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ORIGINAL PAPER

Integration of preclinical and clinical knowledge to predict intravenous PK in human: Bilastine case study

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Abstract Modern pharmacometrics can integrate and leverage all prior proprietary and public knowledge. Such methods can be used to scale across species or comparators, perform clinical trial simulation across alternative designs, confirm hypothesis and potentially reduce development burden, time and costs. Crucial yet typically lacking in integration is the pre-clinical stage. Prediction of PK in man, using in vitro and in vivo studies in different animal species, is increasingly well theorized but could still find wider application in drug development. The aim of the present work was to explore methods for bridging pharmacokinetic knowledge from animal species (i.v. and p.o.) and man (p.o.) into i.v. in man using the antihistamine drug bilastine as example. A model, predictive of i.v. PK in man, was developed on data from two pre-clinical species (rat and dog) and p.o. in man bilastine trials performed earlier. In the knowledge application stage, two different approaches were used to predict human plasma concentration after i.v. of bilastine: allometry (several scaling methods) and a semi-physiological method. Both approaches led to successful predictions of key i.v. PK parameters of bilastine in man. The predictive i.v. PK model was validated using later data from a clinical study of i.v. bilastine. Introduction of such knowledge in development permits proper leveraging of all emergent knowledge as well as quantification-based exploration of PK scenario, e.g. in special populations (pediatrics, renal insufficiency, comedication). In addition, the methods permit reduction or elimination and certainly optimization of learning trials, particularly those concerning alternative off-label administration routes.

Keywords Bilastine · Preclinical pharmacokinetics · Quantitative pharmacology · Allometric scaling · Semiphysiological models · Knowledge integration · Drug development

1 Introduction

Drug development is a complex and multidisciplinary process lasting several years from molecule discovery to commercialization of therapeutic medication. Although lately progress has been made in molecular screening, there is no equivalent in preclinical and clinical development. This mishap is mostly due to pharmacokinetic (PK) studies aimed at discovering general kinetic traits (e.g. linearity) typically applying simple non-compartmental analyses methods that have no predictive capacity and commonly remain specific to each development stage (or department). Instead, modern pharmacometric approaches can integrate and leverage all prior proprietary and public knowledge. They can be used to scale across species or comparators (Chien et al. 2005), perform clinical trial simulation across alternative designs confirm hypothesis and potentially reduce development burden, time and costs (Lockwood et al. 2003). Crucial yet typically lacking in integration is the pre-clinical stage.

Prediction of PK in man, using in vitro and in vivo studies in different animal species, is increasingly well theorized but could still find wider application in drug development. The most common approximation is body

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weight-based scaling across species that predicts the PK parameters in man (allometry). In vitro studies complete such knowledge extracted from animal testing. Another approach, less empirical, but that can be complementary to the weight-based, is the use of the relation between PK parameters and physiology. This method takes into consideration the intrinsic PK properties of the compound and their relation to species physiology so that the in vivo is simulated in animal then also by extension into man.

Here, both approaches have been applied in the development of the novel antihistamine H1 antagonist, bilastine, patented and developed entirely by FAES Farma SA (Leioa, Vizcaya, Spain). This non-sedative antihistamine drug has excellent PK characteristics and safety profile. The novel chemical structure of bilastine, different from other existing chemical entities, has Class I (FDA classification) solubility and permeability. The drug's optimal physicochemical properties provide for good absorption and distribution of the molecule without access to the CNS. In vitro metabolism studies in human microsomes and hepatocytes indicated the absence of metabolism at systemic or pre-systemic (first pass) level.

At the time, the present study was started, the general kinetic behavior of bilastine was known after oral (p.o.) and intravenous (i.v.) administration in rat and dog. The PK in healthy human subjects was known only after p.o. dosing solely. During the study, further data from i.v. and p.o. in man emerged.

The objective of the present work was to, a posteriori, explore methods for integrating pharmacokinetic knowledge from i.v. and p.o. studies in animal and p.o. in man in order to predict i.v. in man, using the antihistamine drug bilastine as example. The predictions were then contrasted with the human i.v. data for bilastine.

2 Methods

The in vivo animal studies performed on male Wistar rats and both on male and female Beagle dogs and used here for bilastine are summarized in Table 1. All animals were treated humanely, adhering to the "Principles of Laboratory Animal Care" (NIH publication #85-23, revised in 1985). These studies were used to investigate bilastine PK behavior in rat and dog (p.o. and i.v.). Compartmental PK parameters were estimated here for each species separately and for each administration route available.

Table 2 lists the phase I bilastine study results after oral administration in 311 healthy volunteers (Jauregizar et al. 2009) also used in modeling here. Bilastine showed linear PK in the studied dose range (2.5–220 mg/day). As in the pre-clinical species, bilastine was characterized by two-compartmental kinetics with a rapid absorption phase.

Table 1 Animal study designs of bilastine in rats and dogs after single intravenous (i.v.) and oral (p.o.) administration (in vitro protein binding studies were also performed)

Study	Animals (*N* sex)	Administration route: dose (mg)
1. PK linearity (in vivo)	Rat (23M)	p.o: 5, 10, 20 and 40
2. PK (in vivo)	Rat (4M)	i.v: 10
3. PK linearity (in vivo)	Dog (2F–2M)	p.o: 10, 20 and 50
4. PK (in vivo)	Dog (2F–2M)	i.v: 10

F female, *M* male

Protein binding experiments were also conducted "in vitro" at different concentration levels, in plasma samples from different species including humans to calculate the unbound fraction (*fu*). The complete set of parameters used in the present analysis is listed in Table 3, including the unbound fraction.

Oral dose (p.o.) PK parameters in rat, dog and man and the i.v. in rat and dog were then qualified and quantified via combined modeling and used to bridge into i.v. in man. The present work was carried out in three stages: inter-species learning stage, knowledge application and then model validation stages.

2.1 Learning stage: qualitative relationship between the oral PK parameters of rat, dog and human and body weight

In this stage, the regression model across the available species (p.o. and i.v.) for each PK parameter was developed for protein bound and unbound parameters. The three species in p.o. were used in model training for 4 PK parameters. Then, these models were applied in two species allometry in i.v.

However, each PK parameter can have a completely different predictive relationship across species versus weight. Generally in allometry, at least three species should be used for regression based extrapolation. Here, for those parameters whose relation p.o. was linear and assuming that this linearity is maintained across p.o. and i.v., two species were used for extrapolation in i.v. For those PK parameters that did not have a standard allometric relation, single species scaling-based extrapolation was developed, using the p.o. data to apply in i.v. parameter predictions.

The relationship between the p.o. PK parameters of rat, dog, human and body weight was analyzed to explore (1) the form of the relationship within each species (linear, exponential, etc), (2) the differences across species, and (3) find the most relevant single species for scaling-based extrapolation of those PK parameters with nonlinear relations.

Table 2 Summary of phase I clinical studies, evaluating the pharmacokinetics and pharmacodynamics of bilastine in healthy volunteers

Study number	Description	Dosing regimen	No. of healthy adult subjects
1	Double-blind, ascending, single. Dose study to evaluate the safety tolerability and pharmacokinetic of Bilastine	SOD: 5, 10, 50 and 100 mg	36
2	Pharmacokinetic study to assess the single-dose bioavailability of Bilastine under fed and fasted conditions	SOD: 20 mg	12
3	Randomized, multiple-dose to evaluate the safety and tolerability and pharmacokinetic of Bilastine at escalating doses	MOD: 10, 20, 50 and 100 mg/day for 14 days	36
4	Randomized, single-dose, placebo-controlled, four period crossover study to evaluate the safety and tolerability, pharmacokinetic and antihistaminic activity of Bilastine at five dose levels compared with cetirizine	SOD: 2.5, 5, 10, 20 and 50 mg	21
5	Open-label study to assess the effects of age and gender on the pharmacokinetics and pharmacodynamics of Bilastine	SOD: 20 mg	32
6	Randomized, double-blind, crossover, placebo-and positive standard controlled, single-centre clinical trial for evaluation of CNS effects of Bilastine at different doses after single and repeated oral administration	MOD: 20, 40 and 80 mg/day for 7 days	20
7	Pharmacokinetic and safety study evaluating the potential interaction of erythromycin and Bilastine under steady-state conditions	SOD: 20 mg	24
8	Pharmacokinetic and safety study evaluating the potential interaction of ketoconazole and Bilastine under steady-state conditions	SOD: 20 mg	24
9	Randomized, double-blind, placebo-controlled, sequential group study to evaluate the safety, tolerability and pharmacokinetic of single, ascending doses of Bilastine and of multiple doses of Bilastine	SOD: 120, 160, 200 and 220 mg MOD: 140 and 220 mg/day for 7 days	54
10	Randomized, multiple-dose, double-blind-five-way crossover study of the ECG effects of Bilastine	MOD: 20 and 100 mg/day for 4 days	30
11	Randomized, open-label, two-way crossover study to evaluate the effect of grapefruit juice on the single-dose pharmacokinetic of Bilastine	SOD: 20 mg	11
12	Randomized, open-label, two-way crossover study to evaluate the effect of diltiazem on the single-dose pharmacokinetic of Bilastine	SOD: 20 mg	11

CNS central nervous system, *ECG* electrocardiographic, *MOD* multiple oral dose, *SOD* single oral dose

General relationships between oral PK parameters (from three species) versus weight were first explored using standard allometric forms. Typically these functions, relate a PK parameter (Y) to a power of the body weight (WT) as follows (Mahmood 2005),

$$Y = a \times \mathrm{WT}^{b} \quad (1)$$

where a and b are the allometric coefficient and exponent, respectively. The forms were fitted to the three species of the p.o. group for both total and protein unbound parameters (parameters corrected by the unbound fraction, fu).

Single species allometric scaling relations were developed in model training by predicting the observed p.o. in man, as follows:

$$_{\text{total or unbound}}\frac{\mathrm{CL}}{F}\ \text{human} = {}_{\text{total or unbound}}\frac{\mathrm{CL}}{F}\ \text{species} \times \left(\frac{\text{Weight}_{\text{human}}}{\text{Weight}_{\text{species}}}\right)^{\text{exponent}} \quad (2)$$

2.2 Knowledge application stage: prediction of intravenous parameters in man

Two different extrapolation methods were used in the second stage to predict the i.v. kinetics in man: allometric scaling and semi-physiological modeling.

2.2.1 Method 1: allometric scaling

Allometric scaling (based on Eq. 1) of intravenous PK parameters in man was performed based on the i.v. parameters for rat and dog. After the learning stage, those parameters which resulted in nonlinear allometric relationships, when using all species, were extrapolated using only the i.v. parameters from the most relevant species (application of Eq. 2 and i.v. parameters).

Extrapolation of PK parameters to man was done for an average adult weight of 70 kg, using an allometric exponent of 0.75 or 1, depending on the learning stage outcome.

Table 3 Compartmental oral (p.o.) pharmacokinetic parameters of bilastine in rat, dog and in human and intravenous (i.v.) pharmacokinetic parameters of bilastine in rat and dog used to establish the allometric relationships

Species	V_c/F (L)	CL/F (L/h)	V_{ss}/F (L)	V_p/F (L)	Q/F (L/h)	f_u
Oral PK parameters						
Rat ($n = 4$; 0.25 kg)	0.40	1.24	0.50	0.10	0.02	0.16
Dog ($n = 3$; 16 kg)	10.71	14.50	20.71	10.00	0.58	0.42
Human ($n = 310$; 70 kg)	60.40	18.70	91.80	31.40	1.51	0.13
Species	V_c (L)	CL (L/h)	V_{ss} (L)	V_p (L)	Q (L/h)	
Intravenous PK parameters						
Rat ($n = 4$; 0.25 kg)	0.16	0.50	0.20	0.04	0.008	
Dog ($n = 3$; 16 kg)	5.36	7.25	10.4	5.04	0.290	

GFR: rat = 0.0775 L/h, dog = 5.76 L/h and human = 8.4 L/h

2.2.2 *Method 2: semiphysiological approach*

This method is based on the physiological connection to PK characteristics and model parameters for each species. The prediction of steady state volume of distribution (V_{ss}) in humans was based on the comparison of body volumes in rat and dog (considering that volumes of distribution behave as physiological processes) (Savage 2004). Physiological information was obtained from literature (Davis and Morris 1993; Mahmood 2005). Central and peripheral volumes of distribution (V_c and V_p, respectively) were calculated from PK volume relationships assuming no interspecies differences.

Decisions regarding extrapolation of bilastine's intrinsic clearance after i.v. (CL) to man focused on the known lack of metabolism of the drug in any tested species and in man. In man, CL was estimated by scaling of the i.v. clearances (in rat and dog) with the glomerular filtration rates (GFR). Valid prediction of the renal excretion between humans and animals using the GFR has been confirmed (Lin 1995).

Cardiac output (CO) is a reported marker of intercompartmenal clearance (Q) (Van Sassenbroeck et al. 2002; Björkman et al. 2005). The CO/Q ratio was used to scale the Q. The ratios were assumed to be maintained across species.

2.3 Confirming stage: observational and visual predictive check validation of the extrapolation in man

Human plasma concentrations after i.v. administration of bilastine (obtained from a later bioavailability study in volunteers, $n = 12$) were used to estimate via direct population compartmental modelling the "true" PK parameters of bilastine i.v. These estimates were used to validate the i.v. predictions of the mechanistic models from the present exercise. Mean prediction errors percent (MPE%) were calculated as, MPE% = 100 × (true − predicted)/true.

In addition, Monte Carlo simulation was used to assess the predictive ability of the model parameters extrapolated from preclinical and clinical information. Simulations were performed of a population of $n = 1{,}000$ individuals with the parameters from the two extrapolation methods above (allometry and semiphysiological) and assuming that these "extrapolated" parameters have the same variability as the p.o. parameters observed after the oral administration of 20 mg of bilastine in healthy volunteers (Jauregizar et al. 2009). The observations of i.v. administration in man were overlaid on the 95 % confidence interval of the simulations. The model was considered adequate if <10 % of the observations fall outside the confidence interval.

2.4 Software used in the analysis

WinNonLin (version 5.1, Pharsight Co. USA) was used to estimate i.v. and p.o. parameters in rat and dog (not shown here). SPSS (version 10, USA) was used to develop allometric relations at the $p < 0.05$ significance level. Human i.v. data analysis was performed using NONMEM VI (UCSF Board of Regents, San Francisco, CA, USA). Simulations were carried out using NONMEM VI and S-PLUS version 6.2 (Insightful Corp, Seattle, WA).

3 Results

First PK modeling was performed for the i.v. and p.o. data in animals alone. Two compartmental representations best described the kinetics of bilastine in animals. The results of Jauregizar et al. (2009) were applied for p.o. bilastine in man. The PK parameters for all species are listed in Table 3 (for p.o. in rat, dog and man and for i.v. in rat and dog). Table 3 also lists the protein binding fraction (*fu*) for bilastine in these three species.

3.1 Learning stage: observed relationship between the oral PK parameters of rat, dog, human and body weight

Qualitative relationships were established across species in the p.o. group for the total parameters and also for unbound bilastine parameters (scaled by the unbound fraction). The unbound parameter corrects for potentially large differences in the unbound fraction between animal and human. PK parameters estimated based on p.o. data, implicitly include (unknown) bioavailability (F) and hence appear in tables as divided by F.

The most significant relationships are shown in Table 4. Each PK parameter could have a different allometric relationship. Those for volumes of distribution/F and Q/F were linear. An example is depicted in Fig. 1.

There were no significant three species allometry relations between weight and CL/F (total oral clearance). However, visual exploration showed power of weight relationships with unbound (oral) clearance. Fits were then performed using only one species applying Eq. 2.

Two different allometric exponents, 0.75 and 1, were tested when predicting human CL/F from only one species. An exponent of 0.75 is usually applied for dynamic processes, such as clearance that includes metabolism (Anderson and Holford 2008), while the exponent = 1 is used for less dynamic or first-order-related processes, such as the distribution volumes, for which a proportional relationship with weight is expected (Savage 2004). For bilastine, with no metabolic pathways involved in the clearance, both exponents were tested. Moreover, for both rat and dog, prediction from total and unbound clearances was performed. Then, the deviation was calculated using the prediction error in man as a criterion. This process also aims at discovering the species most relevant to extrapolate bilastine clearance in man.

An example of model training is listed in Table 5. The table shows the predicted CL/F (i.e. for p.o. dosing) in man using only one species at a time, either rat or dog. The corresponding prediction error as compared to the true value for CL/F in man of 18.7 L/h is listed as well. The CL/F in man is calculated with an allometric exponent of 0.75 or 1 and for the total and unbound clearances in the two species. A CL/F of 84.9 L/h in man was obtained with an exponent of 0.75 and rat total CL/F with a prediction error of 354 %. Exponents <1 are indicative of active elimination processes in a species (here in rat) not applicable in man. On the other extreme with unbound CL/F in dog and exponent of 1, a 5 % prediction error was obtained. This last relation was selected as the most similar species for predicting in man, in accordance with the known allometric relationship of renally eliminated drugs (Mahmood 2005). Although the rat had *fu* more similar to humans than dog, the actual mechanism of the dog was closer to man. Unbound fraction for parameters from dog was then used to correct for *fu* differences.

Table 4 Relationships linking the oral (p.o.) PK parameters of bilastine and body weight across species

Parameter	Equation	p value
Central distribution volume	$\frac{V_c}{F} = 1.37 \times WT^{0.89}$	0.000
Unbound clearance	$\frac{CL_u}{F} = 1.096 \times e^{0.36 \times WT}$	0.033
Steady state volume of distribution	$\frac{V_{ss}}{F} = 1.96 \times WT^{0.93}$	0.042
Intercompartimental clearance	$\frac{Q}{F} = 0.07 \times WT^{0.79}$	0.042

p value (statistic significance): obtained using a log–log regression technique with SPSS

WT body weight in kilograms

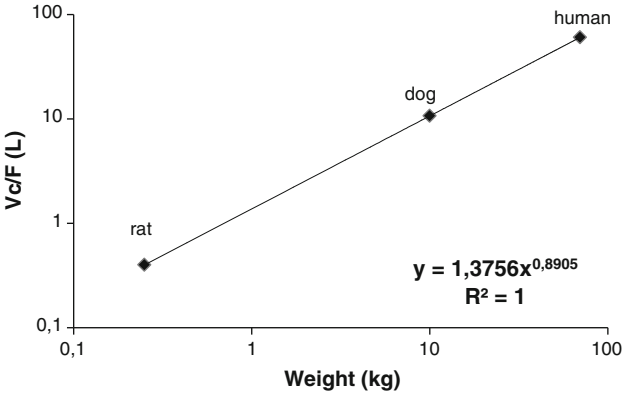

Fig. 1 Example of the allometric exploration performed in the learning stage. Bilastine interspecies (rat, dog and human) relationship between volume of distribution and weight by standard allometry

3.2 Knowledge application stage: Prediction of intravenous parameters in man

3.2.1 Method 1: allometric scaling

Since the volumes of distribution/F and Q/F after bilastine p.o. in rat, dog and human were linearly related, similar behavior was assumed for i.v. administration. However, the most relevant species for extrapolation of i.v. unbound clearance from animal to man was the dog (Table 5). Then, scaling as application of single species scaling (Eq. 2) and for i.v. parameters was as follows:

$$_{\text{unbound}}\text{CL}_{\text{human}} = {}_{\text{unbound}}\text{CL}_{\text{dog}} \times \left(\frac{70}{\text{Weight}_{\text{dog}}}\right)^{1}$$

where the exponent was 1 and a weight of 70 kg was used for the average adult human. Although dog has different protein binding as compared to man, the unbound

Table 5 Evaluation of the predictive accuracy using various scaling methods for bilastine clearance from only one species each time; the standardized error when predicting in man (p.o.) is shown

Method	Allometric exponent	Clearance/F (L/h)	Percentage of error[a]
Allometry from rat	0.75	84.9	−354
Total CL/F	1	347	−1756
Allometry from rat	0.75	69.0	−269
Unbound CL/F	1	282	−1403
Allometry from dog	0.75	43.3	−132
Total CL/F	1	62.6	−235
Allometry from dog	0.75	13.5	28
Unbound CL/F	1[b]	19.6	−5

CL/F observed in human = 18.7 L/h

[a] $\%\ error = \frac{(observed - \text{predicted})}{observed} \times 100$

[b] Best approach to predict human CL based on the prediction error (%)

parameter was used in scaling thus correcting for the difference. The estimated unbound parameter was then back-transformed into total parameter using the unbound fractions.

For V_c and V_{ss} the allometric exponents were 0.89 and 0.93, respectively. The i.v. PK parameters predicted in man as well as the corresponding allometric coefficients and power for Eq. 1 are shown in Table 6. This table also shows the results for the allometric scaling of Q (allometric exponent of 0.86).

3.2.2 *Method 2: semiphysiological approach*

Table 6 lists the relations used to predict i.v. PK parameters for bilastine in man based on the physiology. The V_{ss} after i.v. bilastine in rat and dog were similar to the physiological total body water (TBW) volumes (ratio close to 1 in both cases). This relation was assumed to be maintained in man and TBW was used to predict the i.v. V_{ss} in man to be 42 L. The value represents the global distribution of the drug in man.

Moreover, the relation of V_c to V_{ss} in rat and dog was of 0.8 and 0.52, respectively. The mean ratio (0.66) was used to predict V_c in man. Then, peripheral volume (V_p) in man was calculated from the relation $V_{ss} = V_c + V_p$.

Since, as seen earlier, the dog was the most relevant species for predicting the CL of bilastine in man, the CL in dog was contrasted with its corresponding GFR. As the renal clearance is the major elimination route for bilastine in both species, the relationship was assumed to be maintained in man. The systemic clearance in dog (7.25 L/h) was over 100 % GFR (5.76 L/h). The i.v. clearance in man was predicted to be equal to the GFR, 8.40 L/h.

The average CO/Q ratio was used to estimate human intercompartmental clearance as $Q = 0.835$ L/h.

3.3 Confirming stage: observational and visual predictive check validation of the extrapolation in man

"True" intravenous PK parameters of bilastine were estimated using plasma concentrations from human healthy volunteers ($n = 12$) via direct population compartmental modelling. The calculated mean prediction errors percentage

Table 6 Estimation of i.v. PK parameters in man for bilastine with the allometric weight based scaling method and semi-physiological method

Parameter	Estimated value	Exponent	Coefficient	Extrapolation approach
Allometric scaling				
CL (L/h)	9.98	1	–	Single species allometry (dog)
V_c (L)	18.6	0.844	0.515	Two species allometry
V_{ss} (L)	42.3	0.950	0.746	Two species allometry
V_p* (L)	23.7	–	–	From $V_{ss} = V_c + V_p$
Q (L/h)	1.04	0.863	0.026	Two species allometry

Parameter	Estimated value	Extrapolation approach
Semi-physiological method		
CL (L/h)	8.4	From dog GFR
V_{ss} (L)	42.0	Across species relationships between TBW and V_{ss}
V_c (L)	27.7	Across species relationships between V_{ss} and V_c
V_p (L)	14.3	From $V_{ss} = V_c + V_p$
Q (L/h)	0.835	Across species relationships between CO and Q

GFR glomerular filtration rate, *CO* cardiac output

(MPE%) are shown in Table 7. In general, all the PK parameters were accurately predicted. The higher MPE was found for the intercompartmental clearance, Q, extrapolated with the semiphysiological approach. However, this parameter has not much impact on bilastine exposure.

Moreover, the predicted parameters from the allometric and semi-physiological inter-species scaling methods were used to simulate the mean behavior and interval (Fig. 2a, b, respectively). The 95 % confidence interval (CI) was contrasted to observed data from p.o. in man. Less than 10 % of the observations fell outside the interval. Thus, the VPC test definitely proves the validity of the proposed model and also of both extrapolation approaches. Although the mean model appears to overpredict the observed elimination phase (Fig. 2), the observations are contained within the 95 % CI of the mean, i.e. they lie within the expected significant variability of the mean kinetic profile.

4 Discussion

The effort of defining the PK profile in man during development of a new chemical agent is crucial not only for first time in man estimation but also for knowledge on the drug's behavior in general. It is not unusual to have fractured knowledge of i.v. PK and parameters, e.g. in some animal species and not in man, as i.v. may not be the appropriate dosing route. Because the p.o. PK contains implicitly the bioavailability factor, extrapolation to the relevant PK after i.v. may not be straightforward either. Notwithstanding, vast knowledge may reside in pre-clinical data, regarding e.g. clearance/metabolism mechanisms that can best be leveraged via an integrative or translational modeling exercise.

Bilastine is an antihistaminic drug taken orally and whose elimination is entirely via the renal route. In this study, independent per-species and combinatorial analysis was performed of all available pre-clinical and limited clinical (p.o.) data to rationalize an extrapolation to i.v. PK parameters in man. The PK parameters of bilastine after p.o. in two animal species (rat and dog) and in man and i.v. in the two animal species were explored. The process involved methods that, apart from the model-based quantification of PK processes and the extrapolation to man, dramatically increased knowledge on the intrinsic processes behind the parameters for bilastine. This know-how is crucial for rational decision making across alternative therapeutic settings (special groups, renal insufficiency, etc).

In a first step, the allometric relations between PK parameters and body weight, within and across species, were explored. This was done to classify alternative species in terms of their adequacy as animal models for bilastine and thus identify the most relevant species for predicting the i.v. PK of bilastine in humans. Eventually, the near linearity between weight and distribution volumes justified the extrapolation into man of i.v. pharmacokinetics using both rat and dog. However, for systemic clearance there was no simple and significant allometric relationship. Nevertheless, the unbound clearances showed an exponential relation with body weight, indicating a differentiation between species and the dog that was concluded to be the most relevant species for predicting CL in man. The large difference in unbound fraction of bilastine between dog and man was corrected when the unbound parameters were used. The fact that the dog was more predictive of clearance is not surprising. The affinity for transporters such as p-glycoprotein is more pronounced in the rat. In that species, the CL obtained after bilastine i.v. was higher than the species GFR (that was not the case with the dog), indicating the participation of processes additional to renal clearance in global elimination, such as feces elimination via p-glycoprotein mediated secretion.

Once the learning stage was complete, the acquired knowledge was applied to perform predictions in man using both allometric and semi physiological methods.

Regarding volumes, with both methods, rat and dog had wide V_{ss} after i.v., close to total body water (TBW) for these species and this relation was used to predict V_{ss} in man (42 L). This volume of distribution is optimal for an antihistamine drug because it is sufficient for reaching the effect sites without accumulation (Tillement 2000). Indeed, in pre-clinical distribution studies with bilastine, no accumulation was observed. This outcome of the present effort for early prediction of the i.v. parameters in man is an example of how knowledge solely of (inflated) p.o. parameters (91.8 L) can lead to uncertainties regarding intrinsic kinetics.

Table 7 Mean prediction errors percent (MPE%) calculated to validate the extrapolated bilastine i.v. PK parameters using the mechanistic models from the present exercise

	CL (L/h)	V_c (L)	Q (L/h)	V_{ss} (L)	V_p (L)
"True" estimates	13.4	27.9	1.68	36.9	9.04
Allometric scaling					
Extrapolated parameter	9.98	18.6	1.04	42.3	23.7
MPE (%)	25.5	33.3	38.1	−14.6	–
Semi-physiological method					
Extrapolated PK parameters	8.40	27.7	0.835	42.0	14.3
MPE (%)	37.3	0.700	50.3	−13.8	–

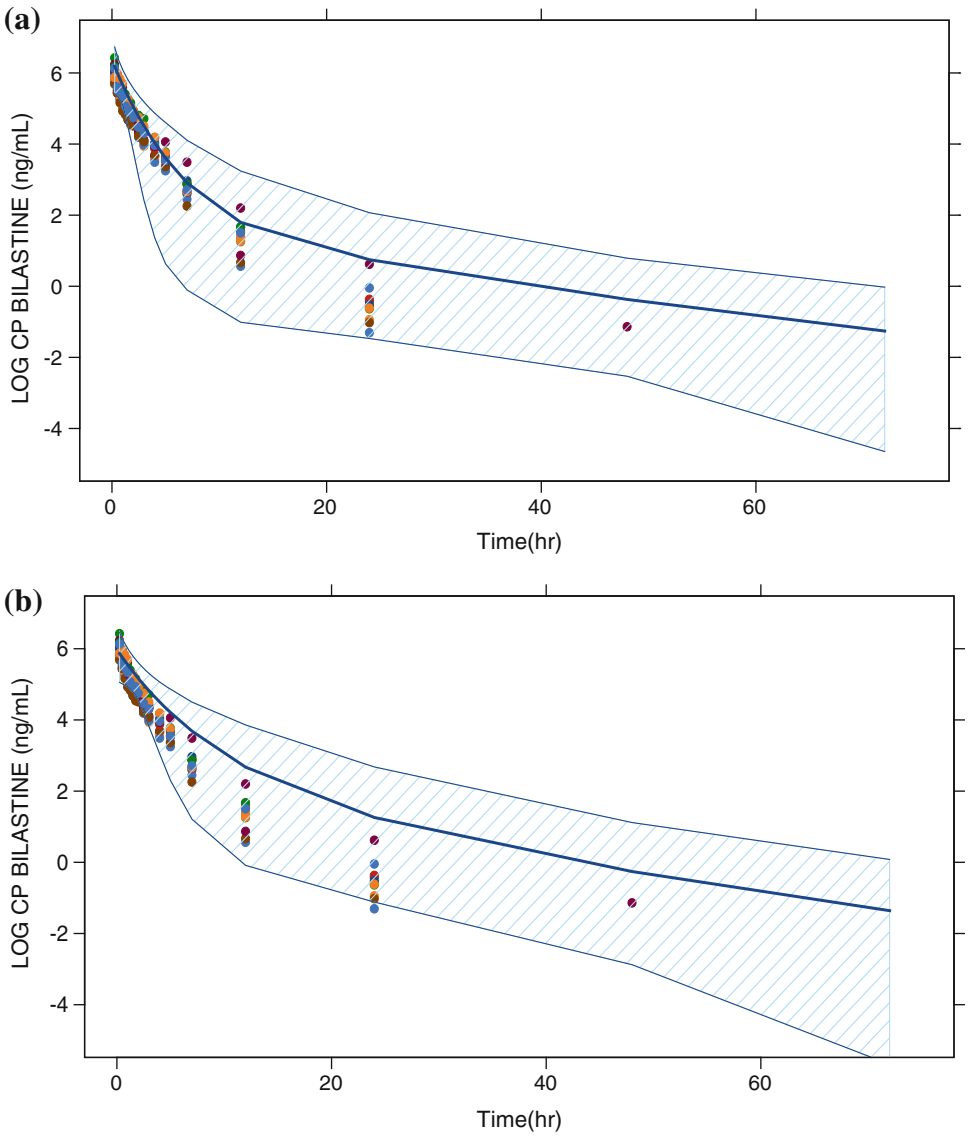

Fig. 2 **a** Allometric scaling prediction comparison: logarithmic concentration–time profile of bilastine in human plasma after a single intravenous dose of 10 mg. *Blue lines* and *shaded area* represent the simulations carried out with the PK parameters obtained from the allometric scaling. Symbols represent the experimental values in healthy volunteers. **b** Semi-physiological modeling prediction comparison: logarithmic concentration–time profile of bilastine in human plasma after a single intravenous dose of 10 mg. *Blue lines* and *shaded area* represent the simulations carried out with the PK parameters obtained from the semi-physiological model. *Symbols* represent the experimental values in healthy volunteers (color figure online)

In addition, the parameters obtained with either of the mechanistic methods employed in this study permit to approximate an a priori value of bioavailability, F, in man e.g. when in early development. Here, given that the goal of the present study was not to perform this calculation, the estimate for F varied between 50 and 70 % (a later bioavailability trial with bilastine estimated F at approximately 60 %).

Validation of the predicted parameters of bilastine in man with either the allometric or the physiological reasoning approaches, led to confirm all the key assumptions: linear relation between volume of distribution and body weight, volume at steady state similar to TBW, the dog as the most similar species to man for bilastine clearance, clearance of the order of GFR, good relation between intercompartmental clearance and cardiac output, and constant relation between volumes.

Each method has its own advantages. Allometry is less complex, hence employs fewer assumptions compared to the semi-physiological approach. On the other hand, the latter method motivates more knowledge acquisition about intrinsic physiological mechanisms. Decision on the trade-off obviously depends on the resource capacity of each development project and understanding of the significance of translational development. In the present exercise (performed a posteriori), the validation simulations showed that the allometric method seemed to be slightly, but not significantly better in predicting bilastine plasma concentrations in human after the i.v. administration.

In conclusion, the use of alternative methods to approximate the i.v. PK of bilastine, as applied here, provided increased certainty since with either method similar conclusions were drawn. The interpretation, qualification and quantification of PK parameters from a physiological

point of view and within mathematical models is both an integrative as well as confirmatory effort regarding the global kinetic characteristics of the drug with importance also in pharmacodynamics, hence the clinic. Application of such methods across species scaling is particularly useful for drugs meant solely for p.o. administration or when i.v. in man is not permitted.

Early introduction of such knowledge in development permits prompt exploration of alternative scenario as e.g. into special populations (pediatrics, renal insufficiency). Importantly, application of such methods may also help reduce the size of, or eliminate completely, trials in humans for the alternative dosing route that is not to be used post marketing.

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