Journal of Pharmaceutical Research International

22(3): 1-7, 2018; Article no.JPRI.41693
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Single-species Allometric Scaling: A Strategic Approach to Support Drug Discovery

Dipal Patel[1*] and Elizabeth Dierks[1]

[1]Pharmaceutical Candidate Optimization, Bristol-Myers Squibb, Pennington, NJ 08534, USA.

Authors' contributions

This work was carried out in collaboration between both authors. Authors DP and ED designed the study and wrote the manuscript. Author DP performed the analysis and managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2018/41693
Editor(s):
(1) Sami Nazzal, College of Pharmacy, University of Louisiana at Monroe, USA.
(2) Ali Nokhodchi, Professor of Pharmaceutics and Drug Delivery, School of Life Sciences, University of Sussex, UK.
Reviewers:
(1) Daohong Chen, China.
(2) Yasir Mehmood, Pakistan.
Complete Peer review History: http://www.sciencedomain.org/review-history/24738

Short Research Article

Received 7th March 2018
Accepted 18th May 2018
Published 23rd May 2018

ABSTRACT

Aims: Multi-species Allometric Scaling (MSS) from at least three species have been used traditionally to predict human CL and Vss. Single-species Scaling (SSS) can be applied to predict these parameters from a single species using a fixed body weight exponent. SSS is less time- and resource-intense compared to MSS and thus appears to be a very promising method to implement in a screening strategy during the drug discovery phase.
Study Design: To evaluate SSS predictivity compared to MSS, six discovery compounds were evaluated in pharmacokinetic studies with the intravenous administration to rat, rabbit, dog, and/or cynomolgus monkey. Human CL and Vss were predicted by MSS and SSS, applying protein binding correction. Relative fold difference between these two methods was calculated to define success rate as a percent of the predictions of SSS within two- to four-fold of MSS predictions.
Results: SSS showed a high success rate for human CL prediction with 67% within 2-fold and 94% within 4-fold of MSS. The success rate of human Vss prediction by SSS was also good with 61% within 2-fold and 89% within 4-fold of MSS.
Conclusion: These data demonstrate the potential application of SSS to streamline the screening strategy of drug discovery programs.

**Corresponding author: E-mail: dipal.patel@bms.com;*

Keywords: Single-species scaling; allometric scaling; drug discovery strategy; clearance; volume of distribution.

ABBREVIATIONS

IV : Intravenous
PK : Pharmacokinetics
CL : Clearance
Vss : Volume of distribution at steady state
SSS : Single-species Allometric Scaling
MSS : Multi-species Allometric Scaling

1. INTRODUCTION

Researchers across the pharmaceutical industry develop drug discovery strategies that help them to screen compounds and identify issues while balancing time lines and resources. There has been a growing demand to predict human PK as early as possible to identify and mitigate potential development risks early in the discovery phase. Minimally, the parameters required for human PK prediction are CL and Vss. Several approaches based on in-vitro or in-vivo preclinical studies can be employed to estimate these parameters [1]. Allometric scaling of CL and Vss from in-vivo preclinical data has been widely used, and its predictive performance has been rigorously analyzed [2].

The relationship between PK parameters (e.g. CL, Vss) and body size can be described mathematically by using the allometric scaling equation $P=aW^b$, where P is the PK parameter, W is the body weight [3]. The constant b is referred to as the exponent which provides a means of describing the effect of size (W) on a given parameter (P). Multiple-species allometric scaling (MSS) using 3 or more species is often employed and has successfully predicted human CL and Vss. However, this method is resource-intense in terms of time, animals, and cost. To address these issues, evaluation of the confidence in predicting CL and Vss by SSS compared to other standard methods was performed. Hosea et al. [4] and Hu et al. [5] conducted retrospective analyses of prediction methodologies for commercial compounds for which both preclinical and clinical data were available. Based on their analyses, SSS from rats resulted in the most accurate predictions for human CL and Vss with decreased animal usage, cost, and time.

With the proven success of SSS, it is very appealing to apply this scaling method in drug discovery as a screening strategy. The objective of this exercise was to determine whether SSS could be implemented as a screening strategy in a discovery program to speed up development candidate selection while decreasing resource use. To confirm the success rate of the SSS prediction method, we selected 6 in-house discovery compounds for which in-vivo PK data in 2 or more preclinical species were available. Human CL and Vss were predicted using both the SSS and MSS methods and the results compared.

2. MATERIALS AND METHODS

2.1 Compound Selection

Six compounds from the same program and chemical series were chosen for this analysis. All compounds were evaluated in IV PK studies in two or more preclinical species, primarily rat, rabbit, dog or cynomolgus monkey.

2.2 Data Analysis

The representative body weights for each species used in this analysis were: rat, 0.25 kg; rabbit, 3 kg; monkey, 5 kg; dog, 10 kg and human, 70 kg. For each compound the total CL (mL/min/kg) and Vss (L/kg) were calculated by noncompartmental analysis (NCA) of observed plasma concentrations, using Phoenix® WinNonlin® version 6.3 (Certara USA, Inc., Princeton, New Jersey). To calculate unbound CL (Equation 1) and unbound Vss (Equation 2), the plasma protein unbound fraction (fu) of each species was applied to the respective total CL and Vss values.

$$\mathrm{CL_u} = \frac{\mathrm{CL}}{\mathrm{f_u}} \quad (1)$$

$$\mathrm{Vss_u} = \frac{\mathrm{Vss}}{\mathrm{f_u}} \quad (2)$$

2.3 Human CL and Vss Prediction by MSS

The CL_u and Vss_u values for each species were normalized by body weight and plotted against body weight on a log-log plot to calculate the allometric co-efficient (a) and exponent (b). The simple allometric equations (Equation 3 and 4) were applied to predict human CL_u and Vss_u using 2 or more species:

$$\mathrm{CL_u\ (human)} = \mathrm{a} * (\mathrm{BW_{human}})^{\mathrm{b}} \quad (3)$$

$$\mathrm{Vss_u\ (human)} = \mathrm{a} * (\mathrm{BW_{human}})^{\mathrm{b}} \quad (4)$$

Equations 5 and 6 were used to calculate total CL and Vss.

$$\mathrm{CL\ (human)} = \mathrm{CL_u} * \mathrm{f_u\ (human)} \quad (5)$$

$$\mathrm{Vss\ (human)} = \mathrm{Vss_u} * \mathrm{f_u\ (human)} \quad (6)$$

2.4 Human CL and Vss by SSS

The human CL and Vss were predicted by applying the theoretical ideal exponents 0.75 and 1 respectively [6], as per the below equations using the CL and Vss obtained from each preclinical species.

$$\frac{CL\ (human)}{f_u\ (human)} = \frac{CL(animal)}{f_u\ (animal)} * \left(\frac{BW_{human}}{BW_{animal}}\right)^{0.75} \quad (7)$$

$$\frac{Vss(human)}{f_u\ (human)} = \frac{Vss(animal)}{f_u\ (animal)} * \left(\frac{BW_{human}}{BW_{animal}}\right)^{1} \quad (8)$$

2.5 Determination of Success Rate

For the data set as a whole, the accuracy of the prediction methods was assessed by relative fold difference (FD) between the predicted CL and Vss by MSS and SSS as per below equation.

$$FD = \frac{CL\ or\ Vss\ predicted\ by\ SSS}{CL\ or\ Vss\ predicted\ by\ MSS} \quad (9)$$

The success rate of SSS was classified based on the total number of CL or Vss predictions that fell within 2-fold or 4 fold of the MSS predicted values.

3. RESULTS AND DISCUSSION

The mean plasma CL and Vss, determined for rat, rabbit, dog, or monkey are summarized in Table 1 along with the free fraction in plasma. Table 2 reports free fraction in human plasma and the predicted human CL and Vss from SSS and MSS as described in the methods. The human CL and Vss predicted by SSS were plotted against the human CL and Vss predicted by MSS as shown in Fig. 1 (a) and (b). In both figures, lines of 1-fold, 2-fold, and 4-fold deviation from unity were inserted to show the closeness of both prediction methods.

These six compounds had similar CL mechanisms which were conserved across all preclinical species evaluated. SSS had a high success rate for human CL prediction with 67% within 2-fold and 94% within 4-fold of MSS. All of the SSS human CL predictions fell within 4-fold of MSS, except for compound B where SSS from rat, resulted in 7.6-fold over-prediction compared to MSS. For compound B, however, the MSS predicted CL resulted in a low exponent (0.4) which indicates the under-prediction of human CL by the rule of exponent [7]. SSS from all other species also over-predicted the CL compared to MSS.

The success rate of human Vss prediction by SSS was also fairly high with 61% within 2-fold and 89% within 4-fold of MSS. As shown in Figure 1(b), there are 2 outliers, mainly related to SSS from a rat. This is consistent with the findings of Berry et al.[8] in their analysis of 67 compounds; rat was the least predictive of human Vss. SSS from rat resulted in 6-fold under-prediction and 12-fold over-prediction, compared to MSS for compounds A and C, respectively. The exponent from MSS was 1.3 (A) and 0.5 (C). Both of these exponents indicate significant deviations from the isometric relationship between Vss and body weight and call into question the validity of these MSS predictions.

Time- and resource-intensive in-vivo preclinical PK screening is a rate-limiting step in program advancement. In-vivo preclinical PK data, however, is critical information for human PK parameter prediction. Rodents are often the preferred species for initial in-vivo PK screening because of their size and availability. Compounds must undergo PK studies in one or more additional species in order to predict the human CL and Vss using the MSS method. Prioritization of the compounds from rodent PK into capacity-limited PD or efficacy testing can also lead to faster progression of compounds. Thus, optimizing the screening strategy at this rate-limiting stage is key for efficient drug discovery. SSS is an attractive method when preclinical PK information is limited. Human PK parameters (CL and Vss) can be predicted by SSS from any one species to prioritize compounds for preclinical efficacy testing. Efficacious compounds then can be prioritized for further preclinical PK testing. As more data become available, the learnings can be used to refine the screening strategy. Thus, employing SSS much earlier in the screening funnel may result in only a fraction of the discovery compounds being dosed in more than one species, saving a significant amount of resources

and time. Additionally, this approach complies with the concept of the 3Rs (Replacement, Reduction and Refinement) of animal usage in drug discovery, supporting the Animal Welfare Act (AWA) [9].

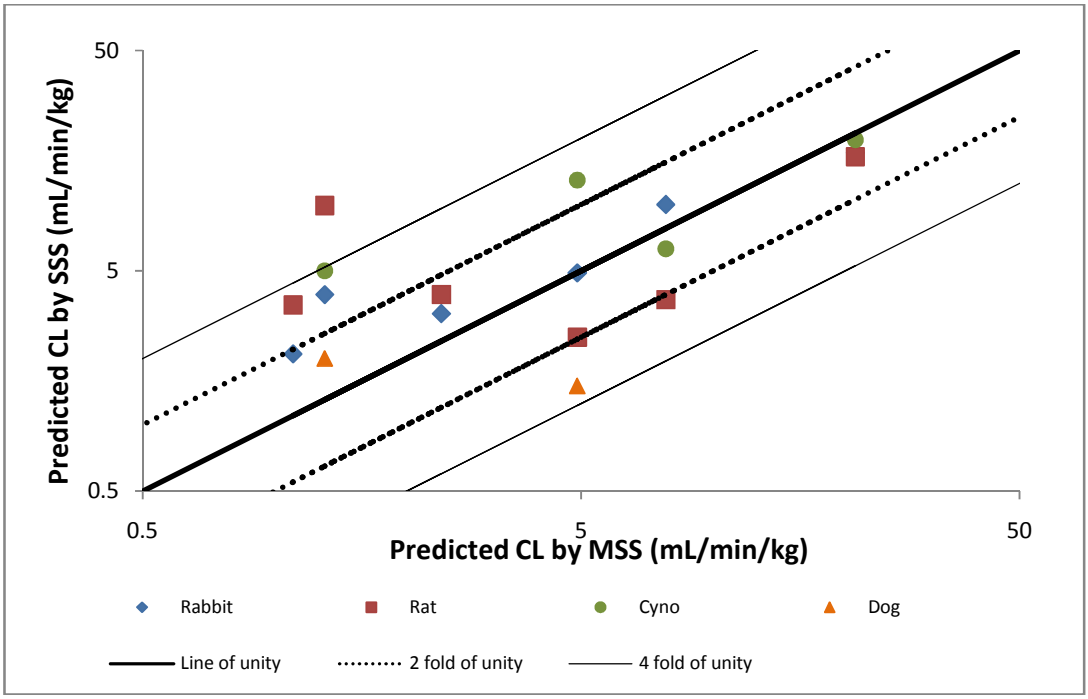

Fig. 1(a)

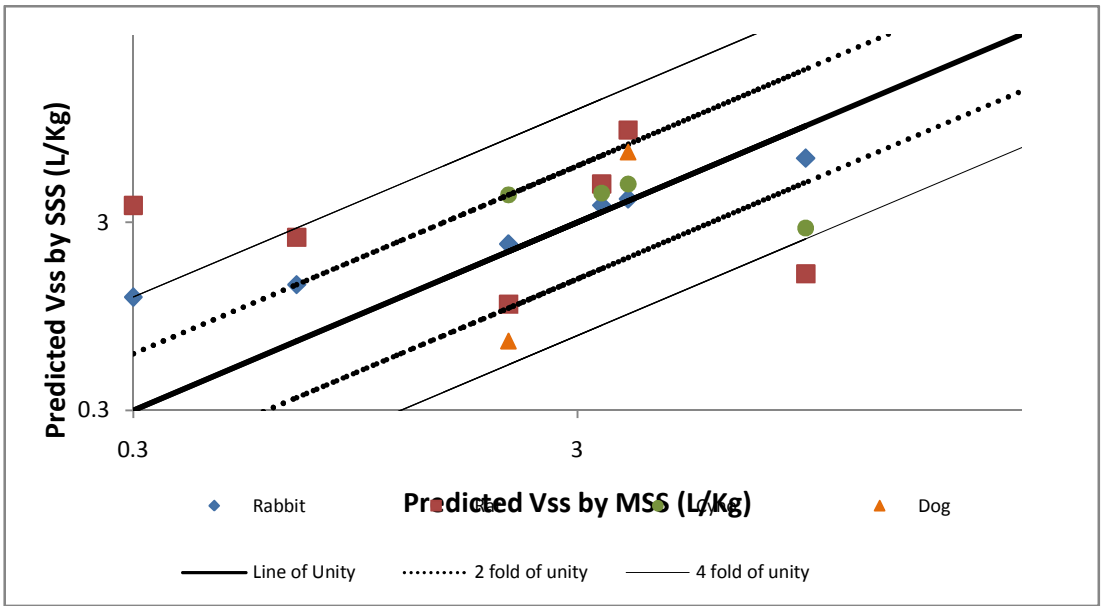

Fig. 1(b)

Fig. 1. (a) Predicted human CL (mL/min/kg) by multi-species allometric scaling (MSS) versus single-species allometric scaling (SSS). (b) Predicted human Vss (L/kg) by multi-species allometric scaling (MSS) versus single-species allometric scaling (SSS)

Table 1. Summary of observed in-vivo CL, Vss and in-vitro free fraction in plasma in the respective preclinical species

Compound	CL (mL/min/kg)				Vss (L/kg)				fu			
	Rat	Rabbit	Monkey	Dog	Rat	Rabbit	Monkey	Dog	Rat	Rabbit	Monkey	Dog
A	8.4	14	26		0.9	4.2	5.9		0.043	0.049	0.165	
B	2.6	14	15	2.9	0.6	6.4	7.5	6.2	0.002	0.05	0.048	0.027
C	1.3	11			0.3	1.9			0.005	0.098		
D	3.6	5.3			0.7	1.7			0.019	0.081		
E	8.5	23.3	41.0		0.6	2.3	4.6		0.026	0.127	0.222	
F	10.1	2.4	22.1	2.9	1.1	0.5	3.7	0.9	0.009	0.002	0.008	0.011

Table 2. Human CL and Vss predicted by SSS from respective species, MSS and in-vitro free fraction of plasma protein binding in human

Compound	CL (mL/min/kg)					Vss (L/kg)					fu
	Rat	Rabbit	Monkey	Dog	MSS	Rat	Rabbit	Monkey	Dog	MSS	Human
A	3.7	10.0	6.3		7.8[1]	1.6	6.6	2.8		9.8[2]	0.077
B	9.9	3.9	5.0	2.0	1.3[3]	9.3	4.0	4.8	7.1	3.9	0.031
C	3.9	3.2			2.4	3.7	1.2			0.3[4]	0.062
D	3.5	2.1			1.1	2.5	1.4			0.7	0.069
E	16.5	17.2	19.7		21.1	4.8	3.7	4.3		3.4	0.206
F	2.5	4.9	12.9	1.5	4.9	1.1	2.3	4.2	0.7	2.1	0.009

1. MLP Correction was applied
2. Poor exponent (1.3)
3. Poor exponent (0.4)
4. Poor exponent (0.5)

Due to mixed views on SSS application in the literature [10,11], it was important to evaluate the predictive validity of SSS compared to MSS with program compounds. The theoretical ideal exponent used in this exercise has been successful in the prediction of human CL and Vss from various animal species [4,5]. Initial human Vss and CL predictions by MSS and SSS were done without applying protein binding (fu) corrections (data not shown). The MSS allometric exponent was poor without fu correction for a few compounds, however. As a consequence, fu correction was applied to all of the Vss and CL predictions. Since protein binding has an impact to varying degrees on CL and Vss, applying the correction when protein binding is widely different among species may improve the prediction of these parameters.

4. CONCLUSION

Both SSS and MSS methods have proved successful at predicting human PK for a variety of compounds in many published retrospective analyses. However, correlations between these two scaling methods were not discussed. We confirmed a good correlation (>60% of compounds within 2-fold) existed between MSS- and SSS-predicted CL and Vss for fifty compounds in the analysis by Hosea, et al. [4], where both SSS and MSS methods predicted the clinical observations with high confidence.

In this study, we have confirmed the predictivity of SSS compared to MSS and employed SSS for a novel purpose, to optimize a drug discovery screening strategy. Since MSS has been shown to be predictive generally of human PK (>70% within 4-fold [4], we were confident that SSS would be reasonably predictive of human PK parameters for our program compounds. By implementing SSS in our screening strategy to prioritize compounds moving from rodent PK studies to efficacy and large animal PK studies, we were able to identify a clinical development candidate within a shorter timeframe and using fewer resources. In conclusion, SSS can be utilized to predict human CL and Vss as a screening strategy at the drug discovery level, although confirmation of the predictivity of SSS to MSS for a few representative program compounds may be desired.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

We thank Dr. Kimberly Lentz and Dr. Punit Marathe for helpful suggestions and critical reading of the manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Obach RS, Baxter JG, Liston TE, et al. The prediction of human pharmacokinetic parameters from preclinical and In Vitro metabolism data. Journal of Pharmacology and Experimental Therapeutics. 1997;283(1):46-58.
2. Huang Q, Riviere JE. The application of allometric scaling principles to predict pharmacokinetic parameters across species. Expert Opinion on Drug Metabolism & Toxicology. 2014;10(9): 1241-53 .
   DOI:10.1517/17425255.2014.934671[published Online First: Epub Date]|.
3. Sharma V, McNeill JH. To scale or not to scale: The principles of dose extrapolation. British Journal of Pharmacology. 2009;157(6):907-21.
   DOI: 10.1111/j.1476-5381.2009.00267.x[published Online First: Epub Date]|.
4. Hosea NA, Collard WT, Cole S, et al. Prediction of human pharmacokinetics from preclinical information: Comparative accuracy of quantitative prediction approaches. Journal of Clinical Pharmacology. 2009;49(5):513-33.
   DOI:10.1177/0091270009333209[published Online First: Epub Date]|.
5. Hu TM, Chiu SJ. Prediction of human drug clearance using a single-species, fixed-exponent allometric approach. Journal of Medical Sciences. 2009;29(6):331-39.
6. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science. 1997;276(5309):122-26.
   DOI:10.1126/science.276.5309.122[published Online First: Epub Date]|.

7. Zou P, Yu Y, Zheng N, et al. Applications of human pharmacokinetic prediction in first-in-human dose estimation. The AAPS Journal. 2012;14(2):262-81.
DOI: 10.1208/s12248-012-9332-y[published Online First: Epub Date]|.
8. Berry LM, Li C, Zhao Z. Species differences in distribution and prediction of human Vss from preclinical data. Drug Metabolism and Disposition. 2011;39(11):2103-16.
DOI: 10.1124/dmd.111.040766[published Online First: Epub Date]|.
9. Russell WMS, Burch RL. The principles of humane experimental technique; 1959.
10. Mahmood I. Application of fixed exponent 0.75 to the prediction of human drug clearance: an inaccurate and misleading concept. Drug Metabolism and Drug Interactions. 2009;24(1):57-81.
11. Huh Y, Smith DE, Feng MR. Interspecies scaling and prediction of human clearance: Comparison of small- and macro-molecule drugs. Xenobiotica; the fate of foreign compounds in biological systems. 2011;41(11):972-87.
DOI:10.3109/00498254.2011.598582[published Online First: Epub Date]|.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/24738