

Prediction of Human Pharmacokinetics of Bendamustine from Preclinical Species Pharmacokinetics Based on Normalizing Time Course Profiles

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ABSTRACT

Bendamustine, an alkylating anticancer agent, is used to treat chronic lymphocytic leukemia by intravenous infusion alone or in combination. The work aimed to develop a method to predict time vs. concentration profile for humans based on preclinical pharmacokinetics using the assumption of superimposability of normalized time course profiles of animals and humans. Standard allometric equations with/without correction factors (CF) were also used in prediction. The V_{ss} was predicted by simple allometry of $0.312W^{0.871}$ ($r^2 = 0.987$), where W is body weight; predicted V_{ss} (19.71 L) was similar to the reported value (20.10 L). However, CL prediction involved both simple and CF allometry. Best proximity CL (543 vs. 598 mL/min) was obtained with maximum life span correction (MLP) [$2.46W^{1.215}$ ($r^2 = 0.988$)]. Normalized curves were obtained by normalizing the time (with mean residence time) vs. concentration (with dose/ V_{ss}) in animal species. The concentration vs. time profile in humans after intravenous infusion was then simulated using normalized curve for each animal species and the values of CL and V_{ss} were predicted for humans. In summary the findings indicate that normalized time course approach could predict the bendamustine human pharmacokinetics and such an approach could be prospectively applied for analog drugs of this class.

Introduction

Bendamustine (CAS no: 16506-27-7; ► **Fig. 1**), chemically known as 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid, is structurally close to chlorambucil. Bendamustine comprises mechlorethamine (nitrogen mustard) group, a benzimidazole ring, and a butyric acid side chain. While the mechlorethamine group is responsible for its potent alkylator properties

causing DNA damage, the benzimidazole ring acts as an antime-tabolite. The presence of butyric acid side chain increases water solubility of bendamustine [1]. While the IC_{50} against several leukemia (acute myeloid, lympholytic, chronic myeloid) and non-Hodgkin's cells lines ranged between 10–200 μ M, at these concentrations it was not cytotoxic to human hepatocytes [2]. Bendamustine is primarily metabolized into mono- and di-hydroxy metabolites by hydrolysis (► **Fig. 1**); these metabolites have little or no activity (IC_{50} : 550 μ M). Bendamustine also undergoes Phase-I metabolism by CYP1A2 and is converted into two metabolites:

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γ -hydroxybendamustine (► Fig. 1; comparable activity to bendamustine) and N-desmethylbendamustine (► Fig. 1; 4 to 5-fold lower activity). Since γ -hydroxybendamustine levels are much lower than bendamustine; anticancer activity is primarily driven by the parent bendamustine [3]. Other minor pathways of metabolism of bendamustine included carboxylic acid formation and generation of Phase-II metabolites like sulphate, cystine and glutathione conjugates. It is also reported that bendamustine undergoes biliary excretion in mice, rats and dogs. Post intravenous administration of radiolabelled bendamustine to preclinical species about 90% of administered drug is recovered in feces [2]. Dubelman et al. (2013) reported that 49% of the ^{14}C -bendamustine derived radioactivity with ~3% of unchanged bendamustine was excreted through urine following administration of ^{14}C -bendamustine (80-95 μCi) to humans as an intravenous infusion at 120 mg/m² for 1 h [4].

In 2008, bendamustine was first approved as a 30 min intravenous infusion (Treanda®) in cancer therapy. Very recently (in 2015) FDA has approved 10 min rapid infusion bendamustine hydrochloride (Bendeka®; product in 50 mL volume). Unlike Treanda®, Bendeka® does not contain dimethylacetamide and it is a ready to dilute formulation to infuse to patients [5].

To date there is no consolidated report on intravenous pharmacokinetics of bendamustine in preclinical species. Hence a series of

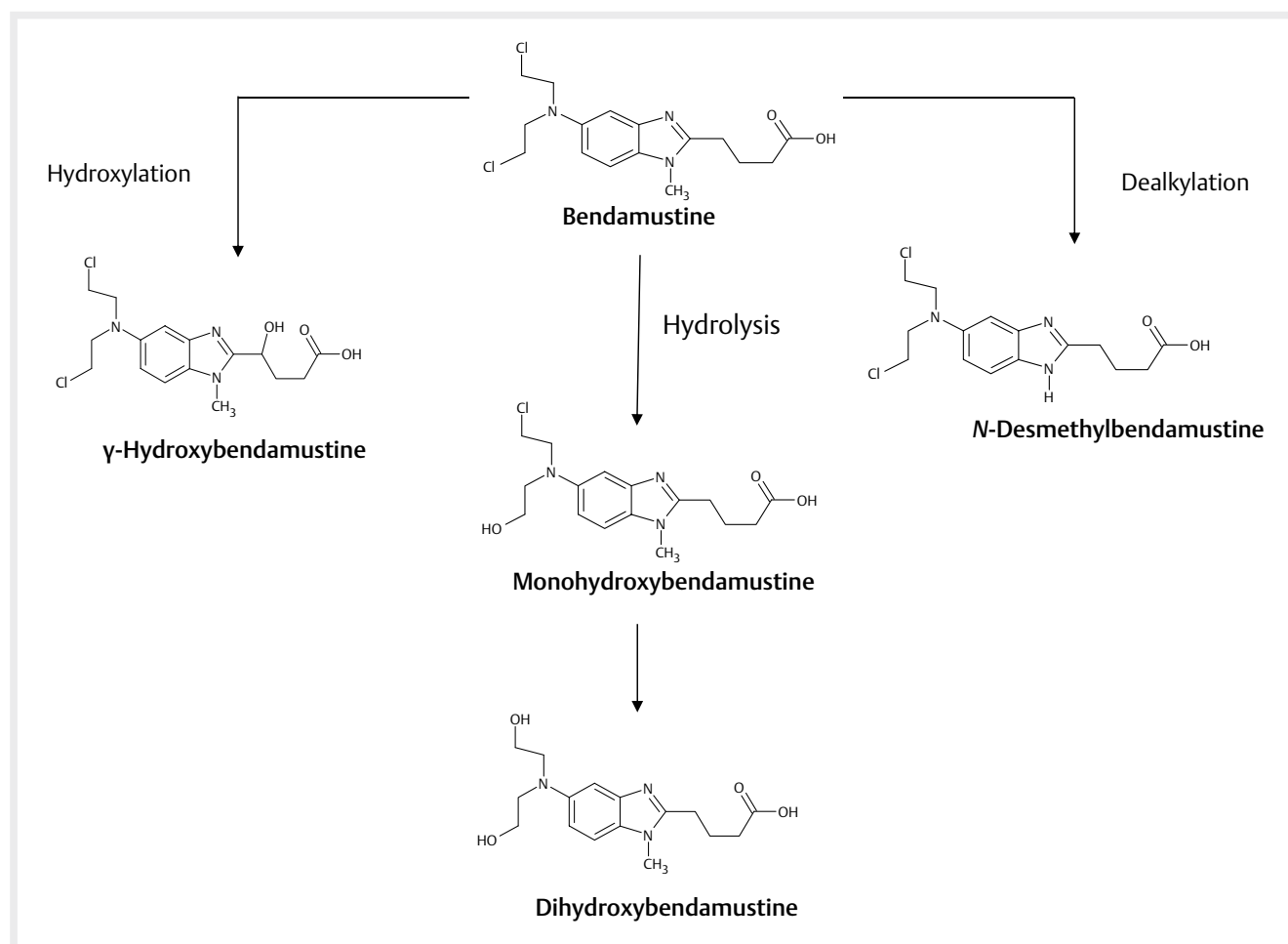
intravenous pharmacokinetic experiments in Balb/C mice, Sprague Dawley rats, New Zealand white rabbits and Beagle dogs were performed to characterize the pharmacokinetics of bendamustine.

The scope of the present work were: (i) to derive pharmacokinetic parameters of bendamustine from 4 preclinical species after intravenous infusion and collate monkey intravenous pharmacokinetic data from published literature (ii) to carry out preclinical species allometric scaling using conventional methods which also considered correction factors, as deemed appropriate to improve the predictions of human pharmacokinetics of bendamustine (iii) to compare the predicted human pharmacokinetic data using various allometric equations with actual Phase-I patient pharmacokinetic data post-digitalization; and (iv) to perform the normalization method reported by Wajima [6] wherein, the individual animal species concentration profiles were used to simulate the human concentration profile to deduce which animal species was closely aligned with human concentration profile.

Materials and Methods

Chemicals and reagents

Bendamustine hydrochloride (purity: >99%) was purchased from MedKoo Biosciences, Inc., NC, USA. HPLC grade acetonitrile, for-



► Fig. 1 Structural representation of bendamustine and its metabolites.

mic acid and methanol were purchased from Rankem, Ranbaxy Fine Chemicals Limited, New Delhi, India. Dimethylsulfoxide (DMSO), Solutol, dipotassium ethylenediaminetetraacetic acid (K₂.EDTA), Tween-80 and phenacetin were purchased from Sigma Aldrich, St. Louis, USA. Methyl cellulose was purchased from SDFCL Chemicals, Mumbai, India. Absolute ethyl alcohol was purchased from Changshu Chemicals, China.

Formulations

The intravenous formulation of bendamustine was prepared using 5% dextrose solution. The volume of administration for intravenous infusion was 10 mL/kg for mice and rats; 7.5 mL/kg for rabbits and 2.5 mL/kg for dogs.

Animal experiments

All the mice, rats and rabbits experimental protocols were approved by Institutional Animal Ethical Committee (IAEC) of Jubilant Biosys (IAEC/JDC/2017/133) nominated by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). Male Balb/C mice (~6-10 weeks old; n = 12) and male Sprague Dawley rats (~7-8 weeks old; n = 4) were procured from Vivo Biotech, Hyderabad, India. Male New Zealand white rabbits (~3-4 months old; n = 3) were procured from Liveon Biolabs, Tumkur, Karnataka, India. Animals were quarantined in Jubilant Biosys Animal House for a period of 7 days with a 12:12 h light:dark cycles, had free access to rodent feed (Altromin Spezialfutter GmbH & Co. KG., Im Seelenkamp 20, D-32791, Lage, Germany) and water ad libitum. For all the experimental work animals were kept for fasting (4 h for mice and 12 h for rats and rabbits) and during this time they were allowed to take water ad libitum. Feed was provided 2 h post-dose and water was allowed ad libitum.

IAEC of Palamur Biosciences, Telangana, India (1312/PO/RcBiBt/S/L/09/CPCSEA) approved studies conducted in dogs. Male Beagle dogs (~1-1.2 year old; n = 3) were housed in Palamur Biosciences Private Limited animal house facility in a temperature (18-28 °C) and humidity (30-70%) controlled room and fed with Pedigree standard pellet feed and water ad libitum for one week before using for experimental purpose. For all the experimental work animals were kept for 12 h overnight fasting and during this time they were allowed to take water ad libitum. Feed was provided 4 h post-dose and water was allowed ad libitum.

Pharmacokinetic studies

Bendamustine was administered to all the animal species as an intravenous infusion in 30 min duration. The infusion rate was 0.4 mL/min (Pump Elite Infusion, Harvard Apparatus). The administered dose was 10, 10, 5 and 12 mg/kg for mice, rats, rabbits and dogs, respectively. Post-infusion serial blood samples [100 µL in case of mice (sparse sampling; n = 3 at each time point), rats and rabbits and 500 µL in dogs] were collected at 0.25, 0.5, 1, 1.25, 1.5, 2, 4, 6 and 8 h (from retro-orbital plexus in case of mice, rats and from marginal ear vein for rabbits) and from jugular vein in case of dogs at 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 36 h. Blood samples were collected in tubes containing K₂.EDTA as the anticoagulant and centrifuged for 5 min at 14000 rpm in a refrigerated centrifuge (Biofuge, Heraeus, Germany) maintained at 4 °C for plasma separation and stored frozen at -80 ± 10 °C until analysis.

Plasma samples processing and analysis

The plasma samples were analyzed using a validated method previously reported by us [7]. Briefly, to an aliquot of 20 µL plasma sample, 10 µL of internal standard solution (phenacetin; 50 ng/mL) was added followed by addition 50 µL of 5% formic acid in water. To this mixture 1.0 mL of ethyl acetate was added and vortexed for 3 min, followed by centrifugation at 14000 rpm for 3 min. Post centrifugation, ~900 µL organic layer was aliquoted and dried under gentle stream of nitrogen. The resultant residue was reconstituted with 200 µL of acetonitrile and clear supernatant was transferred into vials and 10 µL was injected onto LC-MS/MS system for analysis. The linearity range was 0.11-518 ng/mL. In-study quality control (QC) samples, supplemented with concentrations of 0.34, 248 and 428 ng/mL of bendamustine, were analyzed with the unknown study samples. It should be noted because of intravenous dosing, initial plasma samples showed high concentration above the upper limit of quantitation and were subsequently diluted with corresponding species blank plasma to bring the concentration within linearity range.

For plasma samples analysis the criteria for acceptance of the analytical runs encompassed the following: (i) 67% of the QC samples accuracy must be within 85-115% of the nominal concentration (ii) not less than 50% at each QC concentration level must meet the acceptance criteria. Following completion of the analysis both the linearity and quality control samples values were found to be within the accepted variable limits.

Prediction of human pharmacokinetics

The human pharmacokinetics of bendamustine was predicted employing allometric scaling. The in-house generated intravenous infusion pharmacokinetic data in mice, rats, rabbits and dogs (► **Table 1**) were utilized for these scaling exercises. For the purpose of scaling, all volume of distribution (V_{ss}) and clearance (CL) values were converted into L and mL/min, respectively. ► **Table 1** provides the requisite parameters (in house and literature) obtained from all animal species that were employed in this allometric scaling exercise.

Simple allometry

Simple allometric scaling of both V_{ss} and CL was performed according to the below mentioned equations.

$$V_{ss} = aW^x \quad (1)$$

$$CL = bW^y \quad (2)$$

Where, W is the body weight (kg), a and b are the allometric coefficients and x and y are allometric exponents. The pharmacokinetic parameter (V_{ss} or CL) and W were transformed logarithmically and fitted to the equation: log (V_{ss} or CL) = log a + b log W, by linear least-square regression analysis.

The schematic represented in ► **Fig. 2** was chosen, a-priori, to further improve the prediction of clearance value of bendamustine if the exponent value from simple allometry prediction exceeded widely accepted fixed exponent of 0.75 for the clearance parameter. Accordingly, correction factors were applied taking into consideration mathematically derived constants [maximum life span potential (MLP), brain weight (BW)] as well as the physiological pro-

cess [kidney blood flow (KBF), monkey liver blood flow (MLBF)] and excretory mechanisms [bile correction factor; glomerular filtration rate (GFR)].

Incorporation of correction factors

These correction factors summarized in ► **Fig. 2** were incorporated into allometric equations as follows:

$$\log (CL \times MLP/BW/GFR/KBF/bile \text{ correction}) = \log b + y \log W \quad (3)$$

$$\begin{aligned} \text{Predicted human CL} = \\ \text{Monkey CL} \times (\text{human liver blood flow/MLBF}) \end{aligned} \quad (4)$$

Digitalization of reported data and Simulation of concentration-time profile for humans

Some additional efforts were made by digitalizing the reported plots of Phase-I patients pharmacokinetic data [4] and re-analysis the PK data to ensure there were no apparent mismatches between the PK parameters and time concentration profiles with Digitizeit version 2.0.0 [8] (available at <https://www.digitizeit.de/>; accessed on 15 Feb. 2018) and Phoenix WinNonlin 7.0 software (Pharsight, Mountain View, CA, USA).

Normalization method

As per the methodology defined by Wajima et al. (2004) the normalized curves for all the animal species was performed [6]. The normalized curve was derived by dividing the plasma concentration and time scales (on Y-axis) by C_{ss} (= Dose/V_{ss}) and MRT (mean residence time) for the corresponding curve (on X-axis), respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated by a non-compartmental method using Phoenix WinNonlin 7.0 software (Pharsight, Mountain View, CA, USA).

Results

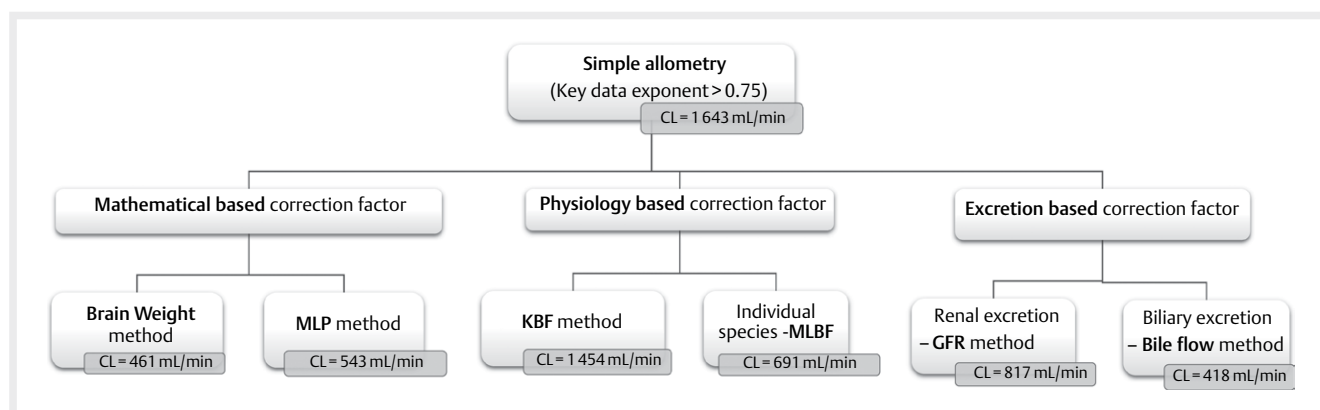
Prediction of human V_{ss}

► **Fig. 3** shows the simple interspecies (mice, rats, rabbits and dogs) scaling plot ($r^2 = 0.987$) for the prediction of human V_{ss} value. The correlation between body weight and V_{ss} appeared satisfactory with an exponent value of 0.871. The predicted human V_{ss} value

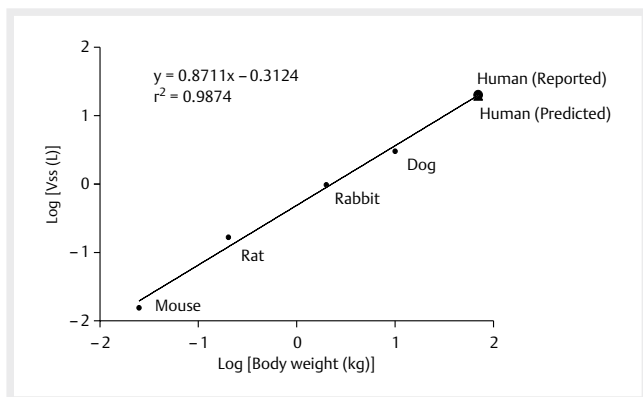
► **Table 1** Pharmacokinetic parameters of bendamustine in mice, rats, rabbits, dogs and monkeys post intravenous bolus/infusion administration.

Species (Sample size)	Dose (mg/kg)	Average body weight (kg)	AUC _{0-∞} (nM × h)	C _{max} (nM)	T _{1/2} (h)	CL (mL/min)	V _{ss} (L)
Balb/C mice (n = 12)	10	0.025	9331 [#]	12877 [#]	0.19 [#]	1.13 [#]	0.016 [#]
Sprague Dawley rats (n = 4)	10	0.203	6731 ± 1155	13572 ± 2975	0.21 ± 0.02	12.3 ± 1.99	0.16 ± 0.03
New Zealand white rabbits (n = 3)	5.0	2.00	8173 ± 2314	11988 ± 3919	0.24 ± 0.01	54.2 ± 13.4	0.97 ± 0.31
Beagle dogs (n = 3)	12	10.0	17362 ± 3226	35790 ± 7049	0.24 ± 0.07	299 ± 58.4	3.02 ± 0.98
Cynomolgus monkeys* (n = 4)	3.0	5.00	5862 ± 2027	15294 ± 6222	0.57 ± NA	106 ± 33.3	1.70 ± 0.55

* Drager et al. [9]; The values are represented in mean ± SD, # is for the sparse sampling method in mouse; NA is not available



► **Fig. 2** Algorithm for bendamustine clearance. GFR: glomerular filtration rate; KBF: kidney blood flow; MLBF: monkey liver blood flow and MLP: maximum life span period.

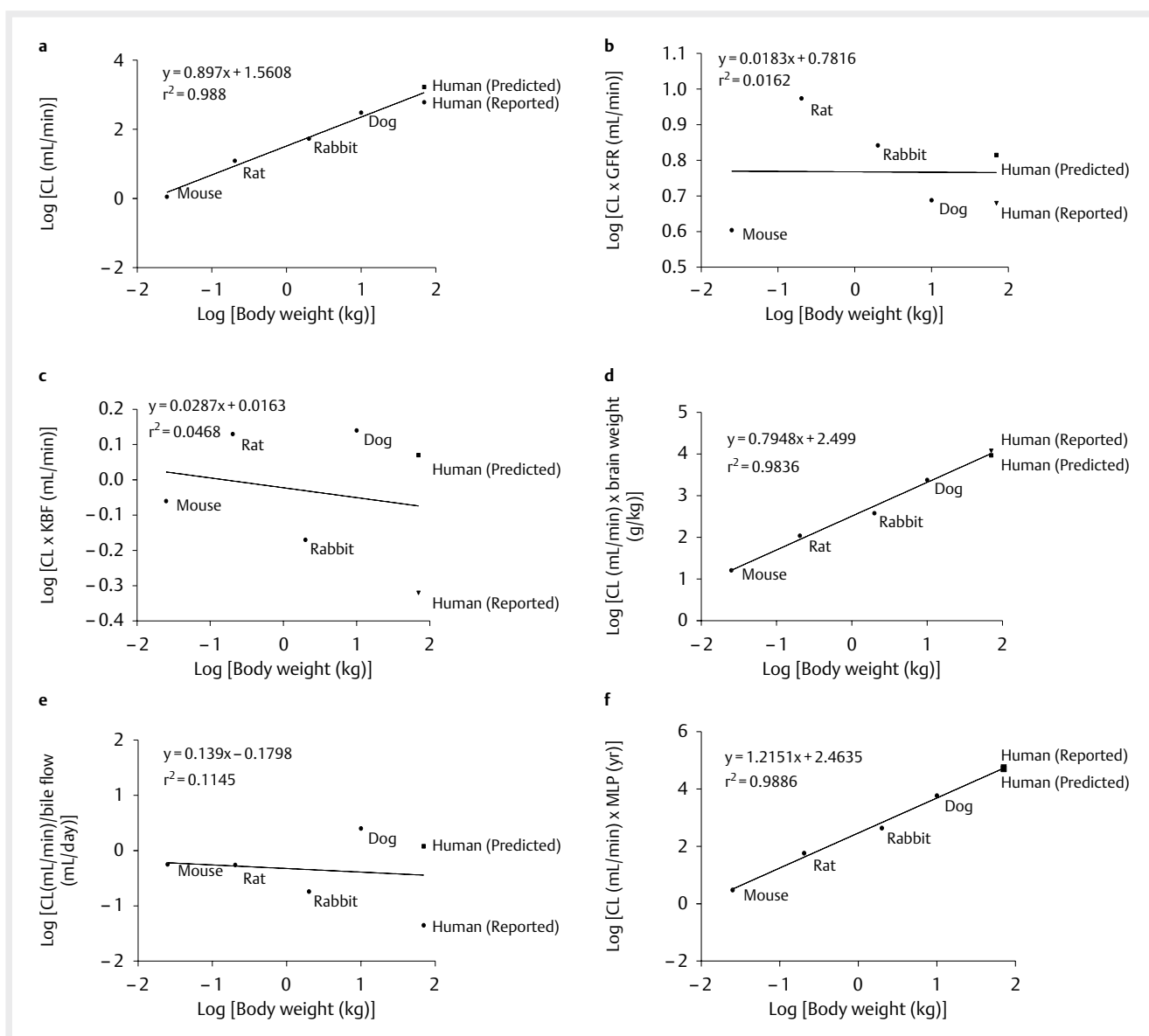


► **Fig. 3** Simple allometric scaling for prediction of human volume of distribution using mouse, rat rabbit and dog data.

based on these calculations was 19.71 L/kg, was in close agreement with the reported value of 20.10 L in humans (► **Table 2**) [4].

Prediction of human CL

► **Fig. 4a** shows the simple allometric scaling plot ($r^2 = 0.988$) for the prediction of human CL value from the four preclinical species. This correlation resulted in an exponent value of 0.897. The predicted value based on these calculations was found to be 1643 mL/min, which is 2.75-fold higher than reported CL value in humans (598 mL/min) (► **Table 2**). Dubbelman et al. (2013) reported that 49% of the ^{14}C -bendamustine derived radioactivity was excreted through urine post-administration of ^{14}C -bendamustine to humans [4]; and therefore, we applied GFR and KBF as the correction factors and predicted the human CL value. The interspecies scaling plot corresponding to GFR and KBF correction factor ($r^2 = 0.016$ and 0.046, respectively) is presented in ► **Figs. 4b and c**, respectively.



► **Fig. 4** Allometric scaling of human clearance from mouse, rat, rabbit and dog **a** simple allometry **b** GFR correction factor **c** KBF correction factor **d** brain weight correction factor **e** bile correction factor **f** MLP.

The predicted human CL value applying GFR correction factor was 817 mL/min, which is 1.37-fold higher to the reported clearance value in humans (► **Table 2**); however the predicted CL value post KBF correction factor (1454 mL/min) was 2.43-fold higher than the reported human CL value (598 mL/min) (► **Table 2**; ► **Figs. 4b and c**). Incorporation of BW correction factor ($r^2 = 0.983$; exponent value of 0.794) predicted 1.3-fold lower CL value (461 mL/min) than the reported CL value (► **Table 2**; ► **Fig. 4d**). It was reported that bendamustine undergoes biliary excretion in mice, rats and dogs; and hence we have used bile correction factor and predicted the CL. By using bile correction ($r^2 = 0.114$; exponent value of 0.139) the human CL was slightly under predicted (1.43-fold lower) to the reported value (► **Table 2**; ► **Fig. 4e**). Drager et al. (2014) reported the intravenous pharmacokinetics of bendamustine in monkeys post administration of a bolus intravenous dose of three different solution formulations [9]. Ward and Smith (2004) and Nagilla and Ward (2004) predicted human clearance from the monkey liver blood flow (MLBF) by investigating 103 compounds [10, 11].

By using MLBF as correction factor the human CL of bendamustine was close (1.16-fold) to the reported value (691 vs. 598 mL/min; ► **Table 2**). Finally, we have used MLP as one of the correction factors to predict the human CL ($r^2 = 0.988$; exponent value of 1.215) and found that the predicted CL was very close (543 vs. 598 mL/min; ► **Table 2**). Overall, MLBF and MLP methods were found to be most accurate for human bendamustine CL prediction among all the correction factors tested (► **Table 2**; ► **Fig. 4f**).

► **Table 2** Predicted and reported human Vss and CL values for bendamustine.

Parameter	Method	Predicted	Reported
Vss (L)	Simple allometry	19.71	20.10
CL (mL/min)	Simple allometry	1643	598
	Glomerular filtration rate (GFR) correction factor	817	
	Kidney blood flow (KBF) correction factor	1454	
	Brain weight (BW) correction factor	461	
	Bile correction factor	418	
	Monkey liver blood flow (MLBF) correction factor	691	
	Maximum life span potential (MLP) correction factor	543	

► **Table 3** Comparison of human digitalized values with the reported values.

PK parameter	Predicted	Reported
$T_{1/2}$ (h)	0.75	0.65
C_{max} (nM)	13579	13478
$AUC_{inf,obs}$ (nM × h)	16799	16209
CL_{obs} (mL/min)	489	598
$V_{ss,obs}$ (L)	21.4	20.1

Digitalization of reported data and Simulation of concentration-time profile for humans

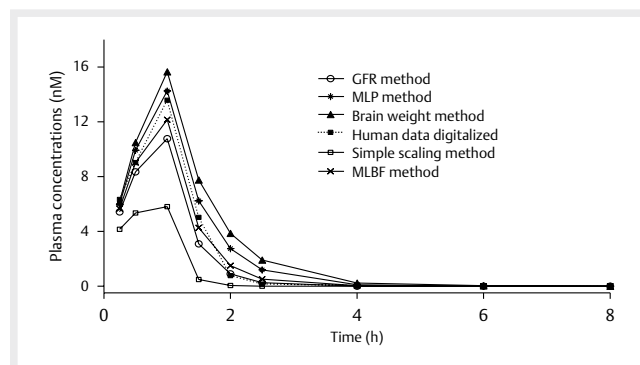
By digitalization of reported Phase-I patient pharmacokinetic profiles using the Digitizelt software, we derived the key pharmacokinetic parameters. The validity of this approach was confirmed by the closeness of the prediction of the reported values (► **Table 3**). Subsequently the reported and digitized patient plasma concentration vs. time profiles were compared with the profiles generated using the allometric scaling. The findings are depicted in ► **Fig. 5**.

Normalization method

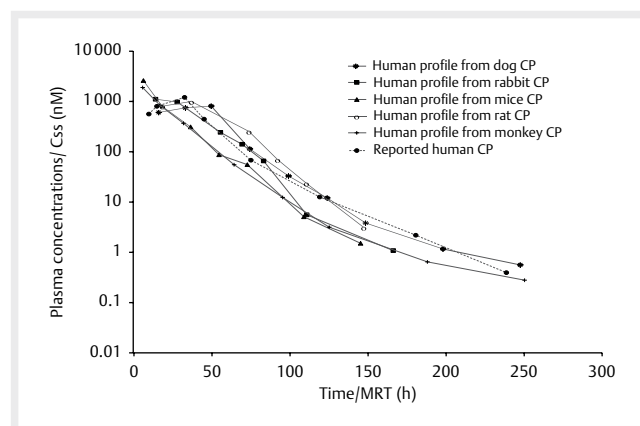
The normalized curves using Wajima approach derived from various preclinical species are shown in ► **Fig. 6**. All species normalized curves show reasonably good superimposition over the reported human profile; however it appeared that rats, rabbits and dogs profiles (concentration/ C_{ss} vs. time/MRT) were more aligned when compared with either mouse or monkey profiles.

Discussion

Bendamustine is a unique cytotoxic agent with multifaceted mechanisms of action [1]. Recently, FDA approved 10 min rapid infusion bendamustine hydrochloride (Bendeka®) for the treatment of patients with CLL and NHL as monotherapy and/or in combination



► **Fig. 5** Predicted intravenous infusion plasma profiles of bendamustine in Phase I patients using various scaling methods in comparison with digitalized human data.



► **Fig. 6** Prediction of human concentration profile (CP) using the preclinical species concentration profiles.

with other agents. To date, the best of our knowledge, there is no literature data reported on the intravenous preclinical pharmacokinetics and allometric scaling of bendamustine. In this study, we generated various pharmacokinetic parameters post-administration of bendamustine as an intravenous infusion for 30 min.

Interspecies scaling based on allometry principles can be used to predict the human pharmacokinetic parameters because it is primarily based on assumption of similarity in anatomical, physiological and biochemical parameters between animal species as compared to humans. These assumptions were first proposed by Boxenbaum and expressed mathematically by allometric equation [12, 13]. It provides a simple and fast option to extrapolate the drug dose or pharmacokinetic parameters from preclinical species. Based on available literature it is well known that volume of distribution can be predicted using simple allometric scaling. However, the clearance was not found to be amenable for simple allometry and therefore, over years the use of correction factors has been proposed and in many instances the usage of such correction factors has led to better predictions of clearance and half-life. Mahmood (2009) clarified the importance of correction factors that may further render allometry as an efficient predictive tool [14]. Srinivas (2010) has reviewed several case studies of allometry work from the published literature and provided balanced perspectives on the utility of allometry [15]. In addition, to scientific challenges and optimization of the experimental designs for better allometry predictions, Srinivas (2010) has provided insights on how to effectively use allometry for clinical candidate selection and answer some early drug development questions [15]. Previously, we have used these concepts in the prediction of pharmacokinetic parameters across diverse compounds representing various therapeutic areas [16–23].

Therefore in this study we explored and executed the allometric scaling using simple allometry as delineated in ► **Fig. 2** with correction factors to identify the best approach(es) to predict the reported Phase-I patient pharmacokinetic parameters for bendamustine. The use of simple allometry resulted in a predicted CL value of 1643 mL/min, which was 2.75-fold greater than the reported human value of 598 mL/min. Hence, the use of correction factors was considered to provide a better estimate of the human CL value of bendamustine. The correction factors that were applied for the clearance of bendamustine are applicable for other drugs in the same class if similar metabolism and excretion mechanisms observed for bendamustine contribute for the disposition of such drugs. The use of mathematically based equations using MLP or brain weight is typically employed without regard to the drug class. Accordingly, incorporation of brain weight and MLP correction factors predicted 1.3-fold and 1.1-fold, respectively lower CL value than the reported value. The application of specific correction factors such as bile flow and glomerular filtration rate can also be relevant for drug classes that exhibit similarity in the disposition of the drug as compared to bendamustine. In accordance, the incorporation of GFR, KBF and bile correction factor resulted in prediction of 1.37-fold higher, 2.43-fold higher and 1.43-fold, respectively lower CL value than the reported human value. The use of monkey liver blood flow has been advocated as an important tool for getting a closer correlation to the human parameter in the absence of human pharmacokinetic data [10, 11]. The use of species specific liver blood flow led to the prediction of

human CL within 1.16-fold to the reported value. The above approach taken by us comprising of mathematical, physiology, excretion based scaling factors may be easily applied to other drug classes belonging to the same chemical analog class. Moreover, the availability of predicted values from multi-scaling modalities may also help in averaging the closely predicted values to provide a better estimate for the human value if not available before, which is the case new drug discovery program.

On the contrary, the prediction of human V_{ss} of bendamustine by simple allometry resulted in an exponent of 0.87, which is within the acceptable range of 0.8–1.10 observed in the literature for most of the compounds [24]. This resulted in a predicted value of 19.71 L which was in close proximity of the observed human value of 20.10 L.

In the next step, the normalization method reported by Wajima, the preclinical species concentration profiles were used to simulate the human concentration profiles to deduce which preclinical species is closely aligned with human concentration profile. Wajima approach provides an opportunity to create a human concentration time profile using the superposition principles from the preclinical data. Recent work of Lombardo et al. (2016) has suggested that Wajima approach using rat, dog and monkey concentration vs. time data yielded a geometric mean of fold error < 2-fold for 63% marketed drugs and another 19% of marketed drugs showed a geometric mean of fold error > 2- but < 3-fold [25]. However, a small portion of the drugs yielded poor prediction using Wajima approach. Because Wajima approach uses superposition principle the prediction of human intravenous profile is not hampered by the poor prediction of human CL value by allometry methods. In the case of bendamustine, we have observed the dog plasma concentration (CP) values closely aligning with the reported human values, when compared to rabbit and rats CP values, while monkey and mice CP values are somewhat distant from the reported human data.

Our accurate human prediction data of bendamustine in conjunction with the existing literature data on Wajima superposition principle can be used for the novel analogues in this highly successful chemical class of treating cancers. We believe by the use of Wajima approach one can create a target product profile based on the critical success factors for the newer analogue in this drug class and use it as a guiding principle in the candidate nomination and subsequent early drug development.

Conclusion

In conclusion, intravenous (infusion) pharmacokinetics of bendamustine was gathered experimentally assessed in (mice, rats, rabbits and dogs) or through literature (monkey). Simple allometry scaled V_{ss} in close proximity to the human value (20.10 L). Appropriate allometric equations based on mathematical models and/or excretory /physiological factors were needed to explore the prediction of CL value. Both MLP (543 mL/min) and MLBF (691 mL/min) methods predicted values comparable to human CL value (598 mL/min). The predicted pharmacokinetic parameters of bendamustine by Wajima superposition principle were in close proximity of human pharmacokinetic data gathered in Phase-I cancer patients. We believe that our overall multi-faceted exercise would aid a prospective prediction of human pharmacokinetic parameters of a close

analogue and/or similar class of drug with differential toxicity profile before first time dosing in cancer patients.

Conflict of Interest

No conflict of interest has been declared by the author(s).

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