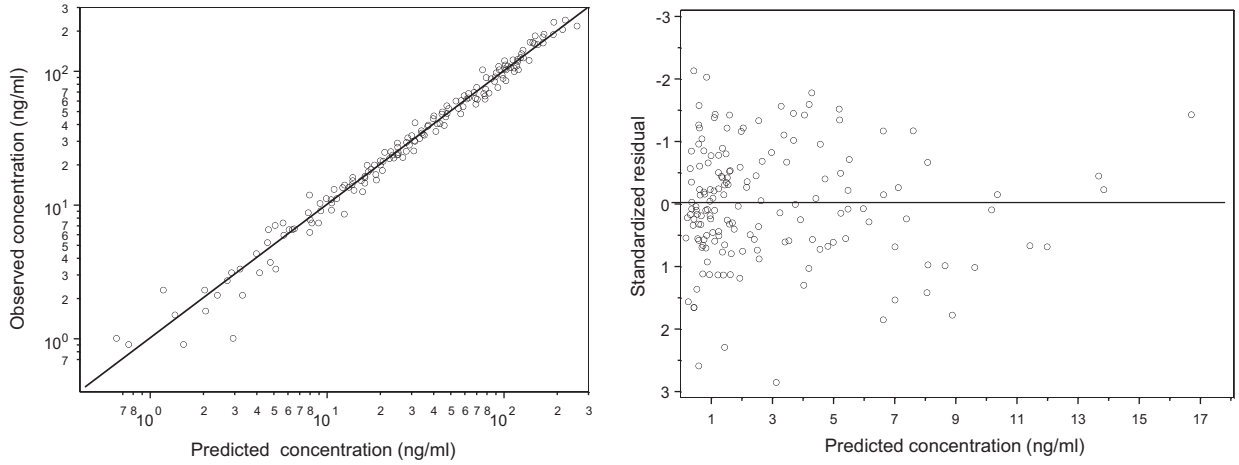

Fig. 2. Plots of individual predicted vs. observed concentrations and standardized residuals vs. individual predictions for the fit of the 15 mg propiverine IV dose data in 10 subjects obtained with a two-compartment model. The solid lines presents the line of identity and the zero reference line, respectively.

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