Teaser For predictions of human renal drug clearance, we rely on nonhuman animal models and allometric scaling, but are these models reliable enough? Are nonhuman animal- and/or drug-specific differences significant obstacles for the determination of first-in-human doses?

Humans are animals, but are animals human enough? A systematic review and meta-analysis on interspecies differences in renal drug clearance

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Various animal models are used to study pharmacokinetics (PK) of drugs in development. Human renal clearance (CLr) should be predictable through interpolation from animal data by allometric scaling. Based on this premise, we quantified interspecies differences in CLr, and related them to drug properties. Using PubMed and EMBASE, we systematically reviewed literature on human and animal CLr measures for 20 renally excreted drugs, calculated average fold errors, and quantified mean differences between animals and humans. Our results show that animal models are generally good predictors for human drug clearance using simple allometry, except for rats, with which human CLr is significantly overestimated.

Introduction

Before new drugs are approved for human use, various preclinical *in silico,* in vitro, and in vivo models are applied to assess drug disposition, efficacy, and safety. The three most established PK prediction methods are physiologically-based PK (PBPK) modeling, in vitro to in vivo extrapolation (IVIVE), and allometric scaling [1–4]. Drug clearance is a standard measure at several stages of drug development, from lead selection and optimization to first-in-human dose determination. For this, PBPK models are powerful methods that mathematically describe anatomical, physiological, physical, and chemical parameters for *a priori* predictions. However, these models are based on simplified descriptions and, as of yet, are not sufficiently sophisticated to fully replace animal models for PK drug profiling [2].

Simple allometry or interspecies scaling of PK variables is premised on a biological law that relates differences between organisms to their respective body size, following Eq. (1):

$$Y = aBW^{b} \quad (1)$$

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where Y is a biological variable, BW is body weight, and a and b are the scaling coefficient and scaling exponent, respectively. A well-known example of simple allometry is Kleiber's Law, where metabolic rate, measured as oxygen consumption, relates to body weight with an exponent of 0.75 [5,6] (Box 1). It is assumed that most allometric relations are ultimately built on anatomical and physiological features of energy consumption [7,8]. This hypothesis is consistent with the principle of symmorphosis: every structure and process within a physiological chain is optimally designed to meet, but not exceed, the requirements. In other words, each functional system is adjusted to the minimally required level for maximal performance, with metabolic rate being the fundamental process [7,9]. It is almost self-evident that the elimination of metabolic waste is a direct responsive system: the more metabolic waste is produced, the more metabolic waste has to be excreted. Consequently, if metabolic rate determines waste elimination, renal drug clearance should scale to body weight in the same way that metabolic rate does (i.e., with an exponent of 0.75). This postulation was originally published earlier by Singer, whose argumentation builds on previous publications by Holford and Mahmood [7,10–12]. In agreement, the glomerular filtration rate from neonates to adults has been shown to be well described by this exponential value [13].

However, there is considerable evidence for interspecies differences in renal function, both during development and after maturation, which could undermine Singer's hypothesis [14–16]. The renal proximal tubule is the primary site of carrier-mediated transport from blood to urine for a range of ionic substrates. Various differences in renal transporter subtypes and specificities, as well as in their expression levels and location along the tubule, have been identified. For instance, both organic cation transporter 1 and 2 (Oct1 and Oct2) are expressed in rodent proximal tubules, whereas OCT2 and OCT3 are expressed in human and monkey proximal tubules, the latter being expressed to a lesser extent [14,17]. Regarding drug clearance prediction, multiple studies have determined exponents for interspecies scaling of drug clearance based on experimental results, aiming for the best fit. Remarkably, reported exponents range from 0.42 to 1.63, thus greatly deviating from Kleiber's Law and Singer's hypothesis [11,18,19]; therefore, do these studies refute their validity? A major challenge in estimating allometric exponents is adequate study design and analysis. Study quality is often limited by small sample size, narrow distribution of weight, or failure to account for confounding factors, such as age and disease [20]. Thus, many estimates of allometric exponents should be treated with caution. Moreover, exponent deviations mostly result from data on hepatically metabolized drugs, whereas, for renally excreted drugs, exponents lie closer to 0.75 and, hence, in line with Kleiber's Law and Singer's hypothesis. Average fold errors (aFEs) are a good measure of the difference between expected and observed variables [19,21–23]. According to Huh *et al.*, aFEs for interspecies clearance prediction are >3 for hepatically eliminated drugs, but only 1.8 for renally excreted drugs [19]. To improve prediction outcomes, allometric scaling is often adjusted by correcting for liver blood flow, brain weight, or maximal lifetime potential [11,19,24,25]. This method, often referred to as Mahmood and Balian's 'rule of exponents', leads to considerable improvement for hepatically metabolized drugs, but not for renally excreted drugs [19].

Prediction errors for drugs that are excreted unchanged via the kidneys could be the result of mere intersubject variability, or of actual interspecies differences. Differences in renal physiology are frequently identified but the consequences are rarely (systematically) quantified [26]. In this systematic review and meta-analysis, we quantify interspecies differences in renal drug clearance based on Kleiber's Law and Singer's hypothesis using the fixed allometric exponent of 0.75. We systematically collected published CLr data from different mammalian species for a diverse set of 20 renally excreted drugs. Using these data, we calculated aFEs as the ratio between the observed and expected CLr values, and mean differences (MDs) between humans and all other animals. Henceforth, the term 'animal' refers to all nonhuman animals that were included in this systematic review. To find possible mechanistic explanations for the observed differences, we related them to the drug excretion profile (filtration versus active secretion), and the physicochemical drug properties [i.e., physiological charge, molecular weight (MW), LogD, hydrogen acceptor and donor count, polar surface area (PSA), and rotatable bond (Rb) count]. The ultimate purpose of this study is to aid in the selection of the most optimal animal model to be used in drug development by providing insight into interspecies differences in CLr.

BOX 1

Kleiber's Law Kleiber's Law, named after its establisher Max Kleiber, is a well-known quantitative law in biology. According to this law, the logarithm of body weight (M) can be linearly related to the logarithm of metabolic rate (Y) with a slope of 0.75 [5]. Many studies offer supportive evidence for $Y=M^b$, where b, the scaling exponent, is 0.75. For instance, a mathematical model by West et al. could derive the exponent of 0.75 from essential features of nutrient and oxygen distribution systems that comprise fractal branching tube networks (e.g., mammalian blood vessels, bronchial trees, or insect tracheal tubes) [53]. There are studies and reviews that question the existence of a universal scaling exponent because of empirical data variability and the fact that none of the physiological explanations offered could yet be accepted without reservations [54]. However, even though Kleiber's Law remains a matter of debate, the allometric power-law phenomenon has established itself as a commonly accepted biological law and widely used scientific prediction method.

Methods

Drug selection and categorization

To quantify interspecies differences in renal drug handling, we selected a diverse set of 20 drugs with extensive renal excretion, no or negligible hepatic metabolism, and diverging physicochemical properties (i.e., physiological charge, MW, LogD, PSA, hydrogen acceptor and donor count, and Rb count). All drugs and their properties are listed in Table 1.

Drugs were categorized based on their physicochemical properties, when possible under consideration of physiological relevance. In terms of physiological charge, drugs were divided into anionic, cationic, or uncharged. LogD (the logarithmic octanol/water distribution coefficient at pH 7.4) is a common measure of lipophilicity, for which drugs were divided into LogD ≤0 (i.e., hydrophilic), and >0 (i.e., lipophilic). PSA, the surface sum over all

TABLE 1

Physicochemical properties of the 20 drugs with negligible hepatic metabolism included in this study[a]

Drug	Physiological charge	MW (Da)	LogD (pH 7.4)	H^+ acceptor count	H^+ donor count	PSA (Å)	Rb count
Acyclovir	0	225	−1.03	7	3	115	4
Atenolol	1	266	−1.80	4	3	85	8
Aztreonam	−1	435	−6.12	10	3	206	6
Carumonam	−2	466	−8.09	5	14	291	10
Cefadroxil	0	363	−2.81	6	4	133	4
Cefazolin	−1	455	−5.01	9	2	156	7
Ceftizoxime	−1	383	−3.61	8	3	147	5
Cephalexin	0	347	−2.50	5	3	113	4
Enprofylline	0	194	−0.23	3	2	78	2
Famotidine	1	337	−2.67	8	4	176	6
Fluconazole	0	306	0.56	5	1	82	5
Gabapentin	0	171	−1.27	3	2	63	3
Levofloxacin	−1	361	−0.51	7	1	73	2
Metformin	2	129	−5.62	5	4	89	0
Ofloxacin	−1	361	−0.51	7	1	73	2
Sinistrin	0	829	−9.32	17	26	427	17
Sotalol	1	272	−2.12	4	3	78	5
Sulpiride	1	341	−0.70	5	2	102	6
Tenofovir disoproxil	0	519	2.65	10	1	185	17
Vancomycin	1	1449	−4.85	24	19	530	13

[a] All data were extracted using the prediction tool ChemAxon (https://chemaxon.com).

polar atoms, greatly determines the molecular capacity to penetrate cell membranes. Given that a PSA $\leq$ 140 Å is required for good membrane permeability [27], drugs were categorized by PSA $\leq$ 140 Å, and >140 Å. For the four remaining properties (i.e., MW, hydrogen acceptor count, hydrogen donor count, and Rb count), a relevant biological rationale for categorization was lacking. MW has a glomerular filtration cut-off of ~40 kDa, but all drugs selected are small molecules with MW < 1.5 kDa [28,29]. Moreover, CLr generally increases with higher hydrogen bonding ability and Rb count, but well-founded cut-off values have not been suggested [30]. Thus, for these four properties, drugs were divided into two categories: $\leq$ median and > median. Table 2 shows the categorization of all 20 drugs based on their net excretion profile and physicochemical properties.

Systematic review protocol and search strategy

For our meta-analysis, we systematically collected and reviewed literature according to the Systematic Review Center for Laboratory animal Experimentation (SYRCLE) (www.syrcle.nl) and PRISMA guidelines (Table S1 in the supplemental information online). The protocol was previously published in the PROSPERO registry for systematic reviews (www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018117425), and was amended in the following way: (i) instead of scoring the quality of the included studies and excluding those studies with a low score, we assessed the study quality using the standard criteria Y/N/U and did not exclude any papers for the meta-analysis; (ii) in addition to humans, mice, and rats, standard weights were also imputed for other species (see 'Data extraction' section); (iii) MD was chosen as effect measure because all extracted CLr values were expressed in the same unit of measurement (ml/min); (iv) because of a lack of data, subgroup analyses based on age, animal strain, sex, and dosage could not be performed; and (iv) two post-hoc analyses were added to the meta-analysis to study the effect of drug protein binding and drug dose.

Searches for relevant literature were performed using the PubMed and EMBASE (through EMBASE.com) databases (April–June 2018, see Table S2 in the supplemental information online for the exact search dates) with the search strings available in Table S3 in the supplemental information online. In addition, references were extracted from the review articles by Dorne *et al.* [31], Walton *et al.* [32], Paine *et al.* [23], and Srinivas *et al.* [33].

Screening and study selection

Using the Early Review Organizing Software (EROS, www.eros-systematic-review.org/), screening of studies based on their title and abstract was performed in randomized order by two independent reviewers. Discrepancies were resolved by inclusion for full-text screening. Title and abstract screening was followed by full-text screening, performed by one reviewer (C.P.C.), and checked for inconsistencies by the second one (K.J). Discrepancies were resolved by consultation with a third reviewer. Study inclusion was based on the following criteria: (i) full-length, original publications of primary studies (in vivo studies, clinical trials); (ii) healthy subjects from any mammalian species; (iii) all drug dosages, timings, and frequencies; (iv) all languages; (v) all publication dates; and (vi) all studies reporting CLr values or an outcome measure related to CLr [i.e., total clearance (CLt), total clearance with bioavailability correction (CL/F), or area-under-the-curve (AUC)]. Excluded papers comprised or contained: (i) reviews, literature-based *in silico* studies, conference papers, commentaries or letters to the editor, and papers with abstract only; (ii) duplicate papers; (iii) in vitro or *ex vivo* studies; (iv) diseased subjects or subjects that had undergone any kind of transplantation; (v) subjects exposed to intervention(s) that might affect CLr; (vi) pre- and neonatal data, or pregnant subjects; (vii) the target drug given as co-medication; (viii) the target drug being chemically modified; and (ix) only outcome measures not related to CLr.

Data extraction

Data extraction was performed by one reviewer (C.P.C.) and checked for inconsistencies by the second reviewer (K.J.). Data were directly extracted from tables or text, when possible. When reported in graphs only, data were extracted using a digital screen ruler (ImageJ 1.46r, National Institutes of Health, USA). The primary outcome measure of this study was CLr (ml/min, or ml/min/kg or ml/min/1.73 m^2 when conversion to ml/min was possible). When human CLr values were reported normalized to body surface area (BSA) and the subject's BSA was not given, we assumed 1.73 m^2. When CLr was not provided, we extracted either CLt, oral clearance (CL/F), or AUC. Given that only renally excreted drugs with no or negligible hepatic clearance were included, we assumed that CLr≃CLt and CL/F. When AUC was extracted, CLt was manually calculated using Eq. (2):

$$CLt = Dose/AUC. \quad (2)$$

Other measures extracted from the studies were: number of subjects included; weight; ethnicity/strain; sex; age; dose; route of administration; preconditioning (e.g., fasting or anesthesia); and the formulae used to calculate CLr, CLt, CL/F, or AUC. For weight and age, we extracted the mean values. In cases where a mean could not be calculated, we used the median. When weight was not reported, we imputed standard average weights for the following species taking into account existing literature: 70 kg for humans [34]; 0.3 kg for rats [34]; 0.025 kg for mice [34]; 3.3 kg and 6.5 kg for 3- and 16-year-old monkeys, respectively [35]; 10 kg for dogs [34]; and 32.5 kg for miniature pigs [36].

Quality assessment

A priori, we designed a customized list of criteria to assess the quality of the included studies. These criteria were based on SYRCLE's risk of bias tool [37]. Two independent reviewers assessed the quality of the papers in randomized order based on these criteria: (i) Is the weight of the subjects clearly reported? No (N) was assigned to papers that reported weights as ranges; (ii) Is the number of subjects clearly reported? No (N) was assigned to papers that reported the number of subjects as ranges; (iii) Are all population baseline characteristics given (i.e., sex, ethnicity/strain, and age)? (iv) Are exposure protocols clearly described [i.e., dose, route of administration (RoA), and timing of treatment]? (v) Is the correct formula used to calculate CLr/CLt reported? (vi) Is the study free of co-administration of drugs that might affect CLr, such as anesthetics? (vii) Are timing and frequency of blood and urine collection reported? (viii) Are incomplete outcome data adequately addressed? (ix) Is the study apparently free of selective outcome reporting? And (x) is the study apparently free of other problems that might result in high risk of bias (including conflicts of interest)?

Data processing and synthesis

Figure 1 illustrates all steps taken for data processing and synthesis. A meta-analysis was performed to quantify differences in renal drug clearance between animals and humans, to relate these interspecies differences in renal drug clearance to the drug excretion profile (glomerular filtration versus active secretion), and to relate these interspecies differences in renal drug clearance to the drug physicochemical properties (Table 2).

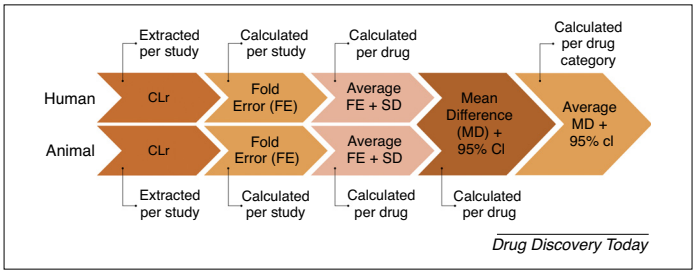

FIGURE 1

Scheme of the meta-analysis data processing and synthesis. Abbreviations: CI, confidence interval; CLr, renal clearance; SD, standard deviation.

To process data for meta-analysis, per drug, all extracted ('observed') human CLr values (ml/min) were plotted on a log scale against body weight (kg). Following Kleiber's Law, the regression line was constrained to a slope of 0.75 (Eq. 3):

$$Expected\ CLr = a * (BW)^{0.75} \quad (3)$$

With the slope and the resulting y-intercept (a), we determined the expected CLr value that corresponds to the body weight of any given species. This expected CLr value can be understood as a hypothetical value for humans with the weight of the respective animal species, but it can also be seen as the value that would be expected from an animal species with perfect predictive value. In other words, allometric principles and human data were used to interpolate CLr values of 'perfect' animal species. Next, we determined the prediction accuracy for every literature-derived ('observed') animal and human CLr value, by calculating a fold-error (FE) (Eq. 4):

$$FE = \frac{Observed\ CLr}{Expected\ CLr} \quad (4)$$

Thus, we converted all CLr values extracted to FE values. These FEs were used to calculate the aFE and standard deviation (SD) per drug and per species. In other words, we averaged the FEs from all included studies that determined the CLr of the same drug in the same animal species, or in humans. Subsequently, using RevMan 5 (Review Manager, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and a random effects meta-analysis, we expressed the difference in aFE per drug between each animal species versus humans as mean difference and its 95% confidence interval (MD [95% CI]).

First, to measure the overall difference in aFEs between animal species and humans, we computed a pooled MD for all drugs taken together. The significance of these pooled MDs was Z-score based. Second, to relate differences in aFE to physicochemical properties, all drugs were grouped in the prespecified drug categories shown in Table 2, and a pooled MD was determined for each subgroup per species. Differences between subgroups within a drug category were identified by testing the heterogeneity across subgroups against a Chi^2 distribution. Finally, I^2 values were used as a general measure of heterogeneity in the analyses.

Effect assessment of protein binding and drug dose

Aside from physicochemical drug properties, protein binding and drug dose can influence drug CLr [38–40]. Protein binding can affect the excretion of drugs because only the unbound plasma

TABLE 2

Drug categorization according to their net excretion profile and physicochemical properties

Physicochemical property	Subgroup	Examples
Net excretion profile	Filtered	Cefazolin, fluconazole, gabapentin, sinistrin, vancomycin
	Secreted	Acyclovir, atenolol, aztreonam, carumonam, cefadroxil, ceftizoxime, cephalexin, enprofylline, famotidine, levofloxacin, metformin, ofloxacin, sotalol, sulpiride, tenofovir
Physiological charge	Anionic	Aztreonam, carumonam, cefazolin, ceftizoxime, levofloxacin, ofloxacin
	Cationic	Atenolol, famotidine, metformin, sotalol, sulpiride, vancomycin
	Uncharged	Acyclovir, cefadroxil, cephalexin, enprofylline, fluconazole, gabapentin, sinistrin, tenofovir
MW	≤Median (354 Da)	Acyclovir, atenolol, cephalexin, enprofylline, famotidine, fluconazole, gabapentin, metformin, sotalol, sulpiride
	>Median (354 Da)	Aztreonam, carumonam, cefadroxil, cefazolin, ceftizoxime, levofloxacin, ofloxacin, sinistrin, tenofovir, vancomycin
LogD	≤0	Acyclovir, atenolol, aztreonam, carumonam, cefadroxil, cefazolin, ceftizoxime, cephalexin, enprofylline, famotidine, gabapentin, levofloxacin, metformin, ofloxacin, sinistrin, sotalol, sulpiride, vancomycin
	>0	Fluconazole, tenofovir
PSA	≤140	Acyclovir, atenolol, cefadroxil, cephalexin, enprofylline, fluconazole, gabapentin, levofloxacin, metformin, ofloxacin, sotalol, sulpiride
	>140	Aztreonam, carumonam, cefazolin, ceftizoxime, famotidine, sinistrin, tenofovir, vancomycin
H^+ acceptor count	≤Median (6.5)	Atenolol, carumonam, cefadroxil, cephalexin, enprofylline, fluconazole, gabapentin, metformin, sotalol, sulpiride
	>Median (6.5)	Acyclovir, aztreonam, cefazolin, ceftizoxime, famotidine, levofloxacin, ofloxacin, sinistrin, tenofovir, vancomycin
H^+ donor count	≤Median (3)	Acyclovir, atenolol, aztreonam, cefazolin, ceftizoxime, cephalexin, enprofylline, fluconazole, gabapentin, levofloxacin, ofloxacin, sotalol, sulpiride, tenofovir
	>Median (3)	Carumonam, cefadroxil, famotidine, metformin, sinistrin, vancomycin
Rb count	≤Median (5)	Acyclovir, cefadroxil, ceftizoxime, cephalexin, enprofylline, fluconazole, gabapentin, levofloxacin, metformin, ofloxacin, sotalol
	>Median (5)	Atenolol, aztreonam, carumonam, cefazolin, famotidine, sinistrin, sulpiride, tenofovir, vancomycin

concentration of drugs can be cleared effectively. CLr is a virtual parameter that measures the volume of blood from which the drug is completely cleared within a certain amount of time. This measure is independent of dose, unless plasma protein binding or elimination mechanisms become saturated with high doses. Such mechanisms would be reflected in an increase in CLr in case of saturated protein binding or reabsorption, or a decrease in CLr in case of saturated active secretion.

Using Eq. (5), we calculated interspecies differences in protein binding:

$$\Delta \text{ protein binding} = (\bar{x}\ \textit{animal protein binding}) - (\bar{x}\ \textit{human protein binding}) \quad (5)$$

where $\bar{x}$ is the mean species-specific protein-binding value obtained from the literature (Table S4 in the supplemental information online). Protein-binding data was derived from literature other than the studies included in this systematic review, and species-specific protein-binding data was not available for all drugs. By means of Spearman correlation tests, differences in protein binding were related to drug aFEs to investigate whether protein binding was the cause of interspecies differences in CLr.

To investigate any dose effect on CLr, we plotted all extracted CLr values to the applied drug dose (i.e. injection or corrected oral dose). To compare doses across species, we converted the applied dose into the human equivalent dose ($mg/kg^{0.75}$).

Results

Study inclusion and characteristics

In total, 1978 studies were retrieved from all 20 searches in PubMed and EMBASE, and the above-mentioned review papers. After removal of duplicates and screening on title and abstract, 453 articles were fully screened, of which 263 articles met all inclusion criteria (Fig. 2). Of note, 12 studies were additionally identified as duplicates because they studied more than one of the selected drugs and, hence, appeared in more than one search. Thus, a total of 251 studies were included in this systematic review. For the meta-analysis, included studies provided sufficient data on CLr values in humans ($N = 242$ from 20 drugs), mice ($N = 24$ from 13 drugs), rats ($N = 145$ from 18 drugs), rabbits ($N = 22$ from seven drugs), dogs ($N = 35$ from 13 drugs), and monkeys ($N = 15$ from eight drugs). Given limited drug clearance data for guinea pigs ($N = 2$ from two drugs), cats ($N = 2$ from two drugs), pigs ($N = 4$ from two drugs), and horses ($N = 1$ from one drug), we excluded them from the meta-analysis. Extracted data from all 251 articles is listed in Table S5 in the supplemental information online.

Reporting quality and risk of bias assessment

All papers included were assessed on reporting quality and risk of bias. The assessment criteria and results can be found in Fig. 3, and in Table S6 in the supplemental information online in more detail. Weight of subjects and/or animals and study sample size were described in 56% (148/263 studies) and 89% (235/263 studies) of studies, respectively. Surprisingly, only 84 papers (32%) reported all population baseline characteristics (sex, ethnicity/strain, and age). However, most studies (99%, 259/263) clearly described the exposure protocols, and only 23 studies (9%) did not report the formula used to calculate CLr. One study was qualified as 'unclear' because the formula was referenced from an inaccessible source. To prevent bias of drug–drug interactions, we excluded studies that involved co-administration protocols. However, the use of

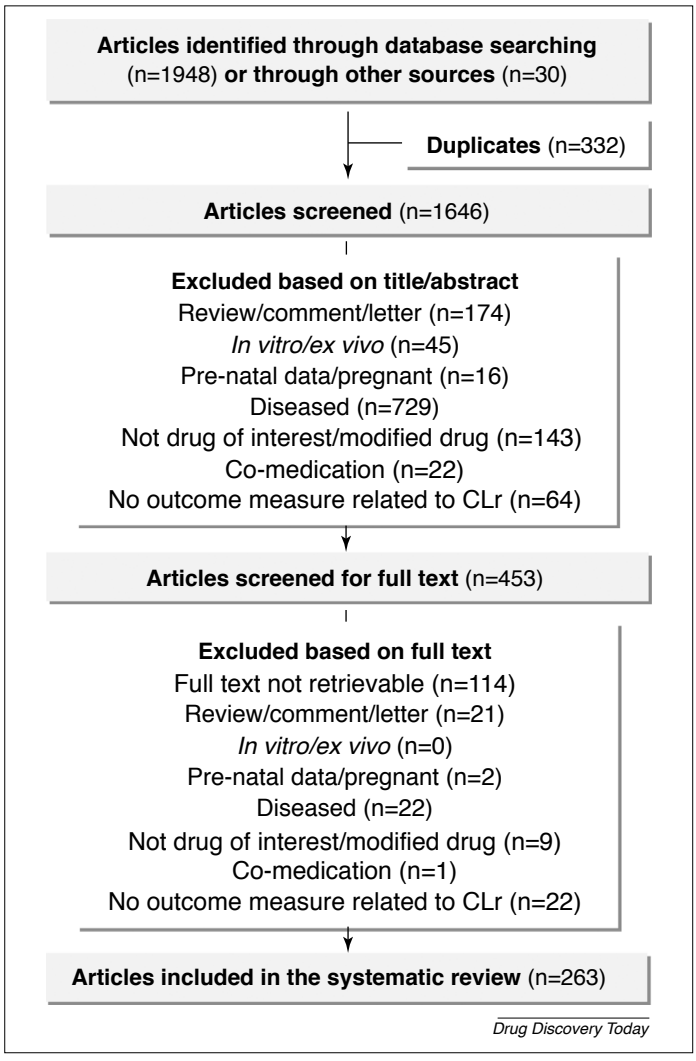

FIGURE 2

Flowchart of the study selection process. This flowchart comprises outcomes of 20 separate searches (i.e., one search for each drug).

sedatives also requires vigilance because of decreases in blood pressure and possible interactions. In total, 43 studies (27%) included anesthesia in the treatment regime that concerned only animal studies; 34 studies (13%) did not involve anesthesia or allowed for recovery before drug administration. In the remaining 183 studies (70%), drug co-administration or the use of sedatives was unclear or not reported. Timing and frequency of both blood and urine collection were clearly described in 97% (254/263) of studies. We also assessed selective outcome reporting, but most studies (96%, 251/263) did not mention the original protocol and, thus, it was unclear whether all intended outcomes had been reported. Only 11 studies referenced their original protocols, which were in conformity with the final publications. Finally, 58% (152/263) of studies had an unclear risk towards other biases, whereas 29% (77/263) had problems that could result in high risk of bias. Most of these problems were conflicts of interest: 62 studies (24%) reported that they had been funded by companies, or that authors were employed in industry. Other problems involved the exclusive inclusion of subjects with a certain genotype that did not represent the general population, and *ex vivo* clearance measurements, among others. Of note, publication bias could not be assessed because of limited data.

The allometric exponent 0.75 is valid for interspecies scaling of CLr

For each drug included, linear regression analysis showed a high correlation between body weight and CLr across species, with an average R^2 of 0.944 (Table S7 in the supplemental information online). The average slope was 0.72 (± 0.08), which supports the validity of Kleiber's Law and the symmorphosis of metabolic waste production and removal systems. Therefore, we considered our hypothesis confirmed and consequently used all human CLr data and simple allometry with a fixed exponent of 0.75 to interpolate the expected CLr for any given weight (Fig. 4).

Overall interspecies differences in CLr

For each study included, FEs were calculated as the ratio between observed and expected CLr and averaged per drug. The resulting aFEs were 1.00–1.31 for humans, 0.45–3.05 for mice, 0.77–3.10 for rats, 0.28–1.61 for rabbits, 0.27–3.40 for dogs, 0.57–1.78 for monkeys, 0.16–0.89 for guinea pigs, 0.74–1.20 for cats, 0.97–1.05 for pigs, and 4.06 for horses.

To assess whether animal deviations were the result of real interspecies differences, or solely because of intraspecies or data variability, we calculated the MD [95% CI] in aFE between animals

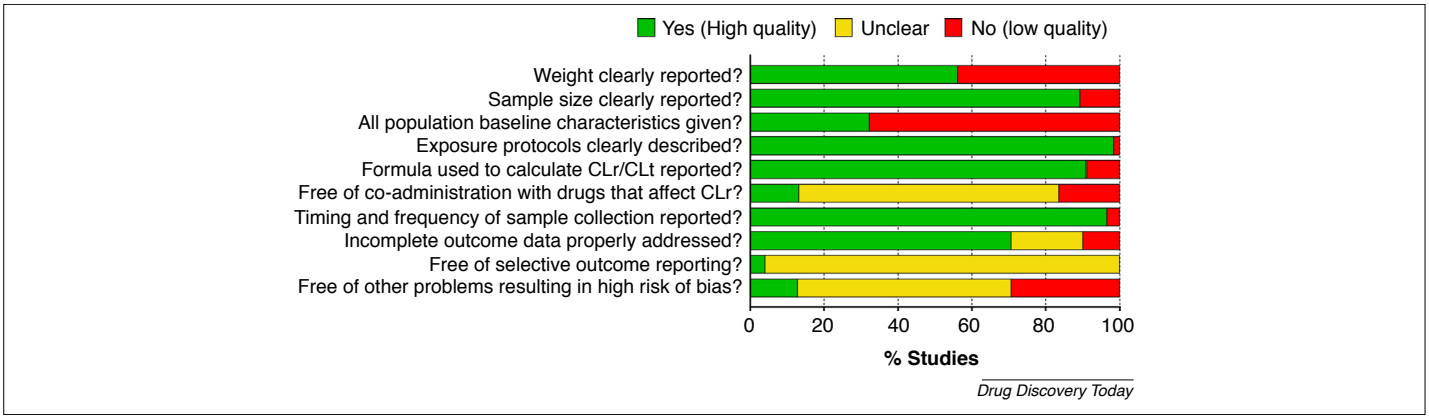

FIGURE 3

Reporting quality and risk of bias assessment of the studies included in this systematic review. Abbreviations: CLr, renal clearance; CLt, total clearance.

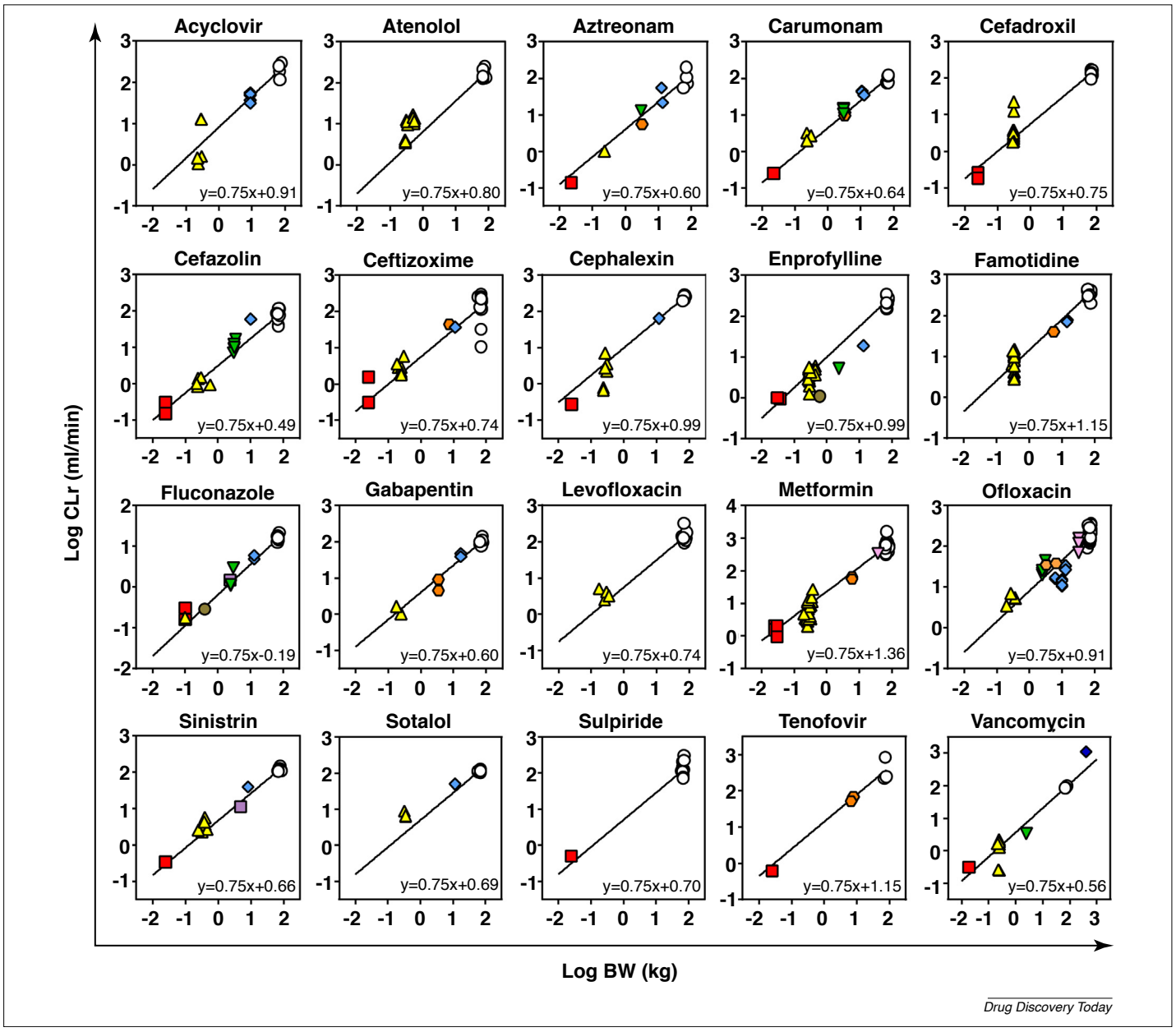

FIGURE 4

Regression lines used to apply simple allometry for all 20 drugs. The slope of all regression lines was constrained to be 0.75. The dots represent data for mice (red), rats (yellow), rabbits (green), dogs (light blue), monkeys (orange), guinea pigs (brown), cats (purple), pigs (pink), horses (dark blue), and humans (white). Abbreviations: BW, body weight; CLr, renal clearance.

and humans for each drug. Fig. 5 shows the forest plots for mice (Fig. 5a), rats (Fig. 5b), rabbits (Fig. 5c), dogs (Fig. 5d), and monkeys (Fig. 5e). For all drugs taken together, the pooled MD in aFE was 0.01 [–0.23, 0.26] for mice, 0.47 [0.17, 0.77] for rats, 0.17 [–0.12, 0.45] for rabbits, 0.23 [–0.13, 0.56] for dogs, and –0.08 [–0.33, 0.16] for monkeys. Thus, most species showed no significant overall difference compared with humans. Only for rats did the overall pooled MD indicate that aFEs were significantly higher than in humans ($Z = 3.20$, $P = 0.001$). The meta-analyses for mice, rabbits, dogs, and monkeys resulted in overall Z scores of 0.10 ($P = 0.92$), 1.13 ($P = 0.26$), 1.23 ($P = 0.22$), and 0.68 ($P = 0.50$), respectively. Of note, there was moderate to high heterogeneity between drugs, as reflected by I^2 statistics of 35%, 83%, 57%, 94%, and 73% for mice, rats, rabbits, dogs, and monkeys, respectively. To gain insight into the sources of the high between-drug heterogeneity, we performed subgroup analyses to assess excretion profile and various physicochemical drug properties as sources of heterogeneity, as described per animal later. In addition, to test the robustness of our meta-analysis, we performed sensitivity analyses regarding the inclusion of outliers, computed SDs, assigned weights, CLt or CL/F as a measure of CLr, as well as route of administration. Some analysis outcomes were ambivalent because of limited data and, hence, are not discussed further. The outcomes of all subgroup and sensitivity analyses can be found in the Tables S8–S12; the results of the subgroup analyses are also summarized in Fig. 6.

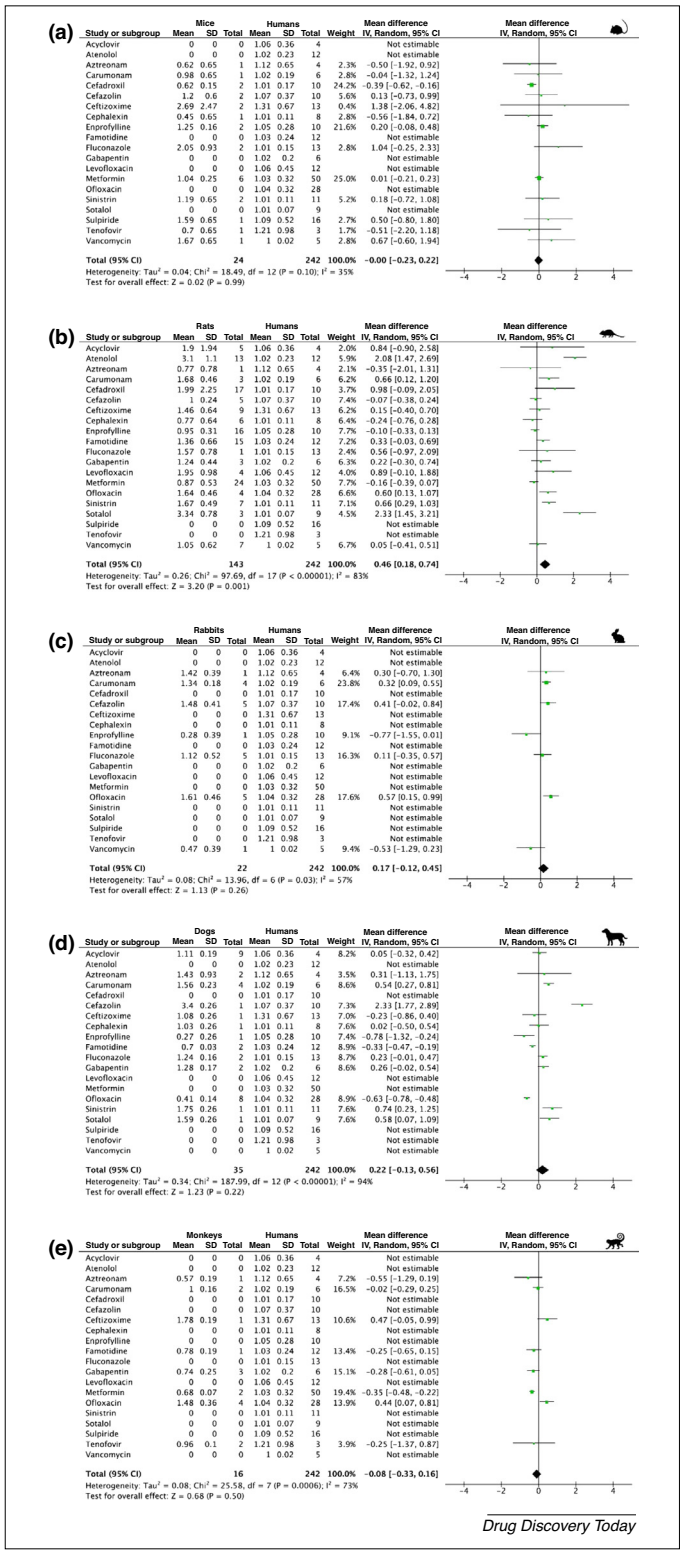

FIGURE 5

Forest plots depicting the mean difference in average fold errors (aFE) of CLr in mice **(a)**, rats **(b)**, rabbits **(c)**, dogs **(d)**, and monkeys **(e)** compared with humans for the 20 renally excreted drugs included in this study. Abbreviations: CI, confidence interval; SD, standard deviation.

Interspecies differences in CLr related to drug properties

Mice

The analysis of 13 individual drugs showed that mouse aFEs were comparable to human aFEs. Only the CLr of cefadroxil was significantly lower in mice than in humans (MD=–0.39 [–0.62, –0.16]). Subgroup analyses based on excretion profile and physicochemical properties did not show any differences between subgroups, except for drugs with higher MW (MD=–0.29 [–0.50, –0.08]), which was maintained after including outliers and only including CLr data (Table S8 in the supplemental information online). The pooled MD did not become significant in any sensitivity analysis.

Rats

For rats, the aFEs of atenolol, carumonam, ofloxacin, sinistrin, and sotalol were significantly different from those of humans. In all cases of significance, the observed rat CLr values were higher than the expected CLr values, leading to higher aFEs. In particular, aFEs of atenolol and sotalol were noticeably high, with an MD of 2.08 [1.4–2.69] and 2.33 [1.45–3.21], respectively. When performing subgroup analyses on physicochemical drug properties, the MDs of all subgroups were significant except for anionic drugs, uncharged drugs, drugs with LogD >0, and drugs with an H^+ donor count > median. With regard to the excretion profile, net secreted drugs were significantly different. Most sensitivity analysis outcomes were in line with the main analysis, except for when only i.v. and CLr data were included (Table S9 in the supplemental information online). In the latter case, also the pooled MD lost significance (P = 0.06).

Rabbits

For rabbits, the aFE values of carumonam and ofloxacin were significantly higher than for humans, with MDs of 0.32 [0.09, 0.55] and 0.57 [0.15, 0.99], respectively. Both drugs are anionic, with MW > median. Subgroup analysis based on physiological charge indicated that only rabbit aFEs for anionic drugs were different from human aFEs (MD = 0.38 [0.20, 0.56]). In addition, the Chi^2 distribution revealed significant heterogeneity among the subgroups (i.e., anionic versus cationic versus uncharged), whereas the I^2 score for anionic drugs dropped to 0% (Table S10 in the supplemental information online). The significant MD for anionic drugs was lost when only i.v. or CLr data were included. Other MDs were mostly insignificant, except when data were analyzed without computed SDs. In this case, new significances occurred in subgroup analyses, and the pooled MD was also significant. However, only four drugs were included in this sensitivity analysis.

Dogs

For dogs, 13 drugs were included, out of which seven (carumonam, cefazolin, enprofylline, famotidine, ofloxacin, sinistrin, and sotalol) showed a significant MD compared with humans. However, the pooled MD was not significant. Deviations were highly heterogeneous between drugs (I^2 = 94%). In particular, cefazolin deviated with an MD of 2.33 [1.77, 2.89], but this was only based on one value. Regarding the net excretion profile, aFEs of net filtered drugs were significantly higher compared with those of humans (MD = 0.85 [0.12,1.58]). In addition, the Chi^2 score of net filtered versus net secreted drugs was significant (5.29, P = 0.02). The significance of net filtered drugs was maintained in all sensitivity analyses except when only i.v. data were included (MD = 1.08 [–0.03,2.20]) (Table S11 in the supplemental information online). Net secreted drugs showed no overall significance (MD=–0.09 [–0.41, 0.24]).

Monkeys

For monkeys, only the aFEs of metformin and ofloxacin were different from those of humans, with a relatively small but significant MD

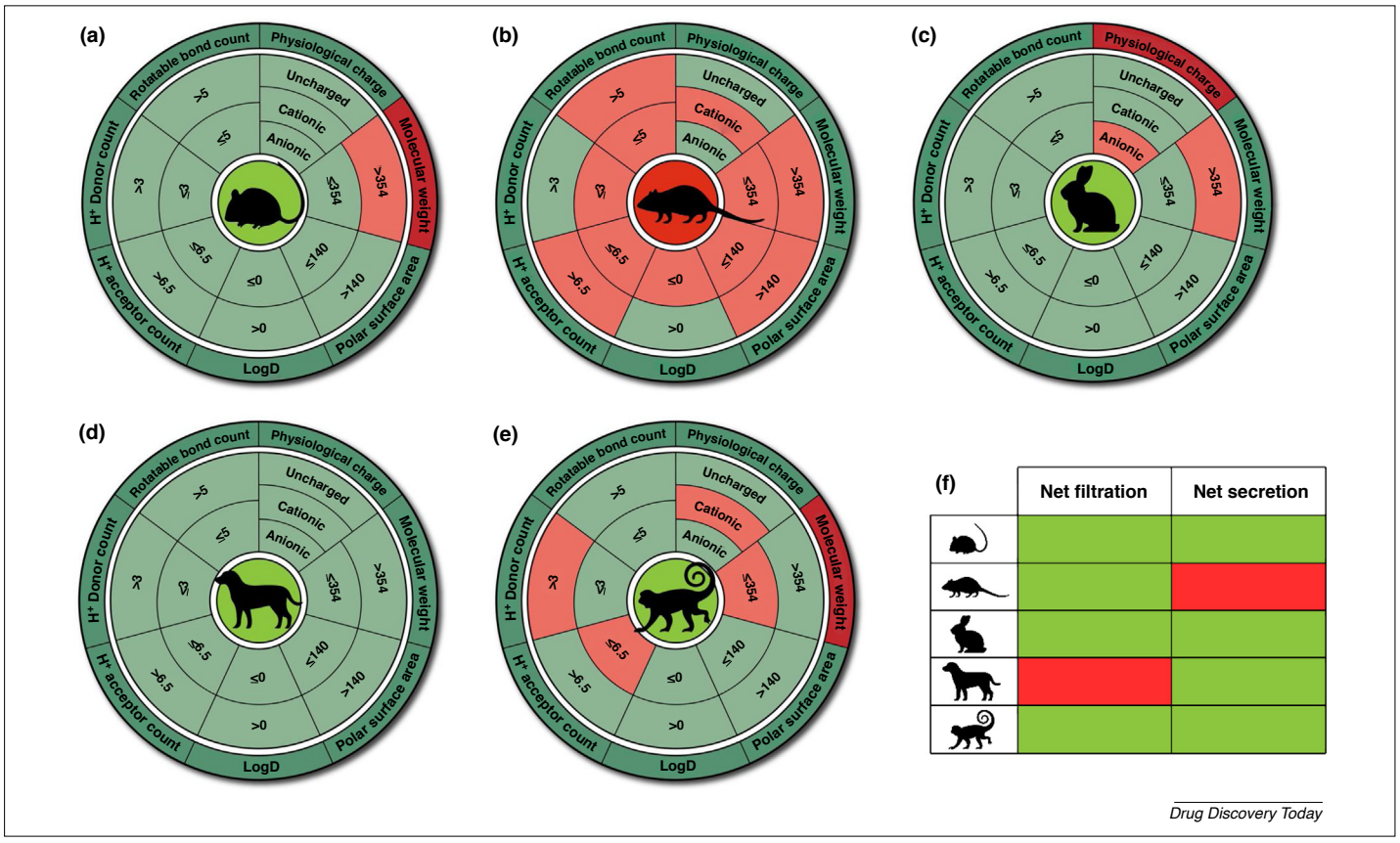

FIGURE 6

Color scheme summary of mean differences in CLr in mice **(a)**, rats **(b)**, rabbits **(c)**, dogs **(d)**, and monkeys **(e)** compared with humans for the studied physicochemical drug properties. **(f)** Summary of the mean differences in renal clearance (CLr) in the studied species for net filtered and net secreted drugs. Subgroups depicted in red showed relevant mean differences (i.e., not overlapping with 0).

of –0.35 [–0.48, –0.22] and 0.44 [0.07, 0.81], respectively. Subgroup analyses revealed significant MDs for cationic drugs, as well as for H^+ acceptor ≤ median, H^+ donor > median, and MW ≤ median. However, all MDs were <0.4 and based on fewer than three drugs per category (Table S12 in the supplemental information online). Heterogeneity among the subgroups was small, except for the Chi^2 distribution in MW (5.93, P = 0.01).

Plasma protein binding and dose effect

Besides physicochemical properties, we also investigated the influence of plasma protein binding and dose on interspecies differences in CLr. In all species, aFEs tended to be >1 when protein binding was higher in humans than in animals, and <1 when protein binding was higher in animals than in humans. However, only in dogs was the correlation between protein binding differences and aFEs significant ($P = 0.009$) (Fig. S1 in the supplemental information online). The highest differences in protein binding between dogs and humans were found for cefazolin and aztreonam (91% versus 47% and 62% versus 20%), followed by carumonam and ceftizoxime, which bind two to three times more in humans than in dogs. In rodents, protein binding of aztreonam was 22–23% higher than in humans. Interestingly, 47% of enprofylline is protein-bound in human plasma, compared with 78% in rat plasma, and only 18% in mouse plasma (Table S4 in the supplemental information online). Yet, neither rodent species showed a significant correlation between protein-binding differences and aFEs.

When plotting all extracted CLr values against the human equivalent dose, we noted that, for 13 out of the 20 drugs included, animal studies were performed with higher doses than the respective clinical studies (Fig. S2 in the supplemental information online). Nonetheless, we observed no clear effect of drug dose on CLr. Only the applied doses of acyclovir and atenolol in rats showed decreasing CLr values with higher doses, whereas levofloxacin showed an increase in CLr. However, these observations were based on individual studies.

Discussion

Renal clearance follows Kleiber's Law based on symmorphosis of waste production and removal

Interspecies scaling is a key tool for prediction of human PK at multiple stages of the preclinical drug development process [19,26]. In literature, exponents for the best fit between animal and human CLr data vary substantially, but mostly scatter around 0.75, a value with rich scientific history (Box 1). Based on Kleiber's Law and the principal of symmorphosis of waste production and removal, we hypothesized that perfect predictive models for human CLr should align with human data using an exponent of 0.75. Consequently, deviations of experimental data (e.g., in fold errors) should allow the quantification of specific

interspecies differences in renal drug handling. Systematically collected literature-derived CLr values for 20 renally excreted drugs in five different species aligned well with the slope of 0.75: linear regression analysis for all species data per drug revealed an optimal slope of 0.72 (±0.08) on average. This underscores the validity of our hypothesis that CLr is set by metabolic rate and, hence, the validity of our approach to calculate expected CLr values.

Rats are suboptimal models for CLr prediction

To account for intraspecies and data sampling variability, we calculated MDs between animal and human aFEs. Heterogeneity between the drugs was relatively high, but, given the diversity of all drugs included, this was a foreseeable outcome and, in fact, enabled the relation of MDs to excretion profile and drug properties by means of subgroup analyses. Overall, however, we found no significant pooled MDs for mice, rabbits, dogs, and monkeys, suggesting that these species are suitable as prediction models for human CLr. By contrast, rat CLr data mostly deviated from the expected CLr, especially for atenolol and sotalol, and, thus, human CLr would be overestimated. Subgroup analysis narrowed down the significance to the physicochemical properties of cationic charge, LogD >0 and a H^+ donor count ≤3, whereas other subgroups lost significance. However, all significant subgroups comprised both atenolol and sotalol. Their deviation might be explained by the fact that both drugs are excreted unchanged in rat urine to a lesser extent than in humans. Humans excrete 85–100% of atenolol unchanged, but only 60% is recovered unchanged from rat urine, whereas the other fraction is hepatically metabolized [41]. Likewise, ofloxacin, another drug with a significantly different aFE in rats compared with humans, is metabolized to a greater extent in rats [32]. This strengthens the speculation mentioned in the Introduction that exponent variations might arise mainly from differences in hepatic metabolism rather than renal clearance. However, exclusion of atenolol and sotalol did not offset the significance of pooled MDs for rats. Only when exclusively i.v. or CLr data were included were significances in various subgroups lost (Table S9 in the supplemental information online). In the case of the latter, the pooled MD also became insignificant, suggesting that the identified interspecies differences have their source in processes of drug disposition other than renal drug handling, such as drug absorption, tissue distribution, and biliary excretion. Nonetheless, no matter the source of differences between rats and humans, our meta-analysis suggests that rats constitute an inadequate model for human CLr prediction compared with other species, which is in line with earlier studies [26,42]. For instance, Jolivette *et al.* quantified extrapolative outliers for monkeys, dogs, and rats, and showed that the latter were most divergent from human data [26].

Differences in dogs and rabbits are based on distinct excretion profiles

Heterogeneity in the overall analyses was high in rats, dogs, and monkeys. For dogs, we found a significant difference to humans for net filtered drugs, but not for net secreted drugs. This outcome was maintained in all sensitivity analyses, except when only i.v. data was included ($P = 0.05$). Subgroup analysis did not identify any physicochemical drug property as source of prediction error. A particular outlier was cefazolin, which is cleared more quickly in dogs than in humans. Approximately 91% of cefazolin is bound to proteins in human plasma, but only 47% in dog plasma (Table S4 in the supplemental information online) [23,43–48]. Therefore, a higher fraction is free for filtration in dogs, which might explain the higher CLr. For rabbits, there was moderate heterogeneity in the overall analysis. Subgroup analysis showed that aFEs of anionic drugs were significantly different from human aFEs. All anionic drugs showed higher CLr values in rabbits than in humans, with significance for carumonam and ofloxacin. Kita *et al.* showed that 40% of carumonam is secreted in rabbits, and to some extent in rodents and monkeys. By contrast, in dogs and humans, carumonam was reported to be excreted solely by filtration [49]. Our data confirmed the differences for rabbits and rats compared with humans, but we also found the CLr of carumonam to be significantly higher in dogs. The reported difference in excretion profiles between rabbits and rodents could be explained by species differences in organic anion transporter 1 (OAT1)-mediated excretion of anionic drugs. Substrate-specific binding differences to OAT1 have been already described (e.g., the clearance of acyclic nucleoside phosphonates revealed different Km values between species [50]). By contrast, observed deviation of canine data is in line with the above-described finding that CLr of net filtered drugs is generally higher in dogs than in humans.

Murine and simian CLr are scalable to human CLr

The CLr of mice and monkeys showed good comparability to human CLr. Both revealed a significant subgroup in MW, with drugs >354 kDa being significant for mice and ≤354 kDa for monkeys. However, these differences are of relatively minor importance when taking into account that all drugs included are small molecules. For mice, this was the only difference compared with humans, although SDs were relatively high. In monkeys, we found more significant MDs within the subgroup analyses, although all MDs were low. Notably, our data suggests that simian CLr for cationic drugs with a high H^+ donor count is lower than that in humans, whereas Shen *et al.* compared expression levels and various properties of OCT2, and multidrug and toxic extrusion 1 and 2 K (MATE1 and MATE2 K) between cynomolgus monkeys and humans, and declared them suitable models [17]. Moreover, significance was mainly determined by metformin and based on limited data (e.g., two cationic drugs with three studies included in total); thus, we consider these MDs nonrelevant and monkeys to be adequate models.

Interspecies differences in relation to protein binding and drug dose

All animal species showed a trend towards greater aFEs when differences in protein binding were higher, although linear correlation was only significant in dogs. The significance was mainly caused by cefazolin, as discussed earlier. Thus, interspecies differences in CLr observed in this study were not relatable to interspecies differences in protein binding.

Converting drug doses into human equivalent doses showed that animals tended to be treated with higher doses than were humans, but most doses fell into comparable ranges. The applied doses only affected the CLr measurements of atenolol and acyclovir in rats, which showed decreasing CLr with higher doses. However, we are unable to pinpoint specific doses that induced

saturated protein binding or elimination. Therefore, we refrain from definite conclusions, and would like to highlight the generally valid guideline to inter- and extrapolate human CLr from dose ranges rather than a single dose, as well as from two different species [12,24].

Study limitations

Unfortunately, because of the lack of data, a relation between interspecies differences in CLr and physicochemical drug properties was only possible to a limited extent. In most cases, individual drugs were the determining factor, but their significance was consistently in line with literature. Moreover, we could not explore the role of subject characteristics, such as ethnicity/strain, age, or gender, on interspecies differences in CLr. Such characteristics have previously been shown to affect CLr, and their evaluation could have shed more light on our results if more data were available [51,52]. Furthermore, for studies where CLr (mg/ml/kg) as a primary outcome measure, or body weight were not given, we applied a set of assumptions (e.g., CLr≃CLt and CL/F for renally excreted drugs) and an average weight. A potential bias of the former is reflected in the loss of significances when only i.v. or CLr data were included in the respective sensitivity analyses (Tables S8–S12 in the supplemental information online). Also, protein binding can affect the excretion of drugs; thus, interspecies comparisons of CLr for unbound drugs would have been a better approach for our meta-analysis. Unfortunately, most studies did not provide information on protein binding or free fraction. Therefore, we used CLr data estimated from total plasma concentration to yield more data, and the effect of plasma protein binding was investigated empirically, based on data from other literature.

Most studies included were original preclinical studies and, hence, rather old; low reporting quality and technical inaccuracies pose a potential risk of bias. Nonetheless, our findings are in line with existing literature, and this study constitutes an innovative application of systematic review and meta-analysis principles: the systematic use of existing (pre)clinical data for meta-analyses can help in the reduction of animal experiments, both as an animal-free research method itself and as a prospective aid for the selection of adequate animal models in drug development.

Concluding remarks

In this systematic review and meta-analysis, we showed that simple allometric scaling with a scaling exponent of 0.75 is a suitable method for the prediction of human CLr for renally excreted drugs. This scaling exponent is contingent on the symmorphosis of metabolic rate and metabolic waste removal. In general, CLr in mice, rabbits, dogs, and monkeys was comparable to human CLr, whereas rat CLr was overall significantly higher, as shown by higher aFEs and significant MDs compared with humans. Based on apparent differences in drug disposition that affect plasma concentration and thereby CLr, we conclude that rats are an inadequate species for preclinical drug clearance testing. In the case of dogs, clearance of net filtered drugs was significantly higher compared with humans, which was partly caused by lower protein binding of cefazolin. Rabbits showed slightly more effective clearance of anionic drugs than did humans. In all species except dogs, subgroup analyses based on physicochemical drug properties led to significant differences, but these differences could not be assigned to the respective drug properties with certainty because of overlapping drug groups and individual drugs as determining factor.

We explored only the predictive value of animal models for the CLr of renally excreted, non-metabolized drugs. Based on our results and supporting literature, we expect interspecies differences to be larger in processes other than CLr that are involved in drug disposition. Therefore, future studies should explore, for instance, the predictive value of animal models for hepatic metabolism.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.drudis.2020.01.018.

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