RESEARCH PAPER

Examination of Urinary Excretion of Unchanged Drug in Humans and Preclinical Animal Models: Increasing the Predictability of Poor Metabolism in Humans

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ABSTRACT

Purpose A dataset of fraction excreted unchanged in the urine (fe) values was developed and used to evaluate the ability of preclinical animal species to predict high urinary excretion, and corresponding poor metabolism, in humans.

Methods A literature review of fe values in rats, dogs, and monkeys was conducted for all Biopharmaceutics Drug Disposition Classification System (BDDCS) Class 3 and 4 drugs (n=352) and a set of Class 1 and 2 drugs (n=80). The final dataset consisted of 202 total fe values for 135 unique drugs. Human and animal data were compared through correlations, two-fold analysis, and binary classifications of high (fe ≥30%) *versus* low (<30%) urinary excretion in humans. Receiver Operating Characteristic curves were plotted to optimize animal fe thresholds.

Results Significant correlations were found between fe values for each animal species and human fe (*p*<0.05). Sixty-five percent of all fe values were within two-fold of human fe with animals more likely to underpredict human urinary excretion as opposed to overpredict. Dogs were the most reliable predictors of human fe of the three animal species examined with 72% of fe values within two-fold of human fe and the greatest accuracy in predicting human fe ≥30%. ROC determined thresholds of ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys had improved accuracies in predicting human fe of ≥30%.

Conclusions Drugs with high urinary excretion in animals are likely to have high urinary excretion in humans. Animal models tend to underpredict the urinary excretion of unchanged drug in humans.

ABBREVIATIONS

BDDCS	Biopharmaceutics Drug Disposition Classification System
fe	Fraction excreted unchanged in the urine
FN	False negative
FP	False positive
NME	New molecular entity
PPV	Positive predictive value
NPV	Negative predictive value
ROC	Receiver Operating Characteristic
TN	True negative
TP	True positive
US FDA	United States Food and Drug Administration

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INTRODUCTION

A significant aspect of preclinical drug development is understanding drug absorption, distribution, metabolism, and elimination, all of which are important in identifying lead

candidates and potential first-in-human doses. The elimination pathway of a new molecular entity (NME) can help guide further steps in development. For instance, if a compound is likely to be administered to patients with renal dysfunction, it may be advisable to instead choose a candidate that is primarily eliminated via hepatic metabolism or biliary excretion. Thus, substantial efforts are taken to deduce if an NME is eliminated by metabolism, biliary excretion, or renal excretion. Consequently, numerous *in silico*, *in vitro*, and *in vivo* models have been developed to predict drug clearance and the elimination pathways of NMEs prior to first-in-human studies [1–15]. We have previously reported on *in silico* and *in vitro* approaches to predict when a drug will likely be metabolized *versus* being eliminated unchanged in the bile or urine [8, 10]. Herein, we explore how *in vivo* animal models may help elucidate the elimination route of an NME early in drug development.

Animal models including rodent species such as the rat, and non-rodent species such as the dog and monkey, are used extensively in preclinical studies to predict drug elimination and other pharmacokinetic parameters. Although much research has gone into developing allometric scaling equations and physiologically-based modeling techniques, many of the proposed prediction methods are complicated and require extensive species and drug data. In general, it is believed that drugs that undergo extensive metabolism in humans are difficult to scale using simple allometric scaling approaches [16–19]. This lack of predictive ability between animals and humans for extensively metabolized drugs likely stems from differences in metabolism due to differences in isoforms, expression, activities, and substrate specificities of drug metabolizing enzymes. In contrast, drugs with minimal hepatic metabolism and drugs predominately excreted renally are generally more amenable to allometric scaling [16, 19]. Furthermore, it is generally believed that there are fewer species differences in pharmacokinetics for drugs that are poorly metabolized [20]. Given that animals poorly predict extensive metabolism in humans, here we ask whether animal models can predict when a drug will likely have limited metabolism in humans and be eliminated through another route, namely urinary excretion of unchanged drug.

For this study, we utilized the Biopharmaceutics Drug Disposition Classification System (BDDCS) that categorizes drugs based upon their solubility and overall extent of metabolism in humans (Fig. 1). Solubility in BDDCS is defined by the United States Food and Drug Administration (US FDA) as the ability of the drug at its highest dose strength to completely dissolve in 250 ml of water over a pH range between 1 and 7.5 at 37°C [21]. Metabolism is defined as the overall extent of metabolism in humans. Class 1 and 2 drugs have an extent of metabolism ≥70%, whereas Class 3 and 4 drugs have <70% metabolism, but the great majority exhibit <30% metabolism [21, 22].

Fig. 1 The Biopharmaceutics Drug Disposition Classification System (BDDCS) as proposed by Wu and Benet (21).

The extent of metabolism in BDDCS corresponds with the fraction of drug excreted unchanged in the urine or the bile. Class 1 and 2 drugs, which have high extents of metabolism, have correspondingly low amounts of drug excreted unchanged. Conversely, Class 3 and 4 drugs, which have low extents of metabolism, have corresponding high amounts of the drug excreted unchanged in the urine or the bile. With this in mind, it is reasonable to use extent of drug excreted unchanged as a marker for the extent of metabolism. In fact, the fraction of drug excreted unchanged in the urine (fe) is easily obtained after administration of a drug intravenously to humans or animals. It should be noted, however, that the extent of biliary excretion of unchanged drug is difficult to experimentally determine in humans due to the invasive techniques needed for sample collection. Taken together, when Benet *et al.* assigned BDDCS classes to over 900 drugs, the percent excreted unchanged in the urine values in humans were utilized along with other data including known biliary excretion and extent of metabolism [22]. Almost all drugs assigned as either BDDCS Class 1 and 2 possess fe values of <30% in humans [22]. The majority of drugs (84%) assigned to either Class 3 or 4 have a human fe value of ≥30% [22]. This means, however, that approximately 16% of the Class 3 and 4 drugs have a human fe of <30% and are likely to have high biliary excretion in humans [22].

In this study, we examine if drugs with high urinary excretion in humans also have high urinary excretion in preclinical animal studies. To do this, we investigated drugs already identified to be poorly metabolized in humans (BDDCS Class 3 and 4 drugs) and conducted an extensive literature review of reported fe values for the three animal species and compared them to human fe values. Our dataset primarily focused on BDDCS Class 3 and 4 drugs since it is generally believed that animals, particularly small animals such as the rat, metabolize

drugs to a greater extent in humans when compared on a weight-normalized basis [20]. In other words, it is generally believed that drugs that are extensively metabolized in humans (BDDCS class 1 and 2) are predominately extensively metabolized in animal models. Thus, we expected that BDDCS class 1 and 2 drugs would have low fe values in animals. To verify this assumption, we conducted a smaller scale literature review of a set of 80 BDDCS Class 1 and 2 drugs. We focused only on urinary excretion rather than biliary elimination due to the difficulty in obtaining biliary values in humans. We recognize this is not a perfect representation since several Class 3 and 4 drugs are predominantly excreted unchanged in the bile and have very low fe values. The developed dataset of fe values was analyzed to explore the relationship of urinary excretion of drugs that are primarily poorly metabolized in humans with that of animals.

MATERIAL AND METHODS

Dataset

Fraction excreted unchanged in the urine (fe) values for rats, dogs, and monkeys were searched in the biomedical literature for BDDCS Class 3 (n=288) and Class 4 (n=64) drugs that were assigned classification in our previously published datasets [22, 23]. In addition, the literature was searched for a small subset of BDDCS Class 1 (n=41) and Class 2 (n=39) drugs [22, 23]. Drugs were included in the analysis even if they display known nonlinearities in their pharmacokinetics. The compound name was cross-referenced with the animal species type (i.e. rat, dog, monkey) and other search terms such as "pharmacokinetics" or "disposition" in a database search such as Pubmed. All original references of animal fe data were obtained and further inspected to ensure compliance with the below criteria. Human fe values for BDDCS Class 1 through 4 drugs were obtained directly from our previously published dataset [22] or searched in the literature.

Inclusion criteria were used to define acceptable parameters for data collection and to ensure consistent data reporting. Obtained fe values were only included in analysis for both animals and humans if the drug was administered intravenously and unchanged drug in the urine was measured. Oral data was not collected due the potential influence of bioavailability. The fraction eliminated as unchanged drug in the bile was not collected due to the difficulty in obtaining biliary values in humans. Studies that evaluated only total radioactivity were not included in the dataset. In some cases, the fe value was not listed but was estimated by dividing renal clearance by total body clearance. No restrictions were made regarding sex of the animal or the particular strain/breed of the animal. Monkey data were obtained from

pharmacokinetic studies using either Cynomolgus monkeys, African green monkeys, rhesus monkeys, or pigtailed macaques.

Data analysis

Obtained fe values from animal models were compared to human fe values by: (1) correlation, 2) analysis of drugs within a two-fold error range, and (3) binary classifications with corresponding sensitivity and specificity analyses. All data were analyzed by Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) or GraphPad Prism 7.02 (GraphPad Software, La Jolla, CA, USA).

Urinary excretion data from each animal species were plotted against human values. The normality of each animal model dataset was assessed by a D'Agostino & Pearson normality test. As rat and dog data were not normally distributed, but monkey data were, both Spearman and Pearson correlations were used to assess statistical significance of correlations between humans and all animal models. Spearman and Pearson correlation coefficients were also calculated. Additionally, human fe values were paired with collected fe values for each animal species and graphed using boxplots for each BDDCS class. Statistical differences in paired fe data between humans and each animal species for each BDDCS class were calculated through Wilcoxon matched-pairs signed rank tests. To complete the two-fold analysis, animal fe values were plotted against human fe values and the proportion of drugs that fell within and outside of a two-fold range was determined.

In addition to completing analyses of the continuous fe data, a binary classification approach was also used to assess how frequently a drug had high urinary excretion in both animals and humans. High urinary excretion in humans was defined as fe ≥30% to match the BDDCS thresholds of poor and extensive metabolism described above. Low urinary excretion in humans was defined as fe <30%. Two different thresholds for segregating high and low urinary excretion were utilized for animal fe data. For the first threshold, collected animal fe data was classified to have either high urinary excretion (fe ≥30%) or low urinary excretion (<30%) and then compared to the same threshold in humans (Fig. 2). The second threshold assessed was determined by Receiver Operating Characteristic (ROC) curves to optimize the animal fe threshold to predict a human fe ≥30% or <30%. ROC curve generation for each animal species was completed using the ROCR package in R [24]. As further defined below, the true positive rate (sensitivity) was plotted against the false positive rate (1-specificity) for each continuous value of animal fe as a predictor of extent of human fe. The threshold that maximized the average between sensitivity and specificity was selected. Compounds were considered true positives (TP) if both the animal fe and human fe were ≥30% or ROC determined threshold. Compounds were considered false positives (FP)

Animal fe values

Fig. 2 A binary classification approach was used to determine how often low or high urinary excretion in animals aligned with low or high urinary excretion in humans. Two fe thresholds were used for each animal species: ≥30% or <30% to directly that match that in human, or thresholds optimized through Receiver Operating Characteristic (ROC) curves.

when animal fe was high but human fe was below the threshold. False negatives (FN) were compounds where animal fe was low but human fe was above the threshold. When both animal fe and human fe were low, the compounds were considered as true negatives (TN).

These binary classifications were evaluated by calculating sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) (Equations 1 through 5). Sensitivity is the percent of positives (compounds with high fe in humans) that were correctly predicted by high fe in animals. Specificity is the percent of negatives (compounds with low fe in humans) that were correctly predicted by low fe in animals. Accuracy is the proportion of true results to all results. PPV is the percent of compounds with high fe in animals that are also high in humans. NPV is the percent of compounds with low fe in animals that are also low in humans.

$$\text{Sensitivity } (\%) = \frac{\text{true positives}}{\text{true positives} + \text{false negatives}} * 100\% \qquad (\text{ation1})$$

$$\text{Specificity } (\%) = \frac{\text{true negatives}}{\text{true negatives} + \text{false positives}} * 100\% \qquad (\text{ation2})$$

$$\text{Accuracy } (\%) = \frac{\text{true positives} + \text{true negatives}}{\text{true positives} + \text{true negatives} + \text{false positives} + \text{false negatives}} * 100\%$$
$$\qquad (\text{ation3})$$

$$\text{PPV} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}} \qquad (\text{ation4})$$

$$\text{NPV} = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}} \qquad (\text{ation5})$$

RESULTS

Dataset

Fraction excreted unchanged data for one or more animal species was collected for a total of 135 drugs. The drug name, BDDCS class, and fe value for each animal species are listed in Table I. The dataset primarily included Class 3 (n=82, 61% of dataset) and Class 4 drugs (n=14, 10% of dataset). For many of the drugs, fe data were collected in more than one species. This allowed collection of 202 total fe values (38 values for Class 1 drugs, 21 values for Class 2 drugs, 121 values for Class 3 drugs, and 22 values for Class 4 drugs). The number of fe values obtained for each animal species and for each BDDCS class are listed in Table II. The rat was the most common animal model that reported fe followed by dog and monkey. A total of 103 drugs with rat fe values, 67 drugs with dog fe values, and 32 drugs with monkey fe values were found.

Box plots of paired animal and human fe values arranged according to animal species and BDDCS classification are shown in Fig. 3. In comparison to human fe values, significantly lower fe values were found for rats ($p<0.05$), dogs ($p<0.05$), and monkeys ($p<0.005$) for the BDDCS Class 3 drugs in the dataset. Significantly lower fe values were also seen for dogs in comparison to humans for the BDDCS Class 4 drugs in the dataset ($p<0.05$). Values of fe were <40% for all species for Class 1 and 2 drugs.

Correlation analysis

Statistically significant correlations between animal fe values and human fe values were seen for rats ($p<0.0001$), dogs ($p<0.0001$), and monkeys ($p<0.0001$) when examining all drugs in the dataset. Spearman rho values of 0.817, 0.818, and 0.730 were calculated for rats, dogs, and monkeys, respectively. Pearson rho values of 0.819, 0.834, and 0.701 were calculated for rats, dogs, and monkeys, respectively.

Two-fold analysis

For the majority of drugs, animal fe values were within two-fold of human fe values (Fig. 4). As expected, fe values for BDDCS class 1 and 2 drugs were very low for both animals and humans, and thus, a greater proportion of Class 3 and 4 drugs fell within two-fold in comparison to Class 1 and 2 drugs (Table III). Of the BDDCS Class 3 and 4 drugs in the dataset, 81% of rat, 83% of dog, and 62% of monkey fe values were within two-fold of their human fe counterparts. BDDCS Class 3 and 4 drugs that fell outside of the two-fold range are listed in Table IV.

Table I Animal and human fe values collected through the literature review

Compound Name	BDDCS Class	% Excreted Unchanged in Urine in Humans	% Excreted Unchanged in Urine in Rats	% Excreted Unchanged in Urine in Dogs	% Excreted Unchanged in Urine in Monkeys	References
Acamprosaic Acid	3	50	95			[22, 25]
Acecainide; N-Acetyl Procainamide	3	81	72			[22, 26]
Acrivastine	3	67		34		[22, 27]
Almotriptan	3	40			30	[22, 28]
Amoxicillin	3	86	52			[22, 29]
Ampicillin	3	88	58			[22, 29]
Atenolol	3	94	66	83		[22, 30, 31]
Aztreonam	3	68	85	86	77	[22, 32]
Benazeprilat	3	18	53			[22, 33]
Betamipron	3	98	67	61	41	[22, 34]
Bisoprolol Fumarate	3	63	10	35	10	[22, 35]
Captopril	3	38		56[a]	83[a]	[22, 36]
Carboplatin	3	77	85	46		[22, 37, 38]
Cefazolin	3	80	74	90	81	[22, 39]
Cefmetazole Sodium	3	80	46	74	64	[22, 33, 39]
Cefodizime	3	80	44	38	65	[22, 40]
Cefotetan	3	67	52	53	60	[22, 39]
Ceftazidime	3	85	93	97		[22, 29]
Ceftizoxime	3	93	86			[22, 33]
Cephalexin	3	91	92			[22, 41]
Cephapirin	3	48		32		[22, 42]
Cidofovir	3	90			98	[22, 43]
Cimetidine	3	62	64[c]	80	36	[22, 44, 45]
Clofarabine	3	55	67			[22, 46]
Dactinomycin (Actinomycin D)	3	10		15		[22, 47]
Dexrazoxane	3	42		27[b]		[22, 48]
Didanosine	3	55			64	[22, 49]
Digoxin	3	60	17		17	[22, 50, 51]
Disopyramide	3	55		26		[22, 52]
Dorzolamide Hydrochloride	3	10	39			[22, 53]
Doxycycline	3	41		90		[22, 54]
Enalaprilat	3	60	76			[22, 33]
Ertapenem Sodium	3	38	17		5	[22, 55]
Famotidine	3	67	65	61	39	[22, 45, 56, 57]
Fexofenadine	3	25	17			[22, 58]
Fluconazole	3	75	82	64		[22, 29]
Gentamicin C1 Sulfate	3	91	93	95		[22, 29]
Ipratropium Bromide	3	50	58	55		[22, 59]
Kanamycin A	3	90		84		[22, 60]
Ketorolac	3	58			31	[22, 61]
Lamivudine	3	67	78[a]		46	[22, 62, 63]
Levetiracetam	3	66	75	62		[22, 64]
Levofloxacin	3	74			62	[22, 65]
Metformin	3	99	76			[22, 66]
Methotrexate	3	81	48	72[b]		[22, 67–69]
Methyldopa	3	40		34		[22, 70]
Mezlocillin	3	45	17			[22, 71]

Table I (continued)

Compound Name	BDDCS Class	% Excreted Unchanged in Urine in Humans	% Excreted Unchanged in Urine in Rats	% Excreted Unchanged in Urine in Dogs	% Excreted Unchanged in Urine in Monkeys	References
Moxifloxacin Hydrochloride	3	22	8.4	8.5	6	[22, 72]
Nadolol	3	73	93			[22, 73]
Neostigmine	3	67		62		[22, 74]
Ofloxacin	3	64	50	50		[22, 29]
Olmesartan	3	43	58			[22, 33]
Pamidronate Disodium	3	46	37			[22, 75]
Pancuronium Bromide	3	67	85			[22, 76]
Pelrinone	3	92	82	83		[23, 77]
Penicillamine	3	45		21		[22, 78]
Penicillin G; Benzylpenicillin	3	79	71			[33, 79]
Pipecuronium Bromide	3	39		78		[22, 80]
Piperacillin	3	71		46		[22, 29]
Pramipexole	3	90			27	[22, 81]
Pravastatin	3	47	26			[22, 33]
Procainamide	3	67	34			[22, 26]
Pyridostigmine	3	85		74		[22, 74]
Ranitidine	3	69	40	51		[82–84]
Rosuvastatin Calcium	3	30	6			[22, 33]
Sitafloxacin	3	75	54	75		[22, 85]
Sotalol	3	85	75			[22, 86]
Stavudine	3	39	78		44	[22, 87, 88]
Tazobactam Sodium	3	77	73	85		[22, 89]
Temocaprilat	3	29.5	17			[22, 33]
Tenofovir Disoproxil	3	82		70		[22, 90]
Terbutaline	3	56	25	90		[22, 91, 92]
Tetracycline	3	58	72			[22, 93]
Tiludronic Acid	3	60	47[d]			[22, 94]
Tirofiban Hydrochloride	3	65	7			[22, 95]
Tobramycin	3	93	88			[22, 29]
Tocainide	3	38	35			[22, 95]
Topotecan	3	40	65			[22, 96]
Vancomycin	3	79	76[b]			[22, 97]
Vecuronium Bromide	3	20	8			[22, 76]
Xamoterol	3	73		54		[23, 98, 99]
Zalcitabine	3	65	88			[22, 100]
Acyclovir	4	75	90	72[b]	21[c]	[22, 101–103]
Candesartan	4	52	49			[22, 33]
Cefditoren	4	70	4			[22, 104]
Cefprozil	4	73		61		[22, 105]
Chlorothiazide	4	92		100	92	[22, 106, 107]
Ciprofloxacin	4	65	54	29		[22, 108, 109]
Fleroxacin	4	72.5	43	19		[22, 110]
Furosemide	4	66	51[e]	35		[22, 111–113]
Medroxyprogesterone Acetate	4	44	1			[22, 114]
Meropenem	4	70	38	24	24	[22, 115]
Nitrofurantoin	4	47	39			[22, 116]
Sulfisoxazole	4	49	68			[22, 117]

Table I (continued)

Compound Name	BDDCS Class	% Excreted Unchanged in Urine in Humans	% Excreted Unchanged in Urine in Rats	% Excreted Unchanged in Urine in Dogs	% Excreted Unchanged in Urine in Monkeys	References
Valsartan	4	13	2			[22, 33]
Vitamin B2 (Riboflavin)	4	75	82			[22, 118]
Acebutolol	1	10	27.4[a,e]			[22, 119]
Amitriptyline	1	1	0.847[b]		0.2	[22, 51, 120]
Caffeine	1	1		2.76		[22, 121]
Chlorpheniramine	1	10		1.1		[22, 122]
Chlorpromazine	1	0.5	0.02[a,e]	1		[22, 123–125]
Desipramine	1	2	2.1			[22, 126]
Diazepam	1	0.5	0[a]	0		[22, 124, 127]
Diltiazem	1	2	0.74	1.1[a,e] [e]		[22, 128, 129]
Enalapril	1	10	0	9.6		[22, 130]
Imipramine	1	1.5	1.2			[22, 131]
Levodopa	1	0.5		1.082[b]		[22, 132]
Lidocaine	1	8	0.2	2		[22, 133]
Metoprolol	1	10		8.68		[22, 134]
Midazolam	1	5.6			1	[22, 51]
Phenobarbital	1	24	11.9 [a,e]			[22, 124, 135, 136]
Prazosin	1	0.5	5	5		[22, 137]
Prednisolone	1	16	0.29			[22, 138]
Propranolol	1	0.25	0.196[e]	4.8		[22, 139–141]
Propylthiouracil	1	1.28	12			[142, 143]
Quinidine	1	18	1.101[a,e]	29	0.6	[22, 51, 124, 144–146]
Sumatriptan	1	22	39.5[a]	35.7[a]		[22, 147]
Tamoxifen	1	0.5	0			[22, 148]
Theophylline	1	18	15[e]	13.85[e]		[22, 135, 149–151]
Timolol	1	15			4.8	[22, 51]
Verapamil	1	1.5	0.306		1.5	[22, 51, 152]
Buspirone	2	0.1	0.5[a]			[22, 153]
Carbamazepine	2	0.5	0.514		1	[22, 154, 155]
Diclofenac	2	0.5	0.1			[22, 156]
Diflunisal	2	6	6 [b,e]	15		[22, 157, 158]
Domperidone	2	0		1.4		[22, 159]
Griseofulvin	2	0.3	0.1	0		[22, 160]
Ibuprofen	2	0.5	0	0.765	18.5	[22, 51, 161, 162]
Ketoprofen	2	0.5	1.7			[22, 163]
Nifedipine	2	0.01			0.057	[22, 51]
Phenytoin	2	2	0[a]			[22, 124]
Ritonavir	2	3.5	0	0		[22, 164]
Tacrolimus	2	0.5	0.0073	1		[22, 165, 166]
Terfenadine	2	0	0			[22, 167]
Warfarin	2	1	0[a]			[22, 124]

[a] Calculated from ratio of CL_{renal} and CL_{total} values.

[b] Calculated as an average fe following multiple doses.

[c] Calculated as an average fe following administration to male and female animals.

[d] Calculated as an average fe following administration to different aged animals.

[e] Average calculated between multiple reports of fe.

ROC curve analysis

ROC curve analysis was used to determine a fe threshold in animals that would predict ≥30% fe in humans. Optimized thresholds of ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys were identified as potential thresholds to optimally predict a human fe of ≥30%. The area under the ROC curve for each animal species (rats=0.96, dogs=0.98, and monkey=0.98) was greater than the generally accepted cutoff of 0.8 indicating the fe in these animal species has a high discriminatory ability to predict extent of urinary excretion of parent drug in humans.

Binary classifications

The ability of animal models to properly classify human fe as ≥30% or <30% is shown in Figure 5. Two thresholds for each animal species were evaluated: ≥30% or <30% to directly match the cutoff in humans or a cutoff determined through ROC curve analysis (above). Each animal species had a large number of drugs that had high urinary excretion in both animals and humans, which were classified as true positives. Very few drugs possessed a high urinary excretion in animals (≥30% or ROC determined threshold) but low urinary excretion in humans (<30%); as a result, very few false positives were seen. In comparison, there were more false negatives for each animal species where the animal fe values were less than the threshold but human fe value was ≥30%. The vast majority of BDDCS Class 1 and 2 drugs in the dataset were classified as true negatives (low urinary excretion in both animals and humans).

Calculations of sensitivity, specificity, accuracy, PPV, and NPV for each animal model to properly classify human fe using both thresholds are shown in Table V. When using the ≥30% threshold to directly match the cutoff in humans, high specificities were attained. In addition, all animal models possessed high positive predictive values (PPV) but low negative predictive values (NPV). When utilizing the ROC optimized thresholds of ≥25% in rats, ≥19% in dogs, and ≥10% in

monkeys, calculated sensitivities, accuracies, and NPVs improved for all three animal species.

DISCUSSION

Here, we report an extensive dataset of fe values for poorly metabolized, BDDCS Class 3 and 4 drugs, along with a smaller set of fe values for highly metabolized, BDDCS Class 1 and 2 drugs. These values were obtained for humans as well as three animal species commonly used in preclinical drug development. The collected fe values were utilized as a marker of extent of urinary excretion, suggestive of extent of metabolism since drugs that are highly metabolized (i.e., ≥70% extent of metabolism) in humans generally have a fe <30% [21]. For drugs that are poorly metabolized in humans (i.e., <70% extent of metabolism), ≥30% of the drug is likely eliminated unchanged in the urine or bile. It should be noted that within this study only urinary excretion data were collected due to the difficulty in collecting biliary data experimentally in humans.

A good relationship between animal fe and human fe was observed with statistically significant correlations found between the fe values of humans and each animal model (r >0.70 for all species). Sixty-five percent of all animal fe values fell within two-fold of human fe values. Dogs were the most reliable predictors of the three species with the largest percentage of fe values within two-fold of human fe (72%), the highest correlation coefficients, and the greatest predictive accuracy (Table V). Interestingly, of the three species, monkeys were the poorest predictors of human fe. Monkeys had the lowest proportion of compounds within two-fold of the human values (53%) and exhibited the lowest correlation coefficients (~0.7). Monkeys further had a very low ROC determined fe cutoff (10%), potentially indicating that monkeys have substantially greater hepatobiliary elimination processes than humans.

Evaluation of physiochemical properties of BDDCS Class 3 and 4 drugs that fell within two-fold *versus* those that were outliers showed no major differences between the two groups of medications in terms of partition coefficient (log P), molecular weight, or water solubility (data not shown). Of the outliers noted in Table IV, two of drugs, dorzolamide and mezlocillin, are known to display nonlinear pharmacokinetics. Differences in plasma protein binding between animals and humans as an explanation for the outliers was not explored due to the paucity of this published information.

As expected, human fe was better predicted by animal models for Class 3 and 4 drugs than Class 1 and 2 drugs. The limited number of Class 1 and 2 drugs having animal fe values within two-fold of the human fe value is likely due to their very low fe values. Such low fe values are likely to produce differences greater than two-fold, but are not physiologically meaningful; for example, griseofulvin had a 0.3% fe in

Table II Summary of fe data collected for each animal species arranged by BDDCS classification

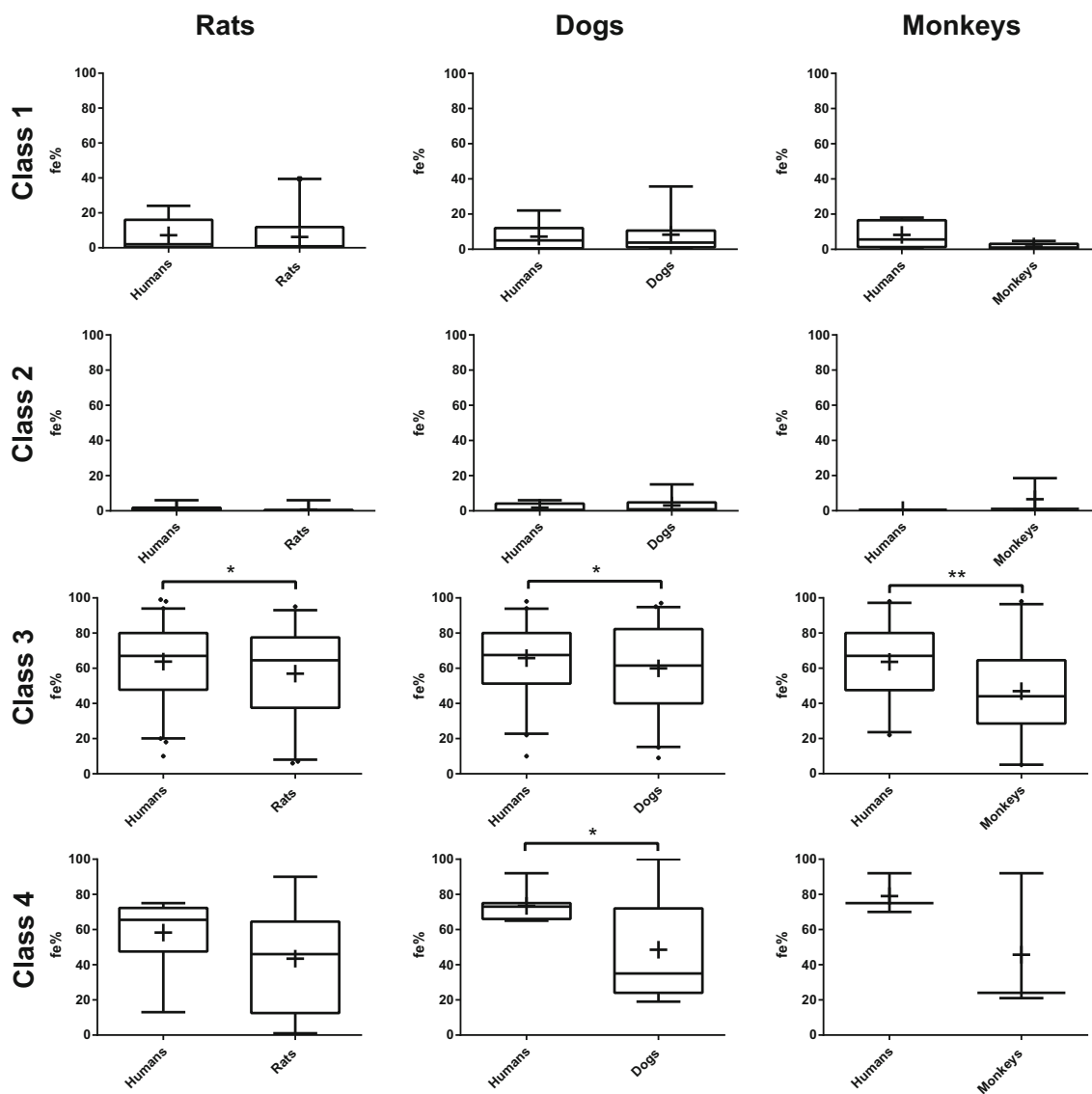| BDDCS class	Number fe values obtained			
	Rat	Dog	Monkey	All animal species
All drugs	103	67	32	202
Class 1 drugs	19	14	5	38
Class 2 drugs	12	6	3	21
Class 3 drugs	60	40	21	121
Class 4 drugs	12	7	3	22

Fig. 3 Box plots of the fraction excreted unchanged in the urine (fe) values in humans that were paired to each animal species arranged by BDDCS class. The center line represents the median, the plus sign indicates the mean, the box itself denotes the interquartile range, the whiskers indicate the 5th and 95th percentiles, and the dots represent values outside the 5th and 95th percentiles. *$p < 0.05$, **$p < 0.005$.

humans and a 0.1% fe in rats, a three-fold difference. It is plausible that predictions for Class 4 drugs were less accurate than Class 3 drugs due to the nature of Class 4 drugs, which

are poorly soluble and poorly permeable. Nonetheless, the graphs in Fig. 4 suggest that it is much more common for animal data to underpredict fe than overpredict fe, likely
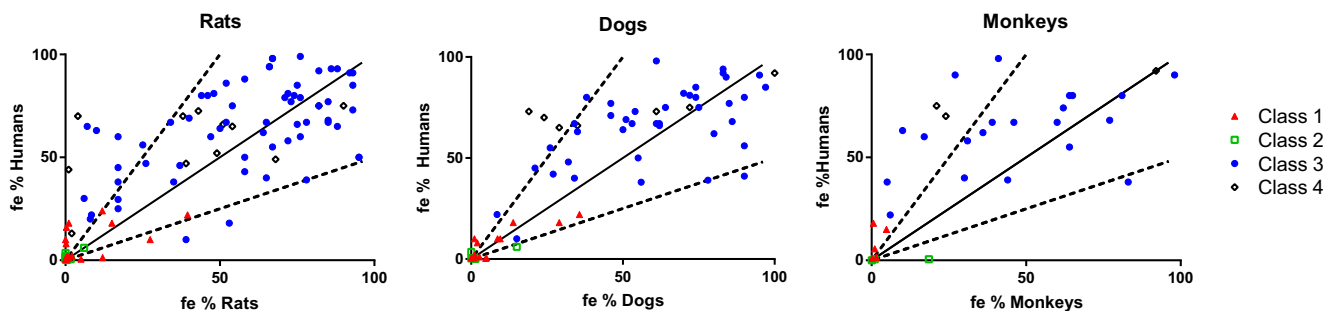
Fig. 4 Plots of rat, dog, and monkey fe values *versus* human fe values. The solid line denotes the line of unity while the dashed lines indicate an area within two-fold range.

Table III Summary of the number and percentage of drugs with animal fe values within a two-fold range of human fe values arranged by animal species and BDDCS class

BDDCS Class	Rat	Dog	Monkey	All animal species
All drugs	67 (65%)	48 (72%)	17 (53%)	132 (65%)
Class 1 drugs only	6 (32%)	7 (50%)	1 (20%)	14 (37%)
Class 2 drugs only	3 (25%)	2 (33%)	1 (33%)	6 (29%)
Class 3 drugs only	49 (82%)	35 (88%)	14 (67%)	98 (81%)
Class 4 drugs only	9 (75%)	4 (57%)	1 (33%)	14 (64%)

due to greater metabolic disposition in animals, compared to humans.

This general tendency for animal models to underpredict the urinary elimination of parent drug in humans is highlighted by the lower ROC determined cutoffs that optimally identify high fe in humans (i.e., fe ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys instead of 30%). Regardless of which cutoff was used, the binary classifications of fe data identified that a substantial proportion of drugs in the dataset were true positives indicating instances where both animals and humans had high urinary excretion (Fig. 5). These drugs would be expected to have poor metabolism in both animals and humans. Additionally, the majority of true negatives (e.g., drugs with low urinary excretion in both animals and humans) were BDDCS Class 1 and 2 drugs. Each animal model had few false positives (animal fe ≥ threshold but human fe <30%), but many true positives, resulting in high PPVs in all species (>90%). This suggests that when high urinary excretion is found in a preclinical animal species, there is a strong

likelihood that humans will also have a fe ≥30%. A poor NPV was seen for the ≥30% threshold in animals, indicating that animal models tended to have lower fe than humans for the same compounds, but NPV values improved for each animal species with the optimized ROC thresholds. This shift in the cutoff may indicate that even relatively low fe values in animals (i.e., fe ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys) are predictive of substantial renal elimination in humans and likely low extents of metabolism.

When both animal and human thresholds were set at ≥30%, the data illustrate high sensitivities between fe values of animals and humans with the dog and rat (85% and 87%, respectively) having better sensitivities than the monkey (74%). Similarly, rats and dogs predicted human fe more accurately (87% and 90%, respectively) compared to monkeys (81%). The high specificities calculated were likely the result of very few drug examples where the animal model had high urinary excretion but low urinary excretion in humans (i.e., false positives). When cutoffs of ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys were used, sensitivities improved for each animal species (88%, 100%, and 96% in rats, dogs, and monkeys, respectively). The optimized thresholds also improved accuracies with the dog having the highest accuracy (97%), followed by the monkey (94%), and then the rat (88%).

To our knowledge, this is the first study to compare fraction excreted unchanged in the urine in animal models to that in humans as a method of predicting extent of metabolism in humans. Our results suggest that drugs with high urinary excretion in humans also often have high urinary excretion in animals. Since high urinary excretion (fe ≥30%) is indicative of poor metabolism (<70%), a drug with a fe of ≥30% in one or

Table IV BDDCS Class 3 and 4 drugs with a greater than two-fold difference in human and animal fe (outliers)

| Rat fe data		Dog fe data		Monkey fe data	
Drug class	Drug name	Drug class	Drug name	Drug class	Drug name
3	Benazeprilat	3	Cefodizime	3	Betamipron
3	Bisoprolol Fumarate	3	Disopyramide	3	Bisoprolol Fumarate
3	Digoxin	3	Doxycycline	3	Captopril
3	Dorzolamide HCl	3	Moxifloxacin HCl	3	Digoxin
3	Ertapenem Sodium	3	Penicillamine	3	Ertapenem Sodium
3	Mezlocillin	4	Ciprofloxacin	3	Moxifloxacin HCl
3	Moxifloxacin HCl	4	Fleroxacin	3	Pramipexole
3	Rosuvastatin Calcium	4	Meropenem	4	Acyclovir
3	Terbutaline			4	Meropenem
3	Tirofiban HCl				
3	Vecuronium Bromide				
4	Cefditoren				
4	Medroxyprogesterone acetate				
4	Valsartan				
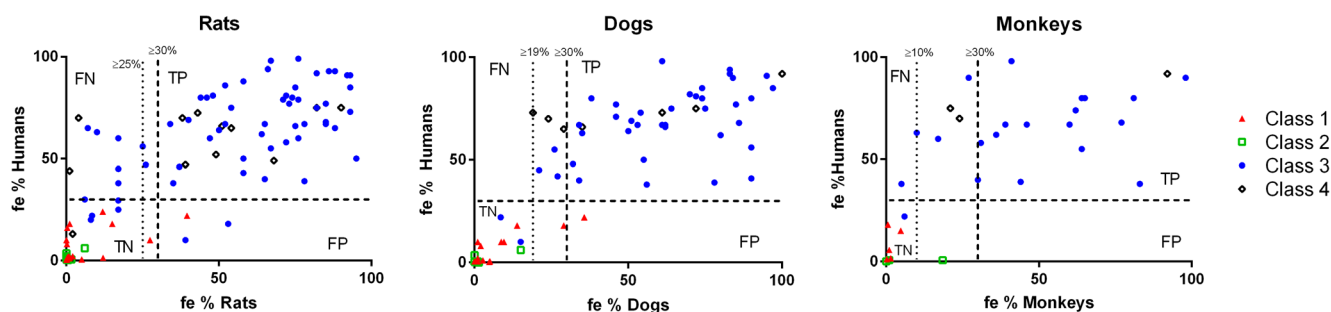
Fig. 5 Binary classification analysis of fe values from rat, dog, and monkey models *versus* human fe values. The dotted lines indicate fe thresholds in both the animal models and humans.

more preclinical animal species will likely have poor metabolism in humans, and therefore, be classified as a BDDCS Class 3 or 4 drug.

Other research groups have investigated the use of preclinical animal species to predict urinary excretion in humans with mixed conclusions. Only one study, to our knowledge, has attempted to compare fe values of preclinical animal species with humans. That study by Fagerholm concluded that there are poor predictions of renal clearance between species including a poor correlation between rat and monkey fe and human fe [168]. This contradiction with our results likely stems from a much smaller dataset used by Fagerholm (n=25 drugs), whereas our dataset includes 137 drugs. Although the specific drug names included in the analysis are not listed, it appears that Fagerholm utilized a broad range of compounds *versus* our dataset that predominately included poorly permeable Class 3 and 4 drugs. Although Fagerholm concludes a poor correlation between animal and fe data, the study goes on to suggest that correlations between fe values in humans and animals is improved for drugs with high passive permeability, drugs with extensive tubular reabsorption, and/ or drugs with high non-renal clearance. Further studies have explored interspecies scaling of urinary excretion amounts. A retrospective study of 13 antibacterial drugs found that the amounts of drug excreted into the urine or the feces was allometrically scalable between various preclinical animal models and humans with better predictions found for drugs with higher urinary excretion [169].

Prediction of clearance from preclinical animal species through allometric scaling has been investigated and reviewed in depth by numerous research groups [1, 2, 5, 6, 16–19, 170, 171]. There is general support in the literature that human pharmacokinetics is more easily predicted for renally eliminated drugs in comparison to those eliminated through metabolism, which aligns with the data presented herein. Briefly, Tang and Mayersohn found that systemic clearance was better predicted for drug excreted renally or in the bile in comparison to those eliminated by metabolism [18]. Similarly, Huh *et al.* investigated various allometric scaling approaches to predict human clearance using data from both small molecules and macromolecules and concluded that clearance in humans is well predicted for renally excreted drugs [17].

A number of studies have also specifically focused on the prediction of renal clearance from animal models. Mahmood determined that it was difficult to allometrically scale drugs that undergo active renal secretion and cautioned the interpretation of clearance parameters of renally secreted drugs [172]. It has been further suggested by Di *et al.* that interspecies allometric scaling of renal clearance may work better for drugs that undergo filtration with only limited active secretion and reabsorption [170]. The results presented here did not attempt to categorize drugs by their extents of active secretion or reabsorption or to identify if nonlinearities in these processes are possible explanations to any drug outliers. As the drugs evaluated in the dataset here were primarily BDDCS Class 3 and 4 drugs, one would expect limited renal reabsorption due to the poor passive permeability of these compounds. It is possible that active secretion may be playing an important role for certain compounds. However, because actively secreted drugs tend to have underpredicted renal clearances in humans when allometrically scaled, one would still anticipate a drug to have high urinary excretion in humans if a drug is highly excreted into the urine in an animal model [172].

Considerable focus has also been placed on evaluating which preclinical animal species is most effective for allometric scaling in humans. Using various scaling approaches, Paine *et al* compared renal clearance predictions from rats and dogs and found the strongest correlation of human renal clearance with dogs [173]. Contrary to our results, other studies have

Table V Performance of binary classifications of fe thresholds for each animal species to properly classify human fe as ≥30% or <30% for all BDDCS Class 1, 2, 3, and 4 drugs in dataset

	Rat		Dog		Monkey	
	≥30%	≥25%	≥30%	≥19%	≥30%	≥10%
Sensitivity	85%	88%	87%	100%	74%	96%
Specificity	92%	89%	95%	91%	100%	89%
Accuracy	87%	88%	90%	97%	81%	94%
PPV	95%	93%	98%	96%	100%	96%
NPV	78%	81%	78%	100%	60%	89%

shown monkeys to be better predictors of clearance in humans [2, 171]. This observation has been attributed to evolutionary similarity between monkeys and humans, as a result of similarities in transporters and drug metabolizing enzymes. In addition, it has been suggested that the monkey is the best of the preclinical animal species in predicting renal clearance no matter if a drug undergoes filtration, reabsorption, or active secretion in the kidney [170]. The fe data we report here indicate monkeys may underpredict urinary excretion to a greater degree than rats or dog. This result may be attributed to the small dataset of the monkey, which had the smallest dataset of the three animal species and consisted of only 32 drugs.

The results presented here have several limitations. First, the dataset was constructed primarily from drugs already identified to have poor metabolism in humans (BDDCS Class 3 and 4 drugs) and may not be fully representative of the distribution of BDDCS classifications of NMEs. To minimize this limitation, we included a literature review of a small set of BDDCS Class 1 and 2 drugs. Of the fe values collected for Class 1 and 2 drugs, all but one drug, sumatriptan (rat fe=39.5%, dog fe=35.7%, human fe=22%), had low urinary excretion in both animals (<30%) and humans (<30%). Second, our dataset was limited to the published literature. As preclinical pharmacokinetic studies are not always published, our dataset may be missing key urinary excretion values that may impact our findings. Third, we focused only on urinary excretion and did not include biliary excretion due to the difficulty in finding such reliable references. Additionally, due to the retrospective nature of this dataset, it only includes mean data from the original experimental studies and not a measure of variability. Also, drugs were included in the dataset even if they exhibit known nonlinearities in their pharmacokinetics, which may impact interpretation of this analysis for those drugs. Finally, we did not investigate the role of filtration, active secretion, or reabsorption for drugs in this dataset nor did we make attempts to categorize the drugs by other parameters that may influence urinary excretion such as fraction unbound.

The results of this study provide another level of evidence, in addition to *in silico* and *in vitro* approaches, to determine the elimination pathway of an NME early on in development. Due to the high correlation between intestinal permeability rate and extent of metabolism, *in vitro* measures of passive membrane permeability including the use of parallel artificial membrane permeability assays (PAMPA), Caco-2 cells, and MDCK cells can be used to predict extent of metabolism [174–176]. Furthermore, a number of *in silico* tools have been published that attempt to predict a drug's permeability and/or elimination pathway based on physicochemical properties such as molecular weight, log P, polar surface area, and others [10, 177–180]. In general, compounds that exhibit high permeability rate *in vitro* or *in silico* are very likely to be metabolized. While compounds with low permeability rates are expected to be eliminated as unchanged drug, a substantial fraction of drugs with relatively low permeability rates *in vitro* or *in silico* are actually metabolized [10]. These drugs with an "intermediate" permeability rates are especially difficult to predict with just *in vitro* or *in silico* data and could benefit from *in vivo* studies in preclinical species to further inform elimination mechanisms. Thus, an evaluation of urinary excretion in animal models may be useful in identifying which compounds are likely renally eliminated in humans (i.e., lack metabolism), and which are likely eliminated by a hepatic route (i.e., metabolism or biliary excretion). Overall, the results presented here suggest urinary excretion data in preclinical species may be helpful to confirm elimination route and the BDDCS classification suggested with *in silico* and *in vitro* models. Having *in silico*, *in vitro*, and *in vivo* evidence of BDDCS classification provides additional reassurance of the likely extent of metabolism in humans.

CONCLUSIONS

A dataset of animal and human fe values was constructed and evaluated to determine the ability of preclinical animal species to inform when an NME will have high urinary excretion and corresponding poor metabolism in humans. Paired fe values between animals and humans indicate that rats and monkeys have significantly lower fe values than humans for Class 3 drugs, while dogs have significantly lower fe values than humans for both Class 3 and 4 drugs. Statistically significant correlations were found between each animal species (rat, dog, and monkey) and human fe. In addition, a high frequency of Class 3 and 4 drugs had animal and human fe values within a two-fold range. Drugs with animal fe values outside of a two-fold range of human fe values were more likely to underpredict as opposed to overpredict human fe. Alignment between animal and human data was seen when fe values were classified as high (fe ≥30%) or low (fe <30%). ROC curve analysis suggests thresholds of ≥25% in rats, ≥19% in dogs, and ≥10% in monkeys may better predict when human fe values of ≥30% or <30%. High PPVs indicate that when an animal demonstrates high urinary excretion of a drug, high renal excretion of that drug in humans is likely. As high urinary excretion of unchanged drug is a marker for low extent of metabolism, this study indicates that high urinary excretion in animal models is suggestive of poor metabolism in humans and likely classification as a BDDCS Class 3 or 4 drug. Overall, this study provides an additional piece of evidence for predicting elimination pathways early on in drug development that could supplement current *in silico* and *in vitro* approaches.

AUTHOR CONTRIBUTIONS

Original study conception and design was completed by Leslie Benet, Connie Remsberg, and Chelsea Hosey. The literature review and data analysis were performed by Nadia Bamfo, Connie Remsberg, and Chelsea Hosey. The initial draft of the manuscript was written by Nadia Bamfo and Connie Remsberg and critically revised by Chelsea Hosey and Leslie Benet.

DECLARATIONS

Conflict of interest statement The authors declare that they have no conflict of interest.

REFERENCES

1. Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, et al. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. J Pharmacol Exp Ther. 1997;283(1):46–58.

2. Ward KW, Smith BR. A comprehensive quantitative and qualitative evaluation of extrapolation of intravenous pharmacokinetic parameters from rat, dog, and monkey to humans. I. Clearance. Drug Metab Dispos. 2004;32(6):603–11. https://doi.org/10.1124/dmd.32.6.603.

3. Obach RS, Lombardo F, Waters NJ. Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. Drug Metab Dispos. 2008;36(7):1385–405. https://doi.org/10.1124/dmd.108.020479.

4. Yang X, Gandhi YA, Duignan DB, Morris ME. Prediction of biliary excretion in rats and humans using molecular weight and quantitative structure-pharmacokinetic relationships. AAPS J. 2009;11(3):511–25. https://doi.org/10.1208/s12248-009-9124-1.

5. Hosea NA, Collard WT, Cole S, Maurer TS, Fang RX, Jones H, et al. Prediction of human pharmacokinetics from preclinical information: comparative accuracy of quantitative prediction approaches. J Clin Pharmacol. 2009;49(5):513–33. https://doi.org/10.1177/0091270009333209.

6. Ring BJ, Chien JY, Adkison KK, Jones HM, Rowland M, Jones RD, et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 3: comparative assessement of prediction methods of human clearance. J Pharm Sci. 2011;100(10):4090–110. https://doi.org/10.1002/jps.22552.

7. Varma MV, Chang G, Lai Y, Feng B, El-Kattan AF, Litchfield J, et al. Physicochemical property space of hepatobiliary transport and computational models for predicting rat biliary excretion. Drug Metab Dispos. 2012;40(8):1527–37. https://doi.org/10.1124/dmd.112.044628.

8. Hosey CM, Broccatelli F, Benet LZ. Predicting when biliary excretion of parent drug is a major route of elimination in humans. AAPS J. 2014;16(5):1085–96. https://doi.org/10.1208/s12248-014-9636-1.

9. Sharifi M, Ghafourian T. Estimation of biliary excretion of foreign compounds using properties of molecular structure. AAPS J. 2014;16(1):65–78. https://doi.org/10.1208/s12248-013-9541-z.

10. Hosey CM, Benet LZ. Predicting the extent of metabolism using in vitro permeability rate measurements and in silico permeability rate predictions. Mol Pharmaceut. 2015;12(5):1456–66. https://doi.org/10.1021/mp500783g.

11. Watanabe R, Ohashi R, Esaki T, Kawashima H, Natsume-Kitatani Y, Nagao C, et al. Development of an in silico prediction system of human renal excretion and clearance from chemical structure information incorporating fraction unbound in plasma as a descriptor. Sci Rep. 2019;9(1):18782. https://doi.org/10.1038/s41598-019-55325-1.

12. Wajima T, Fukumura K, Yano Y, Oguma T. Prediction of human pharmacokinetics from animal data and molecular structural parameters using multivariate regression analysis: oral clearance. J Pharm Sci. 2003;92(12):2427–40. https://doi.org/10.1002/jps.10510.

13. Wajima T, Yano Y, Fukumura K, Oguma T. Prediction of human pharmacokinetic profile in animal scale up based on normalizing time course profiles. J Pharm Sci. 2004;93(7):1890–900. https://doi.org/10.1002/jps.20099.

14. Jones HM, Parrott N, Jorga K, Lave T. A novel strategy for physiologically based predictions of human pharmacokinetics. Clin Pharmacokinet. 2006;45(5):511–42. https://doi.org/10.2165/00003088-200645050-00006.

15. Poulin P, Jones RD, Jones HM, Gibson CR, Rowland M, Chien JY, et al. PHRMA CPCDC initiative on predictive models of human pharmacokinetics, part 5: prediction of plasma concentration-time profiles in human by using the physiologically-based pharmacokinetic modeling approach. J Pharm Sci. 2011;100(10):4127–57. https://doi.org/10.1002/jps.22550.

16. Sharma V, McNeill JH. To scale or not to scale: the principles of dose extrapolation. Br J Pharmacol. 2009;157(6):907–21. https://doi.org/10.1111/j.1476-5381.2009.00267.x.

17. Huh Y, Smith DE, Feng MR. Interspecies scaling and prediction of human clearance: comparison of small- and macro-molecule drugs. Xenobiotica. 2011;41(11):972–87. https://doi.org/10.3109/00498254.2011.598582.

18. Tang H, Mayersohn M. A global examination of allometric scaling for predicting human drug clearance and the prediction of large vertical allometry. J Pharm Sci. 2006;95(8):1783–99. https://doi.org/10.1002/jps.20481.

19. Huang Q, Riviere JE. The application of allometric scaling principles to predict pharmacokinetic parameters across species. Expert Opin Drug Metab Toxicol. 2014;10(9):1241–53. https://doi.org/10.1517/17425255.2014.934671.

20. Martignoni M, Groothuis GM, de Kanter R. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. Expert Opin Drug Metab Toxicol. 2006;2(6):875–94. https://doi.org/10.1517/17425255.2.6.875.

21. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/ elimination interplay and

development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22(1):11–23.

22. Benet LZ, Broccatelli F, Oprea TI. BDDCS applied to over 900 drugs. AAPS J. 2011;13(4):519–47. https://doi.org/10.1208/s12248-011-9290-9.

23. Hosey CM, Chan R, Benet LZ. BDDCS Predictions, Self-Correcting Aspects of BDDCS Assignments, BDDCS Assignment Corrections, and Classification for more than 175 Additional Drugs. AAPS J. 2016;18(1):251–60. https://doi.org/10.1208/s12248-015-9845-2.

24. Sing T, Sander O, Beerenwinkel N, Lengauer T. ROCR: visualizing classifier performance in R. Bioinformatics. 2005;21(20):3940–1. https://doi.org/10.1093/bioinformatics/bti623.

25. Zornoza T, Guerri C, Polache A, Granero L. Disposition of acamprosate in the rat: influence of probenecid. Biopharm Drug Dispos. 2002;23(7):283–91. https://doi.org/10.1002/bdd.322.

26. Schneck DW, Grove K, Dewitt FO, Shiroff RA, Hayes AH Jr. The quantitative disposition of procainamide and N-acetylprocainamide in the rat. J Pharmacol Exp Ther. 1978;204(1):219–25.

27. McNulty MJ, Deal DL, Nelson FR, Weller S, Chandrasurin P, Shockcor J, et al. Disposition of acrivastine in the male beagle dog. Drug Metab Dispos. 1992;20(5):679–87.

28. Aubets J, Cardenas A, Salva M, Jansat JM, Martinez-Tobed A, Palacios JM. Disposition and metabolism of almotriptan in rats, dogs and monkeys. Xenobiotica. 2006;36(9):807–23. https://doi.org/10.1080/00498250600802508.

29. Walton K, Dorne JL, Renwick AG. Species-specific uncertainty factors for compounds eliminated principally by renal excretion in humans. Food Chem Toxicol. 2004;42(2):261–74.

30. Belpaire FM, de Smet F, Vynckier LJ, Vermeulen AM, Rosseel MT, Bogaert MG, et al. Effect of aging on the pharmcokinetics of atenolol, metoprolol and propranolol in the rat. J Pharmacol Exp Ther. 1990;254(1):116–22.

31. McAinsh J, Holmes BF. Pharmacokinetic studies with atenolol in the dog. Biopharm Drug Dispos. 1983;4(3):249–61.

32. Kripalani KJ, Singhvi SM, Weinstein SH, Everett DW, Bathala MS, Dean AV, et al. Disposition of [14C]aztreonam in rats, dogs, and monkeys. Antimicrob Agents Chemother. 1984;26(2):119–26.

33. Watanabe T, Maeda K, Kondo T, Nakayama H, Horita S, Kusuhara H, et al. Prediction of the hepatic and renal clearance of transporter substrates in rats using in vitro uptake experiments. Drug Metab Dispos. 2009;37(7):1471–9. https://doi.org/10.1124/dmd.108.026062.

34. Kurihara A, Naganuma H, Hisaoka M, Tokiwa H, Kawahara Y. Prediction of human pharmacokinetics of panipenem-betamipron, a new carbapenem, from animal data. Antimicrob Agents Chemother. 1992;36(9):1810–6.

35. Buhring KU, Sailer H, Faro HP, Leopold G, Pabst J, Garbe A. Pharmacokinetics and metabolism of bisoprolol-14C in three animal species and in humans. J Cardiovasc Pharmacol. 1986;8(Suppl 11):S21–8.

36. Singhvi SM, Peterson AE, Ross JJ Jr, Shaw JM, Keim GR, Migdalof BH. Pharmacokinetics of captopril in dogs and monkeys. J Pharm Sci. 1981;70(10):1108–12.

37. Siddik ZH, Newell DR, Boxall FE, Harrap KR. The comparative pharmacokinetics of carboplatin and cisplatin in mice and rats. Biochem Pharmacol. 1987;36(12):1925–32.

38. Gaver RC, George AM, Duncan GF, Morris AD, Deeb G, Faulkner HC, et al. The disposition of carboplatin in the beagle dog. Cancer Chemother Pharmacol. 1988;21(3):197–202.

39. Sawada Y, Hanano M, Sugiyama Y, Iga T. Prediction of the disposition of beta-lactam antibiotics in humans from pharmacokinetic parameters in animals. J Pharmacokinet Biopharm. 1984;12(3):241–61.

40. Matsushita H, Suzuki H, Sugiyama Y, Sawada Y, Iga T, Hanano M, et al. Prediction of the pharmacokinetics of cefodizime and cefotetan in humans from pharmacokinetic parameters in animals. J Pharmacobiodyn. 1990;13(10):602–11.

41. Zhang J, Wang C, Liu Q, Meng Q, Cang J, Sun H, et al. Pharmacokinetic interaction between JBP485 and cephalexin in rats. Drug Metab Dispos. 2010;38(6):930–8. https://doi.org/10.1124/dmd.110.032060.

42. Cabana BE, van Harken DR, Hottendorf GH. Comparative pharmacokinetics and metabolism of cephapirin in laboratory animals and humans. Antimicrob Agents Chemother. 1976;10(2):307–17.

43. Cundy KC, Li ZH, Hitchcock MJ, Lee WA. Pharmacokinetics of cidofovir in monkeys. Evidence for a prolonged elimination phase representing phosphorylated drug. Drug Metab Dispos. 1996;24(7):738–44.

44. Taylor DC, Cresswell PR, Bartlett DC. The metabolism and elimination of cimetidine, a histamine H2-receptor antagonist, in the rat, dog, and man. Drug Metab Dispos. 1978;6(1):21–30.

45. Tahara H, Kusuhara H, Chida M, Fuse E, Sugiyama Y. Is the monkey an appropriate animal model to examine drug-drug interactions involving renal clearance? Effect of probenecid on the renal elimination of H2 receptor antagonists. J Pharmacol Exp Ther. 2006;316(3):1187–94. https://doi.org/10.1124/jpet.105.094052.

46. Bonate PL, Arthaud L, Stuhler J, Yerino P, Press RJ, Rose JQ. The distribution, metabolism, and elimination of clofarabine in rats. Drug Metab Dispos. 2005;33(6):739–48. https://doi.org/10.1124/dmd.104.002592.

47. Lutz RJ, Galbraith WM, Dedrick RL, Shrager R, Mellett LB. A model for the kinetics of distribution of actinomycin-D in the beagle dog. J Pharmacol Exp Ther. 1977;200(3):469–78.

48. Baldwin JR, Lewis RC, Phillips BA, Overmyer SK, Hatfield NZ, Narang PK. Dose-independent pharmacokinetics of the cardioprotective agent dexrazoxane in dogs. Biopharm Drug Dispos. 1996;17(6):541–50. https://doi.org/10.1002/(SICI)1099-081X(199608)17:6<541::AID-BDD975>3.0.CO;2-5.

49. Odinecs A, Pereira C, Nosbisch C, Unadkat JD. Prenatal and postpartum pharmacokinetics of stavudine (2',3'-didehydro-3'-deoxythymidine) and didanosine (dideoxyinosine) in pigtailed macaques (Macaca nemestrina). Antimicrob Agents Chemother. 1996;40(10):2423–5.

50. Harrison LI, Gibaldi M. Pharmacokinetics of digoxin in the rat. Drug Metab Dispos. 1976;4(1):88–93.

51. Akabane T, Tabata K, Kadono K, Sakuda S, Terashita S, Teramura T. A comparison of pharmacokinetics between humans and monkeys. Drug Metab Dispos. 2010;38(2):308–16. https://doi.org/10.1124/dmd.109.028829.

52. Cook CS, Gwilt PR, Kowalski K, Gupta S, Oppermann J, Karim A. Pharmacokinetics of disopyramide in the dog. Importance of mono-N-dealkylated metabolite kinetics in assessing pharmacokinetic modeling of the parent drug. Drug Metab Dispos. 1990;18(1):42–9.

53. Wong BK, Bruhin PJ, Barrish A, Lin JH. Nonlinear dorzolamide pharmacokinetics in rats: concentration-dependent erythrocyte distribution and drug-metabolite displacement interaction. Drug Metab Dispos. 1996;24(6):659–63.

54. Schach von Wittenau M, Twomey TM. The disposition of doxycycline by man and dog. Chemotherapy. 1971;16(4):217–28.

55. Wong BK, Sahly Y, Mistry G, Waldman S, Musson D, Majumdar A, et al. Comparative disposition of [14C]ertapenem, a novel carbapenem antibiotic, in rat, monkey and man. Xenobiotica. 2004;34(4):379–89. https://doi.org/10.1080/00498250410001670643.

56. Lin JH, Los LE, Ulm EH, Duggan DE. Urinary excretion kinetics of famotidine in rats. Drug Metab Dispos. 1987;15(2):212–6.

57. Boom SP, Hoet S, Russel FG. Saturable urinary excretion kinetics of famotidine in the dog. J Pharm Pharmacol. 1997;49(3):288–92.

58. Kamath AV, Yao M, Zhang Y, Chong S. Effect of fruit juices on the oral bioavailability of fexofenadine in rats. J Pharm Sci. 2005;94(2):233–9. https://doi.org/10.1002/jps.20231.

59. Forster HJ, Kramer I, Pook KH, Wahl D. Studies on the pharmacokinetics and biotransformation of ipratropium bromide in the rat and dog. Arzneimittel-Forschung. 1976;26(5a):992–1005.

60. Cabana BE, Taggart JG. Comparative pharmacokinetics of BB-K8 and kanamycin in dogs and humans. Antimicrob Agents Chemother. 1973;3(4):478–83.

61. Mroszczak EJ, Lee FW, Combs D, Sarnquist FH, Huang BL, Wu AT, et al. Ketorolac tromethamine absorption, distribution, metabolism, excretion, and pharmacokinetics in animals and humans. Drug Metab Dispos. 1987;15(5):618–26.

62. Takubo T, Kato T, Kinami J, Hanada K, Ogata H. Effect of trimethoprim on the renal clearance of lamivudine in rats. J Pharm Pharmacol. 2000;52(3):315–20.

63. Blaney SM, Daniel MJ, Harker AJ, Godwin K, Balis FM. Pharmacokinetics of lamivudine and BCH-189 in plasma and cerebrospinal fluid of nonhuman primates. Antimicrob Agents Chemother. 1995;39(12):2779–82.

64. Benedetti MS, Coupez R, Whomsley R, Nicolas JM, Collart P, Baltes E. Comparative pharmacokinetics and metabolism of levetiracetam, a new anti-epileptic agent, in mouse, rat, rabbit and dog. Xenobiotica. 2004;34(3):281–300. https://doi.org/10.1080/0049825042000196749.

65. Hemeryck A, Mamidi RN, Bottacini M, Macpherson D, Kao M, Kelley MF. Pharmacokinetics, metabolism, excretion and plasma protein binding of 14C-levofloxacin after a single oral administration in the Rhesus monkey. Xenobiotica. 2006;36(7):597–613. https://doi.org/10.1080/00498250600674436.

66. Choi YH, Kim SG, Lee MG. Dose-independent pharmacokinetics of metformin in rats: Hepatic and gastrointestinal first-pass effects. J Pharm Sci. 2006;95(11):2543–52. https://doi.org/10.1002/jps.20744.

67. Fahrig L, Brasch H, Iven H. Pharmacokinetics of methotrexate (MTX) and 7-hydroxymethotrexate (7-OH-MTX) in rats and evidence for the metabolism of MTX to 7-OH-MTX. Cancer Chemother Pharmacol. 1989;23(3):156–60.

68. Slordal L, Jaeger R, Kjaeve J, Aarbakke J. Pharmacokinetics of 7-hydroxy-methotrexate and methotrexate in the rat. Pharmacol Toxicol. 1988;63(2):81–4.

69. Lui CY, Lee MG, Chiou WL. Clearance studies of methotrexate in dogs after multiple-rate infusion. Cancer Res. 1985;45(4):1545–8.

70. Kochak GM, Mason WD. The pharmacokinetics of alpha-methyldopa in dogs. J Pharmacokinet Biopharm. 1985;13(4):405–23.

71. Jungbluth GL, Jusko WJ. Dose-dependent pharmacokinetics of mezlocillin in rats. Antimicrob Agents Chemother. 1989;33(6):839–43.

72. Siefert HM, Domdey-Bette A, Henninger K, Hucke F, Kohlsdorfer C, Stass HH. Pharmacokinetics of the 8-methoxy-quinolone, moxifloxacin: a comparison in humans and other mammalian species. J Antimicrob Chemother. 1999;43(Suppl B):69–76.

73. Singhvi SM, Heald AF, Murphy BF, DiFazio LT, Schreiber EC, Poutsiaka JW. Disposition of [14C]nadolol in dogs with reversible renal impairment induced by uranyl nitrate. Toxicol Appl Pharmacol. 1978;43(1):99–109.

74. Hennis PJ, Cronnelly R, Sharma M, Fisher DM, Miller RD. Metabolites of neostigmine and pyridostigmine do not contribute to antagonism of neuromuscular blockade in the dog. Anesthesiology. 1984;61(5):534–9.

75. Pongchaidecha M, Daley-Yates PT. Clearance and tissue uptake following 4-hour and 24-hour infusions of pamidronate in rats. Drug Metab Dispos. 1993;21(1):100–4.

76. Upton RA, Nguyen TL, Miller RD, Castagnoli N Jr. Renal and biliary elimination of vecuronium (ORG NC 45) and pancuronium in rats. Anesth Analg. 1982;61(4):313–6.

77. Scatina JA, Hicks DR, Kraml M, Cayen MN. Metabolic disposition and pharmacokinetics of pelrinone, a new cardiotonic drug, in laboratory animals and man. Eur J Drug Metab Pharmacokinet. 1990;15(1):37–48.

78. Bergstrom RF, Kay RD, Wagner JG. The pharmacokinetics of penicillamine in a female mongrel dog. J Pharmacokinet Biopharm. 1981;9(5):603–21.

79. Thummel KE, Shen DD, Isoherranen N, Sminth HE. Design and optimization of dosage regimens; pharmacokinetic data. In: Brunton LL, editor. Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill; 2006. p. 1787–888.

80. Khuenl-Brady KS, Sharma M, Chung K, Miller RD, Agoston S, Caldwell JE. Pharmacokinetics and disposition of pipecuronium bromide in dogs with and without ligated renal pedicles. Anesthesiology. 1989;71(6):919–22.

81. Patterson TA, Li M, Hotchkiss CE, Mauz A, Eddie M, Greischel A, et al. Toxicity assessment of pramipexole in juvenile rhesus monkeys. Toxicology. 2010;276(3):164–71. https://doi.org/10.1016/j.tox.2010.08.002.

82. McNeil JJ, Mihaly GW, Anderson A, Marshall AW, Smallwood RA, Louis WJ. Pharmacokinetics of the H2- receptor antagonist ranitidine in man. Br J Clin Pharmacol. 1981;12(3):411–5.

83. Eddershaw PJ, Chadwick AP, Higton DM, Fenwick SH, Linacre P, Jenner WN, et al. Absorption and disposition of ranitidine hydrochloride in rat and dog. Xenobiotica. 1996;26(9):947–56. https://doi.org/10.3109/00498259609052496.

84. Boom SP, Meyer I, Wouterse AC, Russel FG. A physiologically based kidney model for the renal clearance of ranitidine and the interaction with cimetidine and probenecid in the dog. Biopharm Drug Dispos. 1998;19(3):199–208.

85. Beconi MG, Reed JR, Teffera Y, Xia YQ, Kochansky CJ, Liu DQ, et al. Disposition of the dipeptidyl peptidase 4 inhibitor sitagliptin in rats and dogs. Drug Metab Dispos. 2007;35(4):525–32. https://doi.org/10.1124/dmd.106.013110.

86. Carr RA, Pasutto FM, Foster RT. Influence of cimetidine coadministration on the pharmacokinetics of sotalol enantiomers in an anaesthetized rat model: evidence supporting active renal excretion of sotalol. Biopharm Drug Dispos. 1996;17(1):55–69. https://doi.org/10.1002/(SICI)1099-081X(199601)17:1<55::AID-BDD938>3.0.CO;2-#.

87. Kaul S, Dandekar KA, Schilling BE, Barbhaiya RH. Toxicokinetics of 2',3'-didehydro-3'-deoxythymidine, stavudine (D4T). Drug Metab Dispos. 1999;27(1):1–12.

88. Kaul S, Dandekar KA. Pharmacokinetics of the anti-human immunodeficiency virus nucleoside analog stavudine in cynomolgus monkeys. Antimicrob Agents Chemother. 1993;37(5):1160–2.

89. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. J Antimicrob Chemother. 1993;(31, Suppl A):39–60.

90. Cundy KC, Sueoka C, Lynch GR, Griffin L, Lee WA, Shaw JP. Pharmacokinetics and bioavailability of the anti-human immunodeficiency virus nucleotide analog 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Antimicrob Agents Chemother. 1998;42(3):687–90.

91. Tegner K, Nilsson HT, Persson CG, Persson K, Ryrfeldt A. Elimination pathways of terbutaline. Eur J Respir Dis Suppl. 1984;134:93–100.

92. Nilsson HT, Persson CG, Persson K, Tegner K, Ryrfeldt A. The metabolism of terbutaline in dog and rat. Xenobiotica. 1973;3(9):615–23. https://doi.org/10.3109/00498257309151550.

93. Oh YH, Han HK. Pharmacokinetic interaction of tetracycline with non-steroidal anti-inflammatory drugs via organic anion transporters in rats. Pharmacol Res. 2006;53(1):75–9. https://doi.org/10.1016/j.phrs.2005.09.003.

94. Davi H, Tronquet C, Caix J, Simiand J, Briot C, Berger Y, et al. Disposition of tiludronate (Skelid) in animals. Xenobiotica. 1999;29(10):1017–31. https://doi.org/10.1080/004982599238083.

95. Vickers S, Theoharides AD, Arison B, Balani SK, Cui D, Duncan CA, et al. In vitro and in vivo studies on the metabolism of tirofiban. Drug Metab Dispos. 1999;27(11):1360–6.

96. Mustafa S, Venkatesh P, Pasha K, Mullangi R, Srinivas NR. Altered intravenous pharmacokinetics of topotecan in rats with acute renal failure (ARF) induced by uranyl nitrate: do adenosine A1 antagonists (selective/non-selective) normalize the altered topotecan kinetics in ARF? Xenobiotica. 2006;36(12):1239–58. https://doi.org/10.1080/00498250600839385.

97. Hodoshima N, Nakano Y, Izumi M, Mitomi N, Nakamura Y, Aoki M, et al. Protective effect of inactive ingredients against nephrotoxicity of vancomycin hydrochloride in rats. Drug Metab Pharmacokinet. 2004;19(1):68–75.

98. Groen K, Warrander A, Miles GS, Booth BS, Mulder GJ. Sulphation and glucuronidation of xamoterol in the dog: dose dependence and site of sulphation. Xenobiotica. 1988;18(5):511–8. https://doi.org/10.3109/00498258809041688.

99. Sorensen EV, Faergeman O, Day M, Bastain W. Pharmacokinetics of xamoterol after intravenous and oral administration to patients with chronic heart failure. Eur J Clin Pharmacol. 1988;35(2):183–5.

100. Oh YH, Han HK. Altered pharmacokinetics of zalcitabine by concurrent use of NSAIDs in rats. Acta Pharmacol Sin. 2006;27(1):119–22. https://doi.org/10.1111/j.1745-7254.2006.00249.x.

101. de Miranda P, Krasny HC, Page DA, Elion GB. The disposition of acyclovir in different species. J Pharmacol Exp Ther. 1981;219(2):309–15.

102. Krasny HC, de Miranda P, Blum MR, Elion GB. Pharmacokinetics and bioavailability of acyclovir in the dog. J Pharmacol Exp Ther. 1981;216(2):281–8.

103. Good SS, de Miranda P. Metabolic disposition of acyclovir in the guinea pig, rabbit, and monkey. Am J Med. 1982;73(1A):91–5.

104. Zhang Q, Liu Q, Wu J, Wang C, Peng J, Ma X, et al. PEPT1 involved in the uptake and transepithelial transport of cefditoren in vivo and in vitro. Eur J Pharmacol. 2009;612(1-3):9–14. https://doi.org/10.1016/j.ejphar.2009.03.081.

105. Barbhaiya RH, Wang L, Shyu WC, Pittman KA. Absolute bioavailability of cefprozil after oral administration in beagles. Antimicrob Agents Chemother. 1992;36(3):687–9.

106. Resetarits DE, Bates TR. Apparent dose-dependent absorption of chlorothiazide in dogs. J Pharmacokinet Biopharm. 1979;7(5):463–70.

107. Gustafson JH, Benet LZ. Saturable kinetics of intravenous chlorothiazide in the rhesus monkey. J Pharmacokinet Biopharm. 1981;9(4):461–76.

108. Nouaille-Degorce B, Veau C, Dautrey S, Tod M, Laouari D, Carbon C, et al. Influence of renal failure on ciprofloxacin pharmacokinetics in rats. Antimicrob Agents Chemother. 1998;42(2):289–92.

109. Abadia AR, Aramayona JJ, Munoz MJ, Pla Delfina JM, Saez MP, Bregante MA. Disposition of ciprofloxacin following intravenous administration in dogs. J Vet Pharmacol Ther. 1994;17(5):384–8.

110. Kusajima H, Ishikawa N, Machida M, Uchida H, Irikura T. Pharmacokinetics of a new quinolone, AM-833, in mice, rats, rabbits, dogs, and monkeys. Antimicrob Agents Chemother. 1986;30(2):304–9.

111. Kim SH, Choi YM, Lee MG. Pharmacokinetics and pharmacodynamics of furosemide in protein-calorie malnutrition. J Pharmacokinet Biopharm. 1993;21(1):1–17.

112. Park JH, Lee WI, Yoon WH, Park YD, Lee JS, Lee MG. Pharmacokinetic and pharmacodynamic changes of furosemide after intravenous and oral administration to rats with alloxan-induced diabetes mellitus. Biopharm Drug Dispos. 1998;19(6):357–64.

113. Data JL, Rane A, Gerkens J, Wilkinson GR, Nies AS, Branch RA. The influence of indomethacin on the pharmacokinetics, diuretic response and hemodynamics of furosemide in the dog. J Pharmacol Exp Ther. 1978;206(2):431–8.

114. Kozutsumi D, Kawashima A, Sugimoto T, Kotohda Y, Fujimori S, Takami M, et al. Pharmacokinetics of 9alpha-fluoromedroxyprogesterone acetate in rats: comparison with medroxyprogesterone acetate. Biopharm Drug Dispos. 1999;20(6):277–84.

115. Harrison MP, Moss SR, Featherstone A, Fowkes AG, Sanders AM, Case DE. The disposition and metabolism of meropenem in laboratory animals and man. J Antimicrob Chemother. 1989;24(Suppl A):265–77.

116. Wang X, Morris ME. Effects of the flavonoid chrysin on nitrofurantoin pharmacokinetics in rats: potential involvement of ABCG2. Drug Metab Dispos. 2007;35(2):268–74. https://doi.org/10.1124/dmd.106.011684.

117. Øie S. Effect of 4-N-acetyl-sulfisoxazole on the disposition of sulfisoxazole in the rat. Int J Pharm. 1979;3(6):311–8. https://doi.org/10.1016/0378-5173(79)90123-6.

118. Christensen S. The biological fate of riboflavin in mammals. A survey of literature and own investigations. Acta Pharmacol Toxicol (Copenh). 1973;32:3–72.

119. Mostafavi SA, Foster RT. Pharmacokinetics of single oral and multiple intravenous and oral administration of acebutolol enantiomers in a rat model. Biopharm Drug Dispos. 1998;19(7):425–31. https://doi.org/10.1002/(sici)1099-081x(199810)19:7<425::aid-bdd121>3.0.co;2-x.

120. Bae SK, Yang KH, Aryal DK, Kim YG, Lee MG. Pharmacokinetics of amitriptyline and one of its metabolites, nortriptyline, in rats: little contribution of considerable hepatic first-pass effect to low bioavailability of amitriptyline due to great intestinal first-pass effect. J Pharm Sci. 2009;98(4):1587–601. https://doi.org/10.1002/jps.21511.

121. Aldridge A, Neims AH. The effects of phenobarbital and beta-naphthoflavone on the elimination kinetics and metabolite pattern of caffeine in the beagle dog. Drug Metab Dispos. 1979;7(6):378–82.

122. Peets EA, Weinstein R, Billard W, Symchowicz S. The metabolism of chlorpheniramine maleate in the dog and rat. Arch Int Pharmacodyn Ther. 1972;199(1):172–90.

123. McIntosh MP, Leong N, Katneni K, Morizzi J, Shackleford DM, Prankerd RJ. Impact of chlorpromazine self-association on its apparent binding constants with cyclodextrins: Effect of SBE(7)-beta-CD on the disposition of chlorpromazine in the rat. J Pharm Sci. 2010;99(7):2999–3008. https://doi.org/10.1002/jps.22064.

124. Sawada Y, Hanano M, Sugiyama Y, Iga T. Prediction of the disposition of nine weakly acidic and six weakly basic drugs in humans from pharmacokinetic parameters in rats. J Pharmacokinet Biopharm. 1985;13(5):477–92. https://doi.org/10.1007/BF01059331.

125. Salzman NP, Moran NC, Brodie BB. Identification and pharmacological properties of a major metabolite of chlorpromazine. Nature. 1955;176(4493):1122–3. https://doi.org/10.1038/1761122a0.

126. Keyler DE, Le Couteur DG, Pond SM, St Peter JV, Pentel PR. Effects of specific antibody Fab fragments on desipramine pharmacokinetics in the rat in vivo and in the isolated, perfused liver. J Pharmacol Exp Ther. 1995;272(3):1117–23.

127. van der Klejin E, van Rossum JM, Muskens ET, Rijntjes NV. Pharmacokinetics of diazepam in dogs, mice and humans. Acta Pharmacol Toxicol (Copenh). 1971;29(Suppl 3):109–27. https://doi.org/10.1111/j.1600-0773.1971.tb03291.x.

128. Sugawara Y, Nakamura S, Usuki S, Ito Y, Suzuki T, Ohashi M, et al. Metabolism of diltiazem. II. Metabolic profile in rat, dog and man. J Pharmacobiodyn. 1988;11(4):224–33. https://doi.org/10.1248/bpb1978.11.224.

129. Yeung PK, Feng JD, Buckley SJ. Effect of administration route and length of exposure on pharmacokinetics and metabolism of diltiazem in dogs. Drug Metabol Drug Interact. 2001;18(3-4):251–62. https://doi.org/10.1515/dmdi.2001.18.3-4.251.

130. Tocco DJ. deLuna FA, Duncan AE, Vassil TC, Ulm EH. The physiological disposition and metabolism of enalapril maleate in laboratory animals. Drug Metab Dispos. 1982;10(1):15–9.

131. Lin TH, Sawada Y, Sugiyama Y, Iga T, Hanano M. Effect of phenobarbitone on the distribution and elimination of imipramine in rats. J Pharm Pharmacol. 1985;37(10):735–8. https://doi.org/10.1111/j.2042-7158.1985.tb04955.x.

132. Coutinho CB, Spiegel HE, Kaplan SA, Yu M, Christian RP, Carbone JJ, et al. Kinetics of absorption and excretion of levodopa in dogs. J Pharm Sci. 1971;60(7):1014–8. https://doi.org/10.1002/jps.2600600703.

133. Keenaghan JB, Boyes RN. The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. J Pharmacol Exp Ther. 1972;180(2):454–63.

134. Murthy SS, Nelson WL, Shen DD, Power JM, Cahill CM, McLean AJ. Pharmacokinetic interaction between verapamil and metoprolol in the dog. Stereochemical aspects. Drug Metab Dispos. 1991;19(6):1093–100.

135. Kamimura H, Koga N, Oguri K, Yoshimura H. Enhanced elimination of theophylline, phenobarbital and strychnine from the bodies of rats and mice by squalane treatment. J Pharmacobiodyn. 1992;15(5):215–21. https://doi.org/10.1248/bpb1978.15.215.

136. Sarhan F, Engasser JM, Batt AM, Magdalou J, Siest G. Effect of diphenylhydantoin and its main hydroxylated metabolite on the pharmacokinetics and the urinary and biliary excretion of phenobarbital and its p-hydroxy metabolite. Eur J Drug Metab Pharmacokinet. 1981;6(2):99–108. https://doi.org/10.1007/BF03189475.

137. Taylor JA, Twomey TM, von Wittenau MS. The metabolic fate of prazosin. Xenobiotica. 1977;7(6):357–64. https://doi.org/10.3109/00498257709035794.

138. Wu WM, Tang Y, Buchwald P, Bodor N. Pharmacokinetics and delta1-cortienic acid excretion after intravenous administration of prednisolone and loteprednol etabonate in rats. Pharmazie. 2010;65(6):412–6.

139. Chow HH, Lalka D. The influence of vitamin K3 treatment on the pharmacokinetics and metabolism of (+)-propranolol in the rat. Drug Metab Dispos. 1992;20(2):288–94.

140. Kwong EC, Laganiere S, Savitch JL, Nelson WL, Shen DD. Alteration in the disposition and metabolism of S(-)-propranolol in rats with active respiratory viral infection. Life Sci. 1988;42(12):1245–52. https://doi.org/10.1016/0024-3205(88)90556-5.

141. Vu VT, Bai SA, Abramson FP. Interactions of phenobarbital with propranolol in the dog. 2. Bioavailability, metabolism and pharmacokinetics. J Pharmacol Exp Ther. 1983;224(1):55–61.

142. Sitar DS, Thornhill DP. Propylthiouracil: absorption, metabolism and excretion in the albino rat. J Pharmacol Exp Ther. 1972;183(2):440–8.

143. Giles HG, Roberts EA, Orrego H, Sellers EM. Disposition of intravenous propylthiouracil. J Clin Pharmacol. 1981;21(11):466–71. https://doi.org/10.1002/j.1552-4604.1981.tb05651.x.

144. Watari N, Wakamatsu A, Kaneniwa N. Comparison of disposition parameters of quinidine and quinine in the rat. J Pharmacobiodyn. 1989;12(10):608–15. https://doi.org/10.1248/bpb1978.12.608.

145. Fremstad D, Jacobsen S, Lunde KM. Influence of serum protein binding on the pharmacokinetics of quinidine in normal and anuric rats. Acta Pharmacol Toxicol (Copenh). 1977;41(2):161–76. https://doi.org/10.1111/j.1600-0773.1977.tb02136.x.

146. Rakhit A, Guentert TW, Holford NH, Verhoeven J, Riegelman S. Pharmacokinetics and pharmacodynamics of quinidine and its metabolite, quinidine-N-oxide, in beagle dogs. Eur J Drug Metab Pharmacokinet. 1984;9(4):315–24. https://doi.org/10.1007/BF03189683.

147. Dixon CM, Saynor DA, Andrew PD, Oxford J, Bradbury A, Tarbit MH. Disposition of sumatriptan in laboratory animals and humans. Drug Metab Dispos. 1993;21(5):761–9.

148. Yang SH, Suh JH, Lee MG. Pharmacokinetic interaction between tamoxifen and ondansetron in rats: non-competitive (hepatic) and competitive (intestinal) inhibition of tamoxifen metabolism by ondansetron via CYP2D subfamily and 3A1/2. Cancer Chemother Pharmacol. 2010;65(3):407–18. https://doi.org/10.1007/s00280-009-1043-4.

149. Nadai M, Kato M, Yasui K, Kimura M, Zhao YL, Ueyama J, et al. Lack of effect of aciclovir on metabolism of theophylline and expression of hepatic cytochrome P450 1A2 in rats. Biol Pharm Bull. 2007;30(3):562–8. https://doi.org/10.1248/bpb.30.562.

150. Saunier C, du Souich P, Hartemann D, Sautegeau A. Theophylline disposition during acute and chronic hypoxia in the conscious dog. Res Commun Chem Pathol Pharmacol. 1987;57(3):291–9.

151. Kuze T, Miyazaki H, Taneike T. Theophylline: pharmacokinetics, metabolism and urinary excretion in dogs. Nihon Yakurigaku Zasshi. 1988;91(5):325–34. https://doi.org/10.1254/fpj.91.325.

152. Han SY, Choi YH. Pharmacokinetic Interaction between Metformin and Verapamil in Rats: Inhibition of the OCT2-Mediated Renal Excretion of Metformin by Verapamil. Pharmaceutics. 2020;12(5). https://doi.org/10.3390/pharmaceutics12050468.

153. Maeng HJ, Doan TNK, Yoon IS. Differential regulation of intestinal and hepatic CYP3A by 1alpha,25-dihydroxyvitamin D3: Effects on in vivo oral absorption and disposition of buspirone in rats. Drug Dev Res. 2019;80(3):333–42. https://doi.org/10.1002/ddr.21505.

154. Lee YS, Kim YW, Kim SG, Lee I, Lee MG, Kang HE. Effects of poloxamer 407-induced hyperlipidemia on the pharmacokinetics of carbamazepine and its 10,11-epoxide metabolite in rats: Impact of decreased expression of both CYP3A1/2 and microsomal epoxide hydrolase. Eur Neuropsychopharmacol. 2012;22(6):431–40. https://doi.org/10.1016/j.euroneuro.2011.10.004.

155. Levy RH, Lockard JS, Green JR, Friel P, Martis L. Pharmacokinetics of carbamazepine in monkeys following intravenous and oral administration. J Pharm Sci. 1975;64(2):302–7. https://doi.org/10.1002/jps.2600640224.

156. Peris-Ribera JE, Torres-Molina F, Garcia-Carbonell MC, Aristorena JC, Pla-Delfina JM. Pharmacokinetics and bioavailability of diclofenac in the rat. J Pharmacokinet Biopharm. 1991;19(6):647–65. https://doi.org/10.1007/BF01080872.

157. Tocco DJ, Breault GO, Zacchei AG, Steelman SL, Perrier CV. Physiological disposition and metabolism of 5-(2',4'-difluorophenyl)salicyclic acid, a new salicylate. Drug Metab Dispos. 1975;3(6):453–66.

158. Dickinson RG, King AR, Verbeeck RK. Elimination of diflunisal as its acyl glucuronide, phenolic glucuronide and sulfate

conjugates in bile-exteriorized and intact rats. Clin Exp Pharmacol Physiol. 1989;16(12):913–24. https://doi.org/10.1111/j.1440-1681.1989.tb02402.x.

159. Meuldermans W, Hurkmans R, Swysen E, Hendrickx J, Michiels M, Lauwers W, et al. On the pharmacokinetics of domperidone in animals and man III. Comparative study on the excretion and metabolism of domperidone in rats, dogs and man. Eur J Drug Metab Pharmacokinet. 1981;6(1):49–60. https://doi.org/10.1007/BF03189515.

160. Lin C, Symchowicz S. Absorption, distribution, metabolism, and excretion of griseofulvin in man and animals. Drug Metab Rev. 1975;4(1):75–95. https://doi.org/10.3109/03602537508993749.

161. Dietzel K, Beck WS, Schneider HT, Geisslinger G, Brune K. The biliary elimination and enterohepatic circulation of ibuprofen in rats. Pharm Res. 1990;7(1):87–90. https://doi.org/10.1023/a:1015847912059.

162. Beck WS, Geisslinger G, Engler H, Brune K. Pharmacokinetics of ibuprofen enantiomers in dogs. Chirality. 1991;3(3):165–9. https://doi.org/10.1002/chir.530030304.

163. Meunier CJ, Verbeeck RK. Glucuronidation kinetics of R,S-keto-profen in adjuvant-induced arthritic rats. Pharm Res. 1999;16(7): 1081-1086. doi: https://doi.org/10.1023/a:1018996018708.

164. Denissen JF, Grabowski BA, Johnson MK, Buko AM, Kempf DJ, Thomas SB, et al. Metabolism and disposition of the HIV-1 protease inhibitor ritonavir (ABT-538) in rats, dogs, and humans. Drug Metab Dispos. 1997;25(4):489–501.

165. Takada K, Usuda H, Oh-Hashi M, Yoshikawa H, Muranishi S, Tanaka H. Pharmacokinetics of FK-506, a novel immunosuppressant, after intravenous and oral administrations to rats. J Pharmacobiodyn. 1991;14(1):34–42. https://doi.org/10.1248/bpb1978.14.34.

166. Venkataramanan R, Warty VS, Zemaitis MA, Sanghvi AT, Burckart GJ, Seltman H, et al. Biopharmaceutical aspects of FK-506. Transplant Proc. 1987;19(5 Suppl 6):30–5.

167. Leeson GA, Chan KY, Knapp WC, Biedenbach SA, Wright GJ, Okerholm RA. Metabolic disposition of terfenadine in laboratory animals. Arzneimittel-Forschung. 1982;32(9a):1173–8.

168. Fagerholm U. Prediction of human pharmacokinetics - renal metabolic and excretion clearance. J Pharm Pharmacol. 2007;59(11): 1463–71. https://doi.org/10.1211/jpp.59.11.0002.

169. Srinivas NR. Interspecies scaling of excretory amounts using allometry - retrospective analysis with rifapentine, aztreonam, carumonam, pefloxacin, miloxacin, trovafloxacin, doripenem, imipenem, cefozopran, ceftazidime, linezolid for urinary excretion and rifapentine, cabotegravir, and dolutegravir for fecal excretion. Xenobiotica. 2016;46(9):784–92. https://doi.org/10.3109/00498254.2015.1121554.

170. Di L, Feng B, Goosen TC, Lai Y, Steyn SJ, Varma MV, et al. A perspective on the prediction of drug pharmacokinetics and disposition in drug research and development. Drug Metab Dispos. 2013;41(12):1975–93. https://doi.org/10.1124/dmd.113.054031.

171. Lombardo F, Waters NJ, Argikar UA, Dennehy MK, Zhan J, Gunduz M, et al. Comprehensive assessment of human pharmacokinetic prediction based on in vivo animal pharmacokinetic data, part 2: clearance. J Clin Pharmacol. 2013;53(2):178–91. https://doi.org/10.1177/0091270012440282.

172. Mahmood I. Interspecies scaling of renally secreted drugs. Life Sci. 1998;63(26):2365–71. https://doi.org/10.1016/s0024-3205(98)00525-6.

173. Paine SW, Ménochet K, Denton R, McGinnity DF, Riley RJ. Prediction of human renal clearance from preclinical species for a diverse set of drugs that exhibit both active secretion and net reabsorption. Drug Metab Dispos. 2011;39(6):1008–13. https://doi.org/10.1124/dmd.110.037267.

174. Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development. J Pharm Sci. 2013;102(1):34–42. https://doi.org/10.1002/jps.23359.

175. Varma MV, Gardner I, Steyn SJ, Nkansah P, Rotter CJ, Whitney-Pickett C, et al. pH-Dependent solubility and permeability criteria for provisional biopharmaceutics classification (BCS and BDDCS) in early drug discovery. Mol Pharm. 2012;9(5):1199–212. https://doi.org/10.1021/mp2004912.

176. Pham-The H, Garrigues T, Bermejo M, Gonzalez-Alvarez I, Monteagudo MC, Cabrera-Perez MA. Provisional classification and in silico study of biopharmaceutical system based on caco-2 cell permeability and dose number. Mol Pharm. 2013;10(6): 2445–61. https://doi.org/10.1021/mp4000585.

177. Varma MV, Feng B, Obach RS, Troutman MD, Chupka J, Miller HR, et al. Physicochemical determinants of human renal clearance. J Med Chem. 2009;52(15):4844–52. https://doi.org/10.1021/jm900403j.

178. Cruciani G, Crivori P, Carrupt PA, Testa B. Molecular fields in quantitative structure–permeation relationships: the VolSurf approach. Journal of Molecular Structure: THEOCHEM. 2000;503(1):17–30. https://doi.org/10.1016/S0166-1280(99)00360-7.

179. Crivori P, Cruciani G, Carrupt PA, Testa B. Predicting blood-brain barrier permeation from three-dimensional molecular structure. J Med Chem. 2000;43(11):2204–16. https://doi.org/10.1021/jm990968+.

180. Camenisch G, Alsenz J, van de Waterbeemd H, Folkers G. Estimation of permeability by passive diffusion through Caco-2 cell monolayers using the drugs' lipophilicity and molecular weight. Eur J Pharm Sci. 1998;6(4):317–24.