Dose Finding in Single Dose Studies by Allometric Scaling

Zheng Lu, Rüdiger Kaspera, Yoichi Naritomi, and Tianli Wang

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Abstract

This chapter reviews common methodologies and applications of scaling for clearance (CL), oral bioavailability (F), volume of distribution (V_d) and half-life ($t_{1/2}$) with respect to its procedures, evaluation, performance and modifications for the dose finding in single dose studies. Methods of allometric scaling have been well established in drug development to predict the dose for single dose studies for first in human trials from preclinical data, generally from one to three or more species such as mouse, rat, dog or monkey. Allometric scaling is the study of body size to diverse biological characteristics, like clearance. The clearance

Z. Lu (✉) • T. Wang
Clinical Pharmacology and Exploratory Development, Astellas Pharma, Northbrook, IL, USA
e-mail: zheng.lu@astellas.com; tlwang2011@gmail.com

R. Kaspera
Clinical Pharmacology and Exploratory Development, Astellas Pharma Europe B.V., Leiden, The Netherlands
e-mail: rudiger.kaspera@astellas.com

Y. Naritomi
Analysis and Pharmacokinetics Research Labs., Astellas Pharma Inc., Ibaraki, Japan
e-mail: yoichi.naritomi@astellas.com

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and other PK parameters are proportional to the body weight among different species. Dose finding in single dose studies by allometric scaling can be either by dose-by-factor approach or pharmacokinetically-guided approach. Besides traditional simple allometry and allometric scaling based on the rule of exponents, many newly proposed methods based on the allometric scaling with different correction factors have been shown either to improve the accuracy of predications or to explore the possibilities of predictions for protein therapeutics. Although the allometric scaling approaches have been widely used to predict human PK parameters of small molecules which is critical to next dose finding step for single ascending dose study, there is a need to have more mechanistic methods based on the allometric scaling, especially for protein therapeutics or some formulations, like liposomal, to improve the predictabilities of first-in-human dose in single ascending dose study.

Purpose and Rationale

In first-in-human (FIH) studies, the single ascending dose (SAD) study, cohorts of six to eight subjects are given a single dose of the new chemical entity (NCE) and monitored for safety, tolerability, and pharmacokinetics (PK) to identify the maximum tolerated dose (MTD) and/or dose-limiting toxicity. Because it is the FIH study, the starting dose in a SAD study must be low enough to be safe but not too low as lead to an excessive numbers of dose levels to reach the MTD. Methods of allometric scaling have been well established in drug development to predict the dose for single dose studies for first-in-human trials from preclinical data. This chapter reviews common methodologies and applications of scaling for clearance (CL), volume of distribution (V_d), and half-life ($t_{1/2}$) with respect to its procedures, evaluation, performance, and modifications for the dose finding in single dose studies.

Procedure

Since drug efficacy and toxicity are usually associated with drug exposure, the projection of human pharmacokinetic (PK) for an early assessment of efficacious doses and dosing regimens is important during clinical development, especially prior to FIH studies (Deng et al. 2011). The allometric scaling approaches have been widely used to predict human PK parameters of small molecules, generally from three or more species such as mouse, rat, dog, or monkey.

Interspecies Scaling of CL

Systemic CL or so-called total CL does not identify the mechanism of the elimination process and considers drug elimination from the entire body. Allometric scaling is applicable to compounds mainly eliminated by cytochrome P450 (P450)-mediated metabolism and to compounds that undergo non-P450 metabolism or are eliminated mainly by urinary excretion as the unchanged drug, and protein binding is inconsequential (Boxenbaum 1984).

There have been a number of comprehensive reviews on the accuracy and precision of various methods to estimate human systemic CL. The most comprehensive report was by Lombardo et al. (2013a) who presented an analysis of 400 drugs (the largest known database in existence) administered intravenously to rats, dogs, monkey, and humans. They used 37 different methods to estimate human CL and calculated the median bias and geometric mean fold-relative error for each method, of which the most important ones are described here and their performance discussed in the following section.

Simple Allometry and Allometric Scaling Based on Rule of Exponents

Simple allometry scaling is based on a power function $CL = a \times Y^b$, generally using three or more species PK data, where Y may be the body weight (BW) or body surface area (SA) and a and b are the coefficient and exponent, respectively. For compounds with high hepatic extraction

ratios, body surface area is expected to be more predictive (Zou et al. 2012a).

The more commonly used equation is:

$$CL_{human} = CL_{animal} \times (BW_{human}/BW_{animal})^{0.75}$$

which is called single species scaling (SSS) (Hosea et al. 2009). This method uses a fixed scaling exponent with one species PK data. Caldwell et al. (2004) proposed that human PK predictions can be obtained using the simple allometric scaling from rats with a fixed exponent: CL(human) approximately = 40 × CL(rat) (L/hr).

Rule of exponents (ROE) can also be applied to human CL prediction as below:

$$\begin{aligned}
&\text{When } 0.55 \le b \le 0.70, \ CL = a \times BW^b \\
&\text{When } 0.71 \le b \le 1.0, CL_{human} = \\
&\quad a \times (MLP_{animal} \times CL_{animal})^b / MLP_{human} \\
&\text{When } b > 1.0, \ CL_{human} = a \times \\
&\quad (BrW_{animal} \times CL_{animal})^b / BrW_{human} \\
&\text{When } b > 1.3, \ CL \text{ may be overpredicted} \\
&\text{When } b < 0.55, \ CL \text{ may be underpredicted}
\end{aligned}$$

where MLP represents maximum lifespan potential and BrW indicates brain weight (Mahmood and Brian 1996).

Allometric Scaling of Hepatically Eliminated Drugs

The interspecies scaling of biliary and renal CL is not discussed within the chapter and the reader is referred to respective publications.

The Liver Blood Flow Method

For hepatically eliminated drugs, a common approach is to extrapolate human CL by the hepatic blood flow (LBF) ratio between humans and animals (Zou et al. 2012a).

$$CL_{human} = CL_{animal} \times (LBF_{human}/LBF_{animal})$$

It has been found that the mouse and monkey LBF methods were more accurate approach for human CL prediction than rat and dog LBF methods (Stoner et al. 2004; Ward and Smith 2004).

Normalization by in Vitro CL

The in vitro results from hepatic metabolism studies using microsomes, hepatocytes, and liver slices can be extrapolated in order to incorporate intrinsic CL. Combining the in vitro intrinsic with the in vivo CL of animals, Lave et al. (1997) predicted the human CL using allometric scaling. The in vivo CL of each species was normalized by multiplying the ratio of CL in human hepatocytes or microsomes versus CL in animal hepatocytes or microsomes. The method seemed to have not been widely used and may not show superiority over other allometric scalings.

Allometric Scaling of Unbound Drug CL

Plasma protein binding of many drugs varies considerably among animal species and only unbound drug can be eliminated. Therefore, protein binding has been considered to potentially influence the distribution and elimination of drugs (Zou et al. 2012a).

$$\text{Unbound CL} = CL/f_u$$

$$\text{Unbound CL} = a \times (BW)^b$$

where f_u is the unbound fraction in plasma.

Although the f_u in rats is observed to be representative of the average f_u in animals, correction for protein binding in each animal species would be more favorable than just considering only rats and humans (Tang and Mayersohn 2005). Tang and Mayersohn (2005) proposed the unbound fraction-corrected intercept method (FCIM) using the ratio of unbound fraction in plasma (f_u) between rats and human (Rf_u), based on 61 sets of CL values in animal species:

$$CL\,(mL/min) = 33.35 \times (a/Rf_u)^{0.77}$$

where a is a coefficient obtained from allometric scaling. It has been shown that, practically, unbound CL cannot be predicted more accurate than total CL, except for some drugs. Typically, protein binding corrections will not be made unless the ratio of f_u between rats and humans is tenfold or more.

Computational (in Silico) Approaches

Wajima et al. (2003) proposed an approach to predict human oral CL (mL/min/kg) by using experimental data for oral CL of the rat and dog, molecular weight (MW), clogP, and the number of hydrogen bond acceptors (Ha):

$$\begin{aligned}\log(CL) = &-0.5927 + 0.7386\log(CLrat) \\ &+ 0.5040\,\log(CLdog) + 0.06014\,c\,logP \\ &- 0.1862\,\log(CLdog) \times c\,logP \\ &+ 0.02893\,MW \times c\,logP + 0.02551\log(CLrat) \\ &\times \log(CLrat) \times c\,logP - 0.03029\,\log(CLrat) \\ &\times \log(CLrat) \times Ha - 0.03051\log(CLrat) \times MW \\ &\times c\,logP + 0.08461\log(CLdog) \\ &\times \log(CLdog) \times \log(CLdog) \\ &- 0.2510\,\log(CLdog) - 0.2510\,\log(CLdog) \\ &\times \log(CLdog) \times MW + 0.04607\log(CLdog) \\ &\times c\log P \times c\,logP - 0.003596\,c\,logP \\ &\times c\,logP \times Ha + 0.0005963\,c\log P \\ &\times Ha \times Ha\end{aligned}$$

Unlike other allometric scaling approaches, the *Wajima* method incorporates molecular structure parameters and is not dependent on the BW. The authors obtained clearance for 68 drugs either eliminated from renal excretion as unchanged drugs or extensively metabolized. The method gave a very good prediction of CL for the drugs studies.

Interspecies Scaling of Oral Bioavailability

The described above allometric scaling approaches predict human systemic CL. For orally administered drugs, it is vital to predict human oral bioavailability (F). F can be predicted based on preclinical in vivo estimates. One method is to use the average of all preclinical species. For example, if mouse, rat, and dog are 40%, 50%, and 60%, the human estimate is 50%. This method, however, is a rule of thumb and should be used carefully.

Since F can be expressed as:

$$F = F_a \times F_g \times F_h$$

where F_a denotes the fraction of the compound absorbed, F_g denotes intestinal availability, and F_h denotes hepatic availability, ideally for predicting F, it is necessary to predict all three parameters: F_a, F_g, and F_h. Assuming that total CL is equal to hepatic CL, it is possible to predict F_h using allometric scaling. On the other hand, to predict F_g and F_h, in vitro-in vivo extrapolation methods (IVIVE) using hepatic microsomes, hepatocytes, and intestinal microsomes have been actively investigated. These approaches are out of the scope of this chapter, and the reader is referred to respective publications.

Interspecies Scaling of V_d

V_d is commonly extrapolated pharmacokinetic parameter from animals. V_d of the central compartment (V_c) is most important in establishing the safety or toxicity for FIH studies by providing initial estimate of the plasma concentration following intravenous administration, and can be predicted with more accuracy than V_d at steady state (V_{ss}) or V_d by area (V_β). For majority of drugs, the exponents of the allometry for V_d revolve around 1.0. It has been suggested that if exponents of the allometry are > 1.1, then the V_d may be dramatically overestimated (Mahmood 2005).

Interspecies Scaling of $t_{1/2}$

Unlike CL and V_d, the $t_{1/2}$ is not directly related to the physiological body function, and thus, the correlation between BW and $t_{1/2}$ across species is poor (Mahmood 2005). Caldwell et al. (2004) proposed a simple allometric scaling for human $t_{1/2}$ approximately $= 4 \times t_{1/2}$ (rat) (hr), using 145 drugs. Another approach is to indirectly predict $t_{1/2}$ from CL and V_c. Alternatively, Mahmood (1998) suggested use of the allometry of mean residence time (MRT) versus BW to predict first MRT. $t_{1/2}$ can be then predicted by dividing the predicted MRT by 1.44. It is suggested that different approaches should be used to provide a range of predicted human $t_{1/2}$ before scientific judgment is used to select an appropriate estimate (Mahmood 2005).

Interspecies Scaling for Protein Therapeutics

It has been commonly believed that the nonhuman primate, usually the cynomolgus monkey, is the most relevant species for conducting preclinical PK studies for therapeutic monoclonal antibodies (mAbs). Human CL of mAbs can be reasonably projected based on monkey CL alone, by simple allometry with a fixed exponent of 0.85 for soluble antigen targets or 0.90 for membrane-bound targets. The dosage range for PK parameter determination was assumed to be linear (Deng et al. 2011).

Evaluation

Two tragic stories, of Tusko (West et al. 1962) which occurred 55 years ago, and of TGN1412 which occurred in 2006, are used as classical examples. Both fatal cases were due to overdoses in first trials.

Tusko, a 14-year-old Indian male elephant, died after intramuscularly dosing of 0.1 mg/kg which was a total dose of 297 mg lysergic acid diethylamide (LSD) on its body weight of 2970 kg. The trial tried to mimic a temporary form of madness in a zoo elephant. The dose was selected based on the observation that the rage in cats was produced with intravenous dose of 0.15 mg/kg LSD. Later, based on the calculations using the allometric approach, the actual dose of LSD to Tusko should have been much less and was in the range of 3–56 mg from different allometric approaches.

TGN1412 was intended to be used to treat leukemia and autoimmune disease such as rheumatoid arthritis. It is an agonistic monoclonal antibody which can bypass the requirement for T cell antigen receptor signaling and activates human T cells by only stimulating co-stimulatory receptor CD28 in the immune system. In the FIH clinical trial, it was dosed at 0.1 mg/kg to six healthy volunteers (Expert scientific group 2006). The dose selection was based on the no observed adverse effect level (NOAEL) which is considered as 50 mg/kg from the repeated dose toxicity study in cynomolgous monkeys (as described in the draft USA Food and Drug Administration (FDA) guideline "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers," 2002) with an additional safety factor of 160. However, extra precautions were not taken when antibodies are used to stimulate rather than neutralize components of the immune system. More than 90% of the CD28 receptors were bound by TGN1412 with proposed FIH dose of 0.1 mg/kg based on later calculations. Without any knowledge on the behavior of this compound in humans, the receptor occupancy of more than 90% was too high and induced massive production of cytokines and uncontrolled inflammatory responses which were observed in all six healthy volunteers in this trial. In conclusion, the preclinical development studies that were performed with TGN1412 did not predict a safe dose for use in humans, even though current regulatory requirement were met. Although the above two stories represented the failed evaluations of allometric scaling for dose finding in single dose studies, the importance of allometric scaling for the selection of "first time dose" in a species appears to be of immense significance. In addition, an understanding of the pharmacokinetic-pharmacodynamic relationship contributes to a much improved judgment.

The most widely used method for FIH dose estimation are "dose-by-factor" approach which is based on the NOAELs in multiple species and the "pharmacokinetically guided" approach. Both of these approaches rely on allometric scaling either of the dose itself or of drug clearance. For the NOAEL-based approach, the following case is used: The NOAEL in the 4-week rat toxicity study was 10 mg/kg/day and 3 mg/kg/day in the 4-week dog toxicity study, the human equivalent doses (HED) using body surface area conversion factor (BSA-CF), 0.16 for rats and 0.54 for dogs, were calculated as 1.6 mg/kg/day, then the maximum recommended starting dose (MRSD) in the FIH clinical trial is estimated as 9.7 mg/man by applying the default safety factor of 10 and based on a 60 kg body weight for a man. Basically, the dose by factor approach applies an exponent for body surface area (0.67), which account for differences in metabolic rate, to convert doses between

animals and humans. Thus, HED is determined by the below equation:

$$\mathrm{HED(mg/kg)} = \mathrm{Animal\ NOAEL(mg/kg)} \times (\mathrm{BW_{animal}(kg)/BW_{human}(kg)})^{0.33}$$

However, the dose by factor approach based on NOAEL does not take into account of systemic exposure (AUC) and the safety factor applied in the calculation of MRSD is very empirical. In the pharmacokinetically guided approach, systemic exposure instead of dose is extrapolated from animal to human, and difference in potency, free fraction in plasma and bioavailability between animals and humans should be also taken into account for the extrapolation. FIH dose from pharmacokinetically guided approach is calculated by the below equation:

$$\mathrm{D} = \mathrm{AUC} \times \mathrm{CL/F}$$

in which AUC is extrapolated human AUC based on the animal AUC corresponding to NOAEL or lowest animal AUC if a NOAEL and its corresponding AUC are available from more than one animal species. Or by the equation:

$$\mathrm{D} = \mathrm{C_{ss}} \times \tau \times \mathrm{CL/F}$$

in which C_{ss} is extrapolated human steady-state plasma concentration based on the animal C_{ss} and τ is the dosing interval. With extrapolated AUC or C_{ss}, the key elements left to project a dose in humans to produce a target AUC or C_{ss} are CL and absolute oral F based on above two equations. Besides predicted from in vitro data, the human oral F is predicted in some practice based on in vivo estimates using the average of all preclinical species. This method, however, is a rule of thumb and should be used with caution. The methods of allometric scaling of CL and F from animals to humans have been extensively discussed in the other sections of this chapter.

In another practice of interspecies allometric scaling to predict human PK parameters and FIH dose, oral plasma PK of ST-246 (Amantana et al. 2013) smallpox therapeutic was evaluated in mice, rabbits, monkeys, and dogs. Simple allometry relating animal oral plasma CL (CL/F) to animal BW was used to determine human CL/F. Using a 70 kg body weight, the human CL/F was predicted as 254 L/h from the approach of simple allometry (point estimate). Based on the ROE, the CL/F was predicted by using the MLP correction, since the scaling exponent was approximately 1.0. The point estimate of human CL/F was predicted as 51.4 L/h from the approach of MLP-corrected allometry. In order to establish good safety margin in a FIH study, a relatively lower CL/F was considered in this practice to determine a safe dose. With a pharmacokinetic-guided approach, the starting oral dose of 485 mg is the product of the lowest observed systemic exposure value (AUC) among the species utilized in this study which is 9.43 h $*$ μg/mL in dog and the scaled human CL/F which is 51.4 L/h based on the approach of MLP-corrected allometry. The trial was conducted from the low and median dose levels of 400 mg and 600mg to 800mg and the observed CL from these three levels of dosing are in close proximity to the predicted human CL/F from the approach of MLP-corrected allometry. Hence, this evaluation shows that allometric scaling of animal PK is useful in dose selection for FIH trials.

The similar approach was used to predict a FIH dose of 7-O-succinyl macrolactin A (SMA) (Keumhan et al. 2017), based on allometric scaling of PK data from mice, rats, and dogs. The human CL of SMA was first predicted by both simple allometric scaling and MLP-corrected allometric scaling of estimated CL from mice, rats, and dogs. The first-in-man dose of SMA was calculated by multiplying the efficacious exposure (AUC) with the predicted human CL from MLP-corrected allometry, which predicted a lower value of human CL of SMA.

Interspecies allometric scaling, including simple allometric scaling and allometric scaling with correction factors of MLP or BrW, has been increasingly applied in recent years to predict human PK properties of mAbs from preclinical data. However, PK allometric scaling across species with above allometric scaling fails in some cases of nonlinear PK and qualitative and quantitative difference in disposition pathways which

are typical for mAbs. Because the PK profiles of mAbs can be affected by their antigen through a target-mediated drug disposition, allometric scaling with correction factor of antigen concentration (AC) was evaluated for human CL estimation of four types of mAbs, including bevacizumab, etanercept, infliximab, and adalimumab (Wang et al. 2016b). In this evaluation, the plasma concentration of vascular endothelial growth factor (VEGF), which is the antigen of bevacizumab, was detected by enzyme-linked immunosorbent assay (ELISA) kits. The concentrations of tumor necrosis factor α which is the antigen of the rest three mAbs were obtained from published studies. The mean CLs of the mAbs in rabbit and dog were divided by the AC of the species and the product plotted as a function of BW on a log-log scale as in the below equation:

$$CL/AC = a \times BW^{b}$$

The predicted human CL of 4.05 mL/day/kg of bevacizumab was close to the observed human CL of 5.73 mL/day/kg based on AC-corrected allometry and allometric scaling having the best prediction of human CL of etanercept and infliximab in comparison with other approaches including simple allometric scaling. Scaling with correction factors of MLP or BrW has equivalent good prediction of human CL of adalimumab with simple allometric scaling and scaling with a correction factor of BrW. These results indicated that AC has reasonably corrected the additional PK differences among the species besides the BW for mAbs. Although further evaluations AC-corrected allometry need to be conducted in the multiple species scaling of mAbs that showed nonlinear PK profiles, it may provide us a new perspective to estimate human PK parameters of mAbs from preclinical data to better find the dose of FIH trial of mAbs.

The allometric scaling for pegylated liposomal and nanoparticle anticancer drugs was first evaluated with the PK of CKD-602(S-CKD602), doxorubicin (Doxil®), and cisplatin (SPI-077) which were all available from mice, rats, dogs, and phase I clinical studies (Caron et al. 2011). Because proposed CL pathways for nanoparticles and liposomes are the monocytes and macrophages of the mononuclear phagocytel system (MPS), liver weight, spleen weight, monocyte count, spleen blood flow, and liver blood flow, and potential factors associated with the MPS were evaluated to determine if parameters other than BW can best allometrically scale the disposition of these anticancer agents. The variable with the strongest relationship to liposomal clearance across all agents was total monocyte count. A − 20.4%, 186%, and −78.2% difference existed between predicted and actual CL for S-CKD602, Doxil®, and SPI-077, respectively, when adding monocyte count into the allometric equation. This evaluation provided the preliminary evidence that factors associated with the MPS, such as monocyte count, may improve the prediction of CL in humans of drugs with liposomal formulations.

Critical Assessment of the Method

Human Systemic CL

The performance of prediction of human systemic clearance by allometric scaling was investigated for nearly 400 compounds (in addition with respect to charge class) by Lombardo et al. (2013a), and followed the assessment by the PhRMA initiative (Ring et al. 2011). In the first, the lowest mean-fold error, as well as frequency within twofold from predicted to observed CL, was observed for the following methods: (a) SSS using monkey, directly, or (b) including a correction of differences in liver blood flow, (c) FCIM, and (d) multiple linear regression (MLR*)* rat-dog. MLR is based on a logarithmic scaling of two species (log(CL human) = 0.4 × log (CL rat) + 0.4 × log(CL dog) – 0.4, Lombardo et al. 2013a).

The FCIM performed very well with a GMFE (geometric mean-fold error) of 1.9 with 62% of compounds <twofold. Across charge classes, SSS including monkey, and FCIM performed best with about 60% of compounds showing a GMFE <2. In general, the correction for the fraction of drug unbound in plasma tends to worsen the accuracy of all methods. The latter publication

(Ring et al. 2011) also demonstrated that the SSS dog and MLR (rat-dog), as well as FCIM, perform with a GMFE < 2 for about 2/3 of the compounds. The *Wajima* method performed well with 60% of the compounds <twofold and 87% < threefold, whereas IVIVE was the least well-performing method. In addition, the *Wajima* method was assessed more thoroughly for PK profile estimation (Lombardo et al. 2016), finding a well predictability for i.v., but the prediction of p.o. PK parameters including absorption constant and F requires more estimation and validation.

V_{ss}

The performance of the prediction of V_{ss} by allometric scaling was investigated by another publication from Lombardo et al. (2013b). The review recommends the use of multiple and best performing methods: SSS using dog (with a GMFE of <2, with 2/3 of the compounds below a twofold prediction), *Øie-Tozer* method (rat, dog, monkey, GMFE 1.5, and 79% under twofold), and *Wajima* method (if monkey data are not available, and GMFE 1.9 and 70% under twofold). Predictive performance decreased when protein binding correction was used and should only be used when human and animals several magnitudes apart. These methodologies are thought to be the most practicable and considered together on their convergence using a coefficient of variation. However, the approach may depend on compound chemistry. The *Øie-Tozer* method only performs best for classical small molecules (Stepensky 2011) and can generate aberrant values for $f_{u,T}$ (fraction unbound in tissue) for polar compounds of low volume, and be sensitive to the ratio of extravascular to intravascular binding (Waters and Lombardo 2010). In addition, the approach to average across the *best* methods improved the prediction of V_d (as well as CL). Using an average of the *Øie-Tozer*, the assumption that V_d (monkey equals V_d (human), and the *Wajima* and MLR improved the prediction (GMFE 1.5 and 88% below twofold) (Lombardo et al. 2016). This data set of 54 marketed drugs also yielded a good superposition of concentration time profiles using the *Wajima* superposition method, finally leaving only 18% of the compounds with a relatively poor prediction. Superiority of the *Øie-Tozer* method over allometry was also shown by Zou et al. (2012b).

$t_{1/2}$

Earlier investigations showed that CL, V_d, and elimination $t_{1/2}$, predicted by using pharmacokinetic constants, were comparable with values predicted by simple allometry (Mahmood 1999). As $t_{1/2}$ is a hybrid of CL and V_d, its prediction has been more thoroughly assessed within methods of human concentration-time profile predictions. Sinha et al. (2011) reported that 65% of 29 chosen compounds had a predicted <twofold error in the prediction of $t_{1/2}$, when C_{max} was estimated using simple allometry, ROE, correction using protein binding, and a direct approach using compartmental modeling. Vz (V_d during terminal phase)/F was estimated using simple allometry and allometry with protein binding corrections. The *Wajima* superposition method (Lombardo et al. 2016), which derived a $t_{1/2}$ from a concentration-time profile prediction using scaled V_d and CL, showed that 69% of 54 compounds were within a twofold error, while 83% were within a threefold error. The PHRMA C_{ss}-MRT method predicted $t_{1/2}$ (p.o.) with lower confidence, 42–49% of 106 to 247 compounds were predicted <twofold, and 60–72% < threefold (Vuppugalla et al. 2011). Additional methods such as physiologically based pharmacokinetic (PBPK) modeling and time invariant methods (Dedrick plot) are not within scope of this chapter and the reader is referred to the PHRMA publication and others (Poulin et al. 2011). However, PBPK-approaches seem to become more common in industry for PK profile predictions. For this purpose, the knowledge of essential physiochemical and preclinical PK parameter is essential (i.e., MW, logP, pKa, fraction unbound, blood-plasma ratio, and a clearance prediction) (e.g., Poulin et al. 2011).

Allometric Scaling of Protein Therapeutics

As indicated earlier, a comparative investigation was published by Deng et al. (2011). Thirteen monoclonal antibodies were tested for which a better correlation was obtained between the observed human CL and the estimated human CL based on cynomolgus monkey PK data and an allometric scaling exponent of 0.85 for CL than other scaling approaches. Human concentration-time profiles were also reasonably predicted from the cynomolgus monkey data using species-invariant time method with a fixed exponent of 0.85 for CL and 1.0 for V_d. The predictive error was less than 50% for CL and below 100% for V_d. In a preceding investigation, six antibodies showed also a reasonable prediction of CL, V_d, but $t_{1/2}$ requires at least three animal species, when four methods were tested: (a) simple allometry, (b) maximum lifespan potential, (c) product of BrW and CL, and (d) fixed exponent (Mahmood 2009). For only one antibody, EGF/r3, the prediction was significantly higher. The prediction of the $t_{1/2}$ was reported with a %error of 43–107, and the use of fixed exponents can have large variability. Using only monkey data for 18 monoclonal antibodies (Ling et al. 2009), pharmacokinetic parameters may be best predicted with a time-invariant method and simple allometry for soluble or membrane-bound receptors. A suggested optimal exponent of 0.85–0.9 gave a percent error of up to 116% (maximum). For the prediction of PK-profiles in particular for nonlinear PK, species-invariant time methods (Dedrick plot), physiologically based PK models, or target-mediated drug-disposition models need to be considered, including PK/PD relationships or FcRn-binding (Wang et al. 2016a).

An additional example of four types of mAbs, including bevacizumab, etanercept, infliximab, and adalimumab, was discussed above (Wang et al. 2016b).

Overall, it is advised that a range of methodologies should be used and scientifically judged for dose selection and safety. Both studies show that clearance of selected biomacromolecules follows well-defined, size-related physiologic relationships, and preclinical PK studies provide reasonable estimates of human disposition under the premises of linear pharmacokinetics.

Coagulation factors have also been tested with a similar outcome. Using simple allometry with exponent to predict human pharmacokinetics for five factors, a three species scaling prediction was advantageous over a two species scaling with good correlation and an error of 11–34% for CL, 13–65% for V_{ss}, but large for $t_{1/2}$ (1–647%). A fixed exponent and single species scaling should be avoided (Mahmood 2009).

Modifications of the Method

Recently, chimeric mice with humanized liver have been developed and used for in vivo PK studies. The livers of the mice have been repopulated with human hepatocytes and express human drug-metabolizing enzymes. Therefore, chimeric mice with humanized liver are considered model animals for mimicking human drug metabolism and pharmacokinetics. Sanoh et al. (2015) reported that SSS using chimeric mice with humanized liver data showed excellent predictability of human CL and V_{ss} for various drugs metabolized by P450 and/or non-P450 enzymes. Further, they predicted human intravenous plasma-concentration curves using the complex Dedrick plot with scaling exponents for CL and V_{ss}, which enabled good prediction. Miyamoto et al. (2017) compared the predictability of SSS using data from chimeric mice with humanized liver, monkeys, and rats for 30 compounds metabolized by various drug-metabolizing enzymes. Data from chimeric mice with humanized liver produced the most accurate prediction of human CL among the species (approximately 80% within threefold range). Data from chimeric mice with humanized liver and monkeys produced comparably predictions of human V_{ss} with approximately 80% of compounds falling within threefold range. In contrast, data from rats produced low predictability. These results suggest that chimeric mice with humanized liver are useful for predicting human pharmacokinetics.

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