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Research Paper

Whole-body physiologically based pharmacokinetic population modelling of oral drug administration: inter-individual variability of cimetidine absorption

Stefan Willmann[a], Andrea N. Edginton[b], Marcus Kleine-Besten[c], Ekarat Jantratid[c], Kirstin Thelen[c] and Jennifer B. Dressman[c]

[a]Bayer Technology Services GmbH, Leverkusen, Germany, [b]School of Pharmacy, University of Waterloo, Ontario, Canada and [c]Institute of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany

Abstract

Objectives Inter-individual variability of gastrointestinal physiology and transit properties can greatly influence the pharmacokinetics of an orally administered drug *in vivo*. To predict the expected range of pharmacokinetic plasma concentrations after oral drug administration, a physiologically based pharmacokinetic population model for gastrointestinal transit and absorption was developed and evaluated.

Methods Mean values and variability measures of model parameters affecting the rate and extent of cimetidine absorption, such as gastric emptying, intestinal transit times and effective surface area of the small intestine, were obtained from the literature. Various scenarios incorporating different extents of inter-individual physiological variability were simulated and the simulation results were compared with experimental human study data obtained after oral cimetidine administration of four different tablets with varying release kinetics.

Key findings The inter-individual variability in effective surface area was the largest contributor to absorption variability. Based on in-vitro dissolution profiles, the mean plasma cimetidine concentration–time profiles as well as the inter-individual variability could be well described for three cimetidine formulations. In the case of the formulation with the slowest dissolution kinetic, model predictions on the basis of the in-vitro dissolution profile underestimated the plasma exposure.

Conclusions The model facilitates predictions of the inter-individual pharmacokinetic variability after oral drug administration for immediate and extended-release formulations of cimetidine, given reasonable in-vitro dissolution kinetics.

Keywords dissolution; inter-individual variability; oral absorption; physiologically based pharmacokinetic; whole-body modelling

Introduction

In-silico modelling of the fate of drugs in an organism following several routes of administration has become a means to both understanding and predicting a drug's pharmacokinetic profile. Software tools that merge physiological models of absorption, distribution, metabolism and elimination (ADME) with physico-chemical properties of the drug have evolved as a cost-effective way of gaining experience with the drug and/or formulation prior to, or during, clinical studies.[1–3] In response to the needs of pharmaceutical scientists, commercial and in-house in-silico software development has kept pace with demand. Continual enhancement is required to address new queries, and one that is of great interest is predictive population pharmacokinetic modelling. Historically, predictive pharmacokinetic models have been used to determine the pharmacokinetic profile of a drug and/or formulation in the mean individual. There is much knowledge to be gained, however, in estimating ADME variability prior to undertaking costly clinical studies.

Recently, a predictive population pharmacokinetic model was developed and used to assess the variability of ciprofloxacin and paclitaxel pharmacokinetics following intravenous administration.[4] This population module was incorporated in PK-Sim software (Bayer Technology Services GmbH, Leverkusen, Germany), which contains

Correspondence: Dr Stefan Willmann, Bayer Technology Services GmbH, Process Technology/Systems Biology, Building E41, D-51368 Leverkusen, Germany.
E-mail: stefan.willmann@bayertechnology.com

a whole-body physiologically based pharmacokinetic (PBPK) model and utilizes predictive algorithms to estimate organ : plasma partition coefficients, organ-specific permeability-surface area products and the rate and extent of gastrointestinal absorption. Previous population analyses for drugs administered intravenously have shown that variability in plasma concentration–time profiles can be well described by taking into account realistic distributions of physiological parameters (e.g. organ volumes, organ blood flows, and renal and hepatic clearance).[4] Thus far, pharmacokinetic variability of drugs administered perorally in various formulations has not been considered in the model. An accurate quantitative determination of the variability in the physiological parameters that define the rate and extent of gastrointestinal absorption is expected to be an integral part of predicting the range of plasma concentration–time profiles of drugs given orally. Furthermore, formulation effects must also be considered in order to accurately predict the ADME profile for a virtual population.

The objective of this study was to incorporate information about the inter-individual variability of relevant physiological absorption parameters into an existing population model in order to facilitate predictions of inter-individual pharmacokinetic variability following oral drug administration.[4] Cimetidine was chosen as a model drug for this study. Cimetidine is an antagonist of the histamine H_2-receptor that inhibits the secretion of gastric acid. This drug is available in a variety of oral dosage forms for the treatment of duodenal and gastric ulcers.[5] Jantratid *et al*. presented plasma concentration–time profiles of cimetidine in 12 healthy male subjects following intravenous and oral administration of a commercially available immediate-release (IR) formulation (Tagamet) as well as three experimental extended-release (ER) formulations.[6] In-vitro dissolution data for each oral formulation were also available. This dataset was found to be suitable for the development and evaluation of the population module for orally administered drugs.

Materials and Methods

Model development: software used

All PBPK simulations were carried out using the population module of the PK-Sim software, Version 3.0 (Bayer Technology Services GmbH, Leverkusen, Germany).[1] PK-Sim is based on a generic PBPK-model with 17 organs and tissues, including arterial and venous blood, adipose tissue (separable adipose, excluding yellow marrow), brain, bone (including yellow marrow), gonads, heart, kidneys, large intestine, liver, muscle, portal vein, pancreas, skin, small intestine, spleen and stomach. The gastrointestinal absorption model as well as the substructure of the organs has been described in detail elsewhere.[7,8] Modelling of absorption into the portal vein after oral administration requires two main substance-specific input parameters: intestinal permeability and solubility.[8] By default, the intestinal permeability coefficient is calculated from the compound's lipophilicity and effective molecular weight (see equation 9 in Willmann *et al*. 2004[8]), but other sources for permeability input are also possible, e.g. permeability coefficients derived from Caco-2 or parallel artificial membrane permeability (PAMPA) assays. In the latter case, a correlation using a set of compounds with known in-vivo absorption has to be established. This can be used to translate the experimentally derived permeability into the intestinal permeability coefficient required by the model. As solubility input, the solubility determined under biorelevant conditions, e.g. using media such as fasted state simulating intestinal fluid (FaSSIF) or fed state simulating intestinal fluid (FeSSIF), is preferred.[9,10] In the case of acids or bases, the pK_a value of every ionizable group is needed in order to calculate the pH dependence of the intestinal solubility and permeability.[11] To predict plasma or tissue concentration–time profiles, additional input parameters are required. The plasma protein binding constant (or alternatively the unbound fraction in plasma) is used together with the compound's lipophilicity to calculate the organ/plasma partition coefficients using a mechanistic approach.[11,12] Lastly, information about the elimination rates has to be parameterized. This can be either in the form of plasma or blood clearance rates (hepatic or renal) or as intrinsic clearance values, which can be defined as elimination rate constants or Michaelis–Menten constants.[11]

Model parameterization

Physico-chemical information

Table 1 presents the relevant physico-chemical parameters of cimetidine. Based on its high aqueous solubility at physiological pH and its low intestinal permeability, cimetidine has been classified as a Biopharmaceutics Classification System (BCS) Class III compound.[6,13,14] This information was used to estimate the organ-specific permeability–surface area products and organ : plasma partition coefficients that determine the rate and extent of distribution into the organs, as described previously.[7] Because of a lack of additional information, these values were held to be the same in each virtual individual except for the plasma unbound fraction, where a uniform distribution within the reported range (73.7–82.0%) was assumed.[15]

Anthropometric data and variation

A virtual population of 100 adult males was created using the approach described previously.[4] Due to the stochastic nature of this approach, it is not possible to exactly match the characteristics of the real study population, but the resulting anthropometric characteristics of the virtual population were very similar to the real study population. The virtual population had a mean age of 21 years with a range of 19–24 years, a mean body height (BH) of 166 cm with a range of 160–171 cm, and a mean body weight (BW) of 61 kg with

Table 1 Physico-chemical parameters used as input parameters for PK-Sim

Physico-chemical parameter	Value
log MA	1.176[8]
Plasma fraction unbound	73.7–82.0%[a]
Molecular weight, M_r	252.34
pK_a	7.1
Water solubility	pH dependent, >2 mg/ml in the whole pH range[15]

[a]Range in concentrations of 0.05–50 μg/l.[16]

a range of 53–67 kg. For comparison, the real study population of Jantratid *et al.* had a mean age of 22 years (range 19–24 years), mean BH of 166 cm (range 160–171 cm) and mean BW of 60 kg (range 53–69 kg).[6] Based on these anthropometric parameters, the algorithm estimated the organ volumes and blood flows for each individual. Variation was then included where an offset was assigned on the basis of previously defined distributions to generate unique individuals in terms of organ volumes and organ blood flows.[4]

Clearance and clearance variability

In addition to the variation of the organ volumes and blood flow rates, which primarily affect the distribution kinetics of the drug once it has reached the systemic circulation, there is a considerable variability in the rate of elimination among different individuals. The primary route of cimetidine elimination is urinary excretion via active tubular secretion. Between 50 and 80% of intravenously administered cimetidine is recovered unchanged in the urine and this is age-dependent (i.e. 65–75% in young individuals, 45–60% in the elderly). A small proportion of the dose is metabolized by the cytochrome P450 system and excreted into the urine as metabolites.[5] The crossover design of the study of Jantratid *et al.* allowed an assessment of the clearance variability of cimetidine in their subjects on the basis of the plasma pharmacokinetics obtained following intravenous administration.[6] The cimetidine plasma concentration–time curves after intravenous administration were fitted for each individual, total plasma clearance being the sole optimized parameter. The resulting distribution of plasma clearance (normal distribution with a mean (± SD) of 9.1 (± 2.9) ml/min per kg) was then applied in PK-Sim for the virtual population. This clearance distribution remained unchanged for all further simulations. Although experimental data at time points greater than 6 h are available in Jantratid *et al.*,[6] such data were omitted in this study. Cimetidine elimination is saturable and obeys a non-linear behaviour leading to right-curvature of the pharmacokinetic profile at time points greater than 6 h in some individuals.[6] Because of the focus on the absorption phase, only the time points up to 6 h have been considered in our analysis.

Gastrointestinal variability

In addition to the anthropometric and clearance variability, the inter-individual variability of the gastrointestinal physiology, including the gastric emptying time (GET), small intestinal transit time (SITT) and total effective surface area available for absorption in the small intestine (A_{eff}), can contribute to the overall inter-individual variability observed after oral administration of cimetidine. These parameters were varied in the population analysis on the basis of the range of values obtained from the literature.

The average GET of liquids in fasted humans is approximately 30 min with a physiological range of 10 to 60 min.[17–19] SITT has been reported to range from 2.7 to 6.6 h with means (ranges are shown in parentheses) of 3.7 h (2.7–4.1 h),[20] 4.0 h (2.5–6.0 h)[18] and 4.0 h (2.7–6.6 h) for young men.[21] In the population simulations, the following normal distributions for GET and SITT were statistically generated in the population module of PK-Sim: GET had a mean (± SD) of 29 min (± 7 min) with a range of 16–47 min and SITT had a mean (± SD) of 4.0 h (± 0.9 h) with a range from 2.4 to 6.8 h.

A_{eff} was varied on the basis of examination of the behaviour of the absorption of drugs where, in addition to the small intestinal length and the diameter of the lumen, the circular folds, villi and microvilli play an important role. These special anatomical features of the small intestine exhibit large intra-intestinal as well as inter-individual variability in size and occurrence, each contributing to the large differences in effective surface area available for absorption. The size and distribution of the circular folds, which represent grossly visible permanent structures, vary from one end of the intestine to the other.[8,22,23] Furthermore, while some of them form crescents, others extend only part of the way around the circumference of the intestine.[23,24] The villi vary in height (~500–1000 μm) and form in different regions of the small intestine. Their number has been estimated to range from 20 to 40 villi/mm^2.[24,25] Similarly, the amplification factor due to microvilli is not uniform along the different regions of each villus, with microvilli in the mid-villus region contributing the greatest amplification factor.[26–28] Considerable variability in the extent of microvillous amplification within each villus region has also been reported. The overall amplification factor determined in jejunal mucosa of four healthy adults ranged from 11.0 to 29.0 and the increase in cell surface area provided by the microvilli in the distal duodenum of six healthy children ranged from 14.0 to 45.5.[26,28] As a result of the reported differences, a quantitative, nine-fold variability in A_{eff} was considered reasonable. In cases of formulations with release profiles that are slow compared to the small intestinal transit time, colonic absorption might contribute significantly to the overall fraction dose absorbed (something that is especially likely for more highly permeable drugs, in which case the high permeability compensates for the much smaller surface area available in the colon than in the small intestinal segments, due to a lack of villi and microvilli). The PBPK model is able to account for colonic absorption.[8] In this study, however, the contribution of the colon to inter-individual pharmacokinetic variability was expected to be low, based on the dissolution profiles,[6] and on the fact that cimetidine is classified as a compound with moderate permeability (BCS class III).[6,13,14]

Intestinal permeability

The intestinal permeability coefficient (P_{int}) is a sensitive parameter in the oral absorption model, especially in the case of a BCS Class III drug.[8] This parameter is, by default, predicted by PK-Sim on the basis of physico-chemical input parameters. For the purpose of this study, P_{int} was also determined by a fit using an independent data set of in-vivo plasma concentration–time data (mean values) obtained following cimetidine administration in form of a solution.[29] When administered in this form, the absorption of the drug is independent of the release and dissolution processes, in contrast to absorption after administration of solid dosage forms. P_{int} was the only parameter optimized using the *fminsearch* optimization routine of MatLab (version 7.0). The objective function was the root mean squared error (RMSE).

Simulations

Five administration scenarios were simulated and compared to plasma concentration–time profiles from the study of Jantratid *et al*.[6] In this study, in-vivo plasma concentration–time data from 12 fasted, healthy, Thai male volunteers was measured following intravenous (300 mg) and oral (400 mg) administration in a cross-over design. One of four oral formulations was a commercial IR tablet (Tagamet). Three other oral formulations were experimental ER tablets with varying content of the release-retarding agent, Eudragit RS PO (7.5, 15 and 26%). In addition, the in-vitro dissolution profiles for the four formulations were previously assessed in different dissolution media with different pH, including the biorelevant dissolution medium, FaSSIF, at pH 6.5.[6] These dissolution profiles were incorporated in the appropriate simulation such that the total drug concentration in the lumen was multiplied by the fraction dissolved to obtain the concentration of the dissolved drug. Between the experimental time points, the fraction dissolved was linearly interpolated.

To study the impact of the inter-individual variability of each gastrointestinal parameter on the plasma concentration–time profile of cimetidine, GET, SITT and A_{eff} were varied alone and in all possible combinations based on the design shown in Table 2. For each oral administration scenario, eight different population simulations were carried out (scenarios A to H, see Table 2). In scenario A, only the anthropometric and clearance variability were taken into account, as in the case of the simulation following intravenous administration. The parameters affecting oral absorption were held identical in all individuals (PK-Sim default values:[8] GET = 30 min, SITT = 4 h and A_{eff} = 70 m^2). In scenarios B, C and D, only one of the gastrointestinal-relevant parameters was varied, in addition to the anthropometric and clearance variability. In scenarios E, F and G, two gastrointestinal parameters were varied in addition to the anthropometric and clearance variability. In scenario H, all sources of inter-individual variability were simultaneously varied.

Assessment of the goodness of prediction

For each simulation, the percentage of experimental plasma drug concentration data points that were included in the simulated 5–95th percentiles was calculated as a measure of the goodness of prediction. Values below 90% indicated that the range of simulated plasma concentration–time profiles is smaller than that observed *in vivo*, while values above 90% indicated that the simulated variability exceeds the inter-individual variability observed *in vivo*.

Table 2 Nomenclature of the population simulation scenarios

Scenario	Anthropometry (BW/BH), clearance (Cl)	Gastric emptying time (GET)	Small intestinal transit time (SITT)	Effective surface area (A_{eff})
A	X			
B	X	X		
C	X		X	
D	X			X
E	X	X	X	
F	X	X		X
G	X		X	X
H	X	X	X	X

The parameters marked with 'X' were stochastically varied in the respective model.

Deconvolution of the in-vivo absorption profiles

The time course of the fraction dose absorbed was calculated via a deconvolution of the experimental plasma concentration–time profiles obtained following oral administration with the corresponding experimental plasma profile following intravenous bolus administration, using the WinNonlin® program Version 4.1 (Pharsight Corp., North Carolina, USA). This was compared to the simulated time course of the fraction dose absorbed from the population simulations.

Results

Optimization of P_{int}

The fit of the plasma concentration–time profile after cimetidine administration in solution form is shown in Figure 1. The optimization resulted in a value of $P_{int} = 5.15 \times 10^{-6}$ cm/s. This value is 1.8 times greater than the value calculated by PK-Sim on the basis of the lipophilicity and molecular weight (2.81×10^{-6} cm/s), as described by Willmann *et al*.[8] This deviation is small considering that the model equation for P_{int} allows deviations between the predicted and observed fraction dose absorbed in the range of about 20% in the case of completely absorbed compounds and about 5% in the case of non-absorbed compounds.[8] The predicted fraction dose of cimetidine absorbed was found to be in this range.[8] The fitted value of $P_{int} = 5.15 \times 10^{-6}$ cm/s was used in all population simulations.

Comparison of population simulations with experimental results

The goodness-of-prediction metrics for the various combinations as defined in Table 2 are presented in Figure 2.

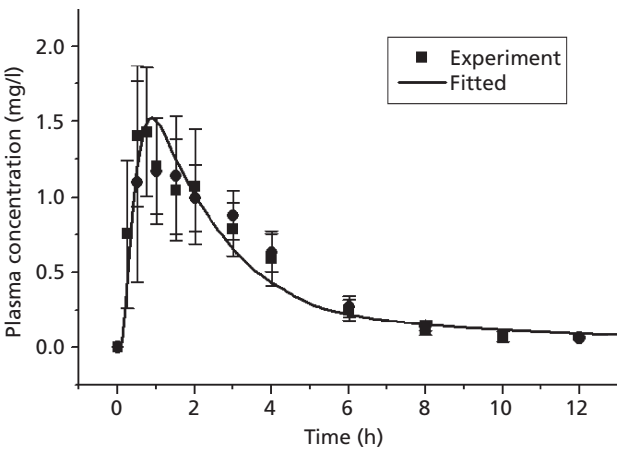

Figure 1 Simulated versus experimental plasma concentration-time profiles of cimetidine. Cimetidine was administered as a solution at a dose level of 300 mg (line) following optimization of the intestinal permeability parameter.[29] Symbols shows the mean ± SD: square, liquid formulation; circle, tablet formulation.

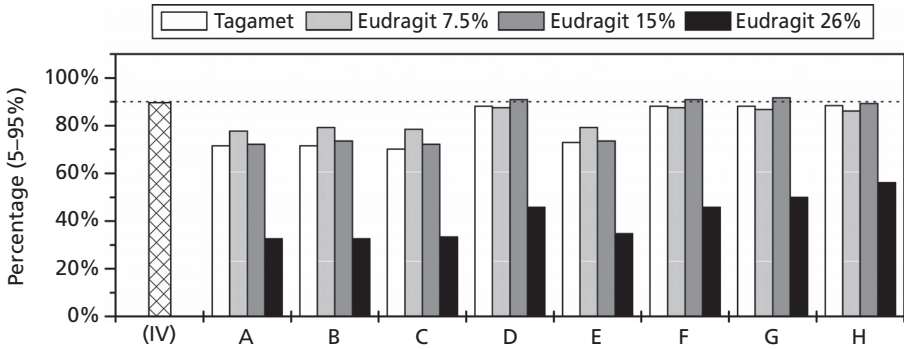

Figure 2 Goodness-of-prediction metrics for population simulations versus experiment. Percentage of experimental plasma concentration–time data points included in the simulated 5–95% confidence interval for the various scenarios A–H (see Table 2). The value of the simulation following intravenous cimetidine administration is shown for comparison.

Following intravenous administration, the simulated 90% confidence interval incorporated 89.7% of the values observed *in vivo* when taking into account anthropometric and clearance variability. In the case of oral administration (scenario A), however, only 72–78% of the experimental data points were found within the 90% confidence interval for the IR, Eudragit 7.5% and Eudragit 15% formulations. For the Eudragit 26% formulation, this value dropped to 33%. In combination with the different sources of gastrointestinal variability, the following pattern could be observed: inclusion of inter-individual variability in GET or SITT (scenarios B and C) did not affect the variability when compared with scenario A, where no gastrointestinal variability was considered. Similarly, the combination of GET and SITT variability (scenario E) showed no effect on the overall goodness-of-prediction. The biggest effect on the inter-individual variability was observed when the variability of A_{eff} was considered. If A_{eff} variability was considered at the same time as GET and SITT variability (scenarios F, G and H) there was little improvement in the goodness-of-prediction compared to consideration of A_{eff} alone (scenario D). It is also evident from Figure 2 that the variability was consistently underestimated in the case of the formulation with the slowest release kinetic (Eudragit 26%), even though the best fit was observed when all parameters were taken into account (scenario H).

Figure 3 presents the comparison of the simulated plasma concentration–time profiles for the virtual population obtained

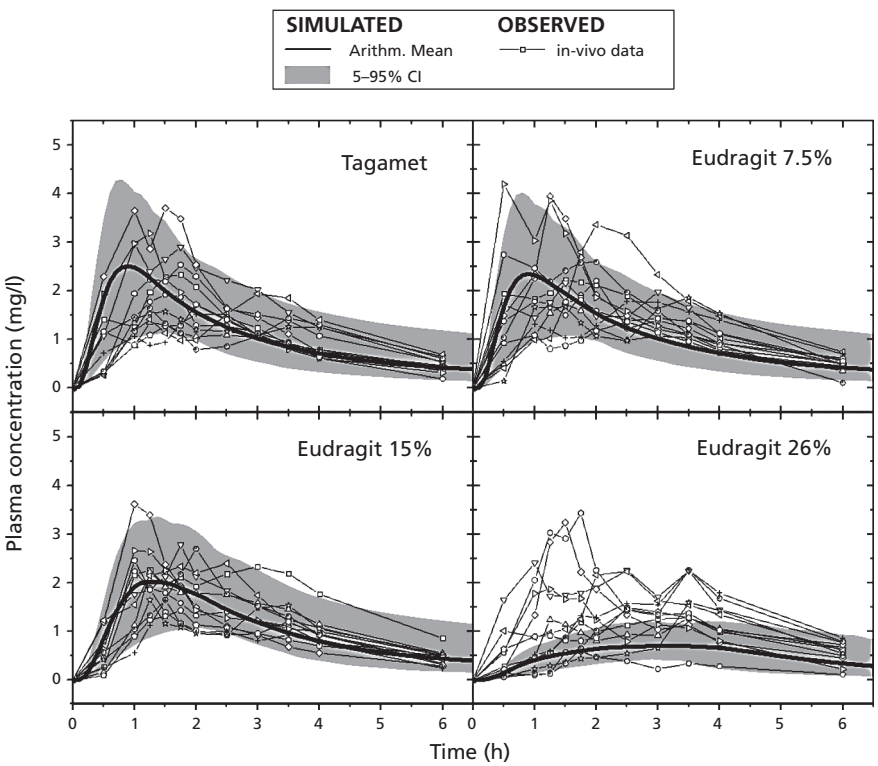

Figure 3 Simulated versus experimental plasma concentration-time profiles for scenario H. Experimental data from Jantratid *et al.*[6]

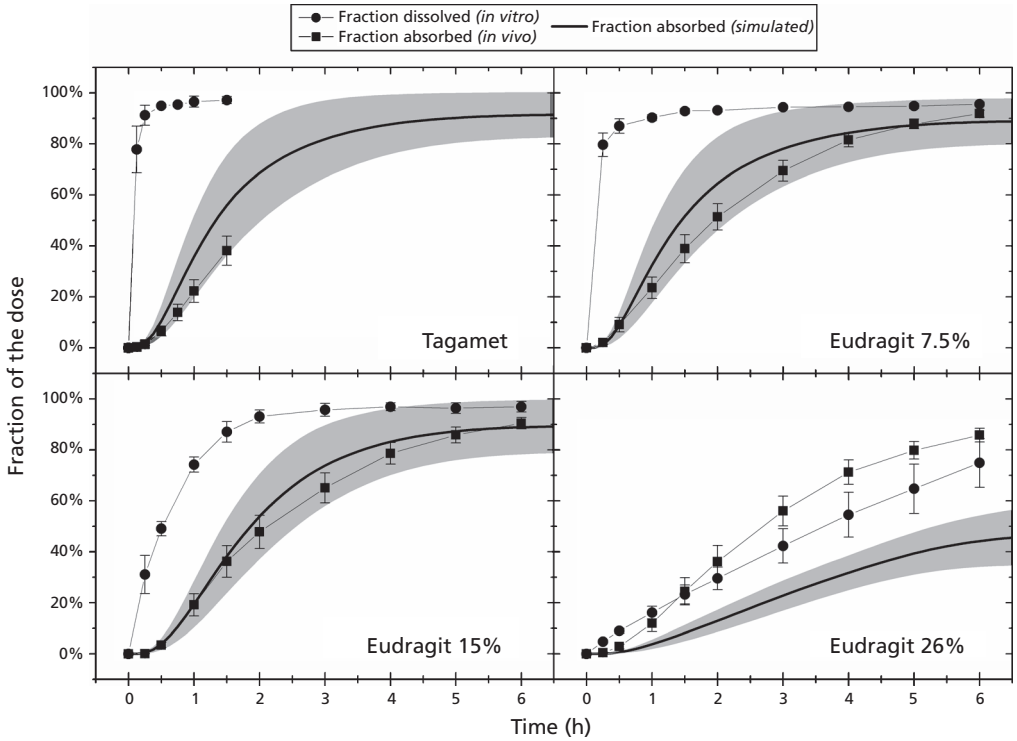

Figure 4 Time courses for the cumulated fraction dose absorbed. Cumulated fraction dose absorbed was obtained from a deconvolution of the measured plasma profiles following oral and intravenous cimetidine administration (filled squares, mean ± SD) and predicted from the simulation model (solid line, mean; gray shaded area, SD). For comparison, the fraction of the dose dissolved measured in the in-vitro assay (filled circles, mean ± SD) is also shown.

using scenario H (which included all sources of inter-individual variability) with the observed data. The range of plasma concentration–time profiles is well described by the Tagamet, Eudragit 7.5% and Eudragit 15% formulations and the simulated 90% confidence interval incorporates 86.1–89.3% of all experimental data. However, for the Eudragit 26% formulation, only 56.1% of the observed data are within the simulated 90% confidence interval.

In Figure 4, the time courses for the cumulated fraction dose absorbed are shown, together with the dissolution kinetics of cimetidine tablets obtained *in vitro* using USP Apparatus 2 (paddle method), at 75 rpm, and 500 ml FaSSIF as a dissolution medium. The absorption kinetics are well described by the model in the case of the Tagamet tablet and the experimental formulations with Eudragit content of up to 15%. For the Eudragit 26% formulation, the rate of absorption is drastically underestimated by the model.

In all simulated individuals, colonic absorption is less than 1% of the dose for all tested formulations in the simulated time span (0–6 h).

Discussion

Several attempts to predict the in-vivo performance of an orally administered compound have been described in the literature.[8,30–34] However, large inter-individual variability in drug absorption, and hence in oral pharmacokinetics, sometimes makes it difficult to adequately describe the in-vivo behaviour of a drug that is administered orally, the most popular and convenient route of drug administration. An important step in intestinal drug absorption is the dissolution and solubility of the drug in luminal fluids. Biorelevant media for simulating the composition of human gastrointestinal fluids have been developed and have proven useful in predicting the in-vivo release of drug substances from orally administered dosage forms under diverse conditions.[9,10,35]

The subsequent permeation of drug in solution across the gut wall is another important event in drug absorption. The development of a physiologically based model for analyzing the dependency of the fraction dose absorbed on these two main physico-chemical parameters (the intestinal permeability and the solubility in the intestinal fluids) has already been described and has been shown to be a useful in-silico tool for studying pharmacokinetics following oral drug administration.[8,36] To assess the influence of variability in physiological and anthropometric properties such as gender, age, body weight and body height on the pharmacokinetic behaviour of drugs, a PBPK population model has recently been developed and used to evaluate the relationship between the variability within the virtual population and the pharmacokinetic outcome of ciprofloxacin and paclitaxel following intravenous administration.[4] However, following oral administration of drugs, the velocity and extent of drug systemically available can additionally be greatly influenced by the gastrointestinal physiology and transit properties, resulting in large inter-individual variability in the absorption behaviour of drugs, especially in the case of permeability-limited drugs.

In the present study, a PBPK population model for gastrointestinal transit and absorption was developed and evaluated for use in the prediction of the expected range of pharmacokinetic plasma concentrations after oral administration. The relevant parameters for this model, such as distributions of GET, SITT and A_{eff} of the intestine, were obtained from the literature. Additionally, the variability in the rate of elimination among different individuals has been taken into consideration. Cimetidine, an H_2-receptor antagonist available in a variety of different dosage forms for the treatment of duodenal and gastric ulcers, was chosen as a model drug for the evaluation because of the availability of a pharmacokinetic data set. Jantratid *et al*. measured plasma concentration–time profiles in 12 healthy Thai volunteers following intravenous and oral administration of one IR formulation as well as three ER formulations in a cross-over study design.[6] Furthermore, the in-vitro dissolution data of the different oral formulations were reported and integrated into the PBPK model. This set of pharmacokinetic data forms an ideal basis for the investigation of the variability following oral drug absorption because (1) the variability of volume of distribution and clearance was obtained after intravenous cimetidine administration in the 12 volunteers, allowing this variability to be separated from the pharmacokinetic variability after oral absorption and (2) the four different formulations of cimetidine allow an assessment of the influence of different release kinetics on the pharmacokinetic variability after oral drug administration.

At the time of the study, the anthropometric and physiological database used in the population module only contained Caucasian American and European individuals, but no Asian individuals. It is therefore an assumption of this model that the Asian study individuals are well represented (in terms of their organ volumes, blood flow rates and tissue composition) by a Caucasian individual of the same height and weight. This seems reasonable because a main contribution to potential race-specific pharmacokinetics originates from differences in the metabolism due to variations in cytochrome P450 expression, for example Bjornsson *et al*.[37] This, however, is not a concern for our model since individual plasma clearance values were derivable using intravenous plasma profiles.[6] Furthermore, studies on roxatidine pharmacokinetics, another H_2-receptor antagonist, revealed similar plasma concentration–time profiles and nearly identical pharmacokinetic characteristics in Japanese, European and North American subjects.[38]

A second assumption of the model is that the experimental uncertainties in measuring cimetidine plasma concentrations are negligible relative to the inter-individual differences. Any uncertainties that arose from experimental or analytical procedures are fully attributed to the inter-individual pharmacokinetic variability.

The inter-individual variability and distribution of each organ weight and blood flow was provided *a priori* and assigned to the individuals of the population via a Monte-Carlo method.[4] This anthropometric variability together with the clearance distribution, assessed on the basis of the plasma pharmacokinetics obtained from an intravenous study in the same study cohort, incorporated almost 90% of the experimental values within the 90% confidence interval of the simulations in the time span up to 6 h. As one would expect, the description of pharmacokinetic variability after oral cimetidine administration was comparatively poor, without any further source of physiological variability (scenario A). Approximately three-quarters of the experimental data points were included within the 90% confidence interval in case of the IR and the Eudragit 7.5%, and 15% formulations, and only one-third for the Eudragit 26% formulation. Thus, just the addition of clearance variability to the anthropometric variability leaves a significant part of the inter-individual pharmacokinetic variability of orally administered cimetidine unexplained. Likewise, the inclusion of inter-individual variability in GET or SITT as well as the combination of these (scenarios B, C and E) did not adequately increase the simulated variability.

The biggest effect on the inter-individual variability in oral cimetidine pharmacokinetics could be seen when the variability of A_{eff} was included in the model (scenarios D, F, G and H). This is perfectly reasonable since, according to Fick's first law of diffusion, the net rate of penetration of this low-permeable compound across the gut wall largely depends on the effective surface area of the membrane available for absorption. For example, doubling the surface area doubles the probability of collision with the membrane and thereby increases the penetration rate two-fold, resulting in an increase in drug substance availability in the systemic circulation.[39] The large intra- and inter-subject variation in each of the anatomical structures in the small intestine, which serve to greatly magnify the surface area available for absorption, contributes to the large overall variability in A_{eff}. In scenario H, where all sources of inter-individual variability were included, the absorption kinetics as well as the range of plasma concentration–time profiles were well described for the Tagamet, Eudragit 7.5% and Eudragit 15% formulations. In contrast, they were clearly underestimated by the model for the Eudragit 26% formulation. Theoretically, physiological aspects, such as regional differences in transporter or metabolizing enzyme expression in the gut wall, can influence the absorption profiles of drugs administered as ER formulations compared to IR formulations. In this case, it is unlikely that regional differences in active efflux or gut wall metabolism contribute to the observed deviation because (1) the plasma profiles of cimetidine could be well described without the assumption of efflux or gut wall metabolism and (2) the profile for the 26% Eudragit formulation was underestimated, not overestimated, by the model. Similarly, a misspecification of colonic absorption can be ruled out as a reason for this deviation because the underestimation of cimetidine plasma levels appears as early as 30 min after oral administration. At this time point it can safely be assumed that the drug has not yet reached the colon. The source of this deviation is probably in the in-vitro dissolution profiles. The variability of the in-vitro dissolution data was greater for the formulation containing 26% Eudragit than for the other formulations, whereas only the mean of the measured dissolution data was given as input for the in-silico predictions via PK-Sim. Most importantly, it is noticeable that the time course of dissolution observed *in vitro* is not representative of the time course of dissolution *in vivo*. This can be concluded

from the fact that the calculated fraction absorbed exceeds the fraction dissolved *in vitro* for time points after 1.5 h (Figure 4). Consequently, the in-silico prediction cannot be accurate. This points to the importance of reproducible in-vitro dissolution measures in adequately predicting the oral absorption profiles of orally administered compounds.

Cimetidine and other H_2-receptor antagonists exhibit an erratic double-peak or multiple-peak phenomenon following oral administration.[15,40–43] Numerous explanations have been proposed for this.[41] This phenomenon primarily occurs in the fasted state, while in the postprandial state the secondary peak does not seem to be present. The extent of cimetidine absorption does not alter and the time to reach maximum plasma drug concentration (T_{max}) is slightly delayed.[5] Several causative factors have been proposed, including fasting gastric pH,[44] gastric emptying related to the interdigestive motility pattern of the stomach[45] and antral motility.[46] This double-peak phenomenon appears to cause the deviation of the observed in-vivo values from the in-silico simulations, as shown in Figure 3. Any secondary peaks tend to be located outwith the simulated area.

In summary, based on in-vitro dissolution profiles, the range of plasma concentration–time profiles could be very well described for all formulations except the formulation with the slowest dissolution kinetic. The biggest effect on the inter-individual variability in plasma concentration–time profiles following oral administration of cimetidine was achieved when the variability of A_{eff} was incorporated in the model.

Conclusions

The PBPK model combines variability of anthropometric parameters and clearance with inter-individual variability of gastrointestinal physiology in order to describe the range of plasma concentration–time profiles of orally administered cimetidine in a population of individuals. The inter-individual variability of the effective surface area that is available for absorption appeared to be the key contributing factor for the explanation of the pharmacokinetic variability observed in the study population. On the basis of in-vitro dissolution profiles, the model is able to reliably simulate IR as well as ER tablet formulations of cimetidine up to an Eudragit content of 15%. It is anticipated that the model described may be useful for predicting the pharmacokinetic variability after oral administration for other drugs prior to in-vivo studies when reasonable experimental measures of dissolution are available. The model can therefore be a helpful tool in the development of formulations or in planning clinical studies in the pharmaceutical industry.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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References

1. Edginton AN *et al*. Whole body physiologically-based pharmacokinetic models: their use in clinical drug development. *Expert Opin Drug Metab Toxicol* 2008; 4: 1143–1152.
2. Nestorov I. Whole-body physiologically based pharmacokinetic models. *Expert Opin Drug Metab Toxicol* 2007; 3: 235–249.
3. Theil FP *et al*. Utility of physiologically based pharmacokinetic models to drug development and rational drug discovery candidate selection. *Toxicol Lett* 2003; 138: 29–49.
4. Willmann S *et al*. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *J Pharmacokinet Pharmacodyn* 2007; 34: 401–431.
5. Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. *Clin Pharmacokinet* 1983; 8: 463–495.
6. Jantratid E *et al*. Feasibility of biowaiver extension to Biopharmaceutics Classification System class III drug products: cimetidine. *Clin Pharmacokinet* 2006; 45: 385–399.
7. Willmann S *et al*. PK-Sim: a physiologically based pharmacokinetic 'whole-body' model. *Biosilico* 2003; 1: 121–124.
8. Willmann S *et al*. A physiological model for the estimation of the fraction dose absorbed in humans. *J Med Chem* 2004; 47: 4022–4031.
9. Dressman J *et al*. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm Res* 1998; 15: 11–22.
10. Galia E *et al*. Evaluation of various dissolution media for predicting *in vivo* performance of class I and II drugs. *Pharm Res* 1998; 15: 698–705.
11. Bayer Technology Services GmbH (2008) PK-Sim User Manual, Bayer Technology Services GmbH, Leverkusen, Germany.
12. Willmann S *et al*. From physicochemistry to absorption and distribution: predictive mechanistic modelling and computational tools. *Expert Opin Drug Metab Toxicol* 2005; 1: 159–168.
13. Jantratid E *et al*. Biowaiver monographs for immediate release solid oral dosage forms: cimetidine. *J Pharm Sci* 2006; 95: 974–984.
14. Lindenberg M *et al*. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm* 2004; 58: 265–278.
15. Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. *J Pharmacokinet Biopharm* 1987; 15: 529–544.
16. Douglas Pharmaceuticals Ltd (1999). CYTINE Cimetidine data sheet. http://www.medsafe.govt.nz/Profs/Datasheet/c/cytinetab.htm (accessed 1 October 2008).
17. Brener W *et al*. Regulation of the gastric emptying of glucose. *Gastroenterology* 1983; 85: 76–82.
18. Davis SS *et al*. Transit of pharmaceutical dosage forms through the small intestine. *Gut* 1986; 27: 886–892.
19. Lin HC *et al*. Inhibition of gastric emptying by acids depends on pH, titratable acidity, and length of intestine exposed to acid. *Am J Physiol* 1990; 259: G1025–G1030.
20. Ofori-Kwakye K *et al*. Gamma scintigraphic evaluation of film-coated tablets intended for colonic or biphasic release. *Int J Pharm* 2004; 270: 307–313.
21. Graff J *et al*. Gastrointestinal mean transit times in young and middle-aged healthy subjects. *Clin Physiol* 2001; 21: 253–259.
22. Snyder WS *et al.* Digestive system. In: International Commission on Radiological Protection. *Report of the Task Group on Reference Man, 23rd International Commission on Radiological Protection*. Oxford: Pergamon; 1975. pp. 122–151.

23. Wilson JP. Surface area of the small intestine in man. *Gut* 1967; 8: 618–621.
24. Tortora GJ, Grabowski SR. The digestive system. In: Tortora GJ, Grabowski SR, eds. *Principles of Anatomy and Physiology*, 10th edn. New York: Wiley; 2003. pp. 851–905.
25. McClean P *et al*. Surface features of small-intestinal mucosa in childhood diarrheal disorders. *J Pediatr Gastroenterol Nutr* 1996; 23: 538–546.
26. Phillips AD *et al*. Microvillous surface area in secondary disaccharidase deficiency. *Gut* 1980; 21: 44–48.
27. Phillips AD *et al*. The structure of the enterocyte in relation to its position on the villus in childhood: an electron microscopical study. *Histopathology* 1979; 3: 117–130.
28. Sinclair TS *et al*. The microvillus in adult jejunal mucosa – an electron microscopic study. *Histopathology* 1984; 8: 739–746.
29. Walkenstein SS *et al*. Bioavailability of cimetidine in man. *Gastroenterology* 1978; 74: 360–365.
30. Dressman JB *et al*. Towards quantitative prediction of oral drug absorption. *Clin Pharmacokinet* 2008; 47: 655–667.
31. Fagerholm U. Prediction of human pharmacokinetics – evaluation of methods for prediction of volume of distribution. *J Pharm Pharmacol* 2007; 59: 1181–1190.
32. Fagerholm U. Prediction of human pharmacokinetics – gastrointestinal absorption. *J Pharm Pharmacol* 2007; 59: 905–916.
33. Kobayashi M *et al*. Development of a new system for prediction of drug absorption that takes into account drug dissolution and pH change in the gastro-intestinal tract. *Int J Pharm* 2001; 221: 87–94.
34. Opara J *et al*. Prediction of pharmacokinetic parameters and the assessment of their variability in bioequivalence studies by artificial neural networks. *Pharm Res* 1999; 16: 944–948.
35. Jantratid E *et al*. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. *Pharm Res* 2008; 25: 1663–1676.
36. Blank K *et al.* Physiology-based models to simulate gut wall metabolism of nifedipine (poster presentation). In: DPhG Jahrestagung; October 10–13; Erlangen 2007.
37. Bjornsson TD *et al*. A review and assessment of potential sources of ethnic differences in drug responsiveness. *J Clin Pharmacol* 2003; 43: 943–967.
38. Bender W, Brockmeier D. Pharmacokinetic characteristics of roxatidine. *J Clin Gastroenterol* 1989; 11: S6–S19.
39. Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3rd edn. Baltimore: Williams & Wilkins; 1995.
40. Macia MA *et al*. Comparative bioavailability of a dispersible formulation of diclofenac and finding of double plasma peaks. *Int J Clin Pharmacol Ther* 1995; 33: 333–339.
41. Marzo A, Reiner V. Open questions on bioequivalence: the case of multiple peak phenomenon. *J Pharm Pharmacol* 2004; 56: 281–282.
42. Plusquellec Y *et al*. A double-peak phenomenon in the pharmacokinetics of veralipride after oral administration: a double-site model for drug absorption. *J Pharmacokinet Biopharm* 1987; 15: 225–239.
43. Weitschies W *et al*. The talinolol double-peak phenomenon is likely caused by presystemic processing after uptake from gut lumen. *Pharm Res* 2005; 22: 728–735.
44. Mummaneni V *et al*. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral administration in dogs. *Pharm Res* 1995; 12: 780–786.
45. Langguth P *et al*. Variable gastric emptying and discontinuities in drug absorption profiles: dependence of rates and extent of cimetidine absorption on motility phase and pH. *Biopharm Drug Dispos* 1994; 15: 719–746.
46. Takamatsu N *et al*. Variability in cimetidine absorption and plasma double peaks following oral administration in the fasted state in humans: correlation with antral gastric motility. *Eur J Pharm Biopharm* 2002; 53: 37–47.