Man versus Beast: Pharmacokinetic Scaling in Mammals

JOYCE MORDENTI

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Abstract □ Land mammals range in size from the 3-g shrew to the 3000-kg elephant. Despite this 10^6 range in weight, most land mammals have similar anatomy, physiology, biochemistry, and cellular structure. This similarity has allowed interspecies scaling of physiologic properties such as heart rate, blood flow, blood volume, organ size, and longevity. The equation that is the basis for scaling physiologic properties among mammals is the power equation $\mathbf{Y} = a\mathbf{W}^b$, where **Y** is the physiologic variable of interest, **W** is body weight, and log *a* is the y-intercept and *b* is the slope obtained from the plot of log **Y** versus log **W**. Animals commonly used in preclinical drug studies (i.e., mice, rats, rabbits, monkeys, and dogs) do not eliminate drugs at the same rate that humans eliminate drugs; small mammals usually eliminate drugs faster than large mammals. Since drug elimination is intimately associated with physiologic properties that are well described among species, it seems reasonable to surmise that drug elimination can be scaled among mammals. Analysis of drug pharmacokinetics in numerous species demonstrates that drug elimination among species is predictable and, in general, obeys the power equation $\mathbf{Y} = a\mathbf{W}^b$. Early papers on interspecies pharmacokinetic scaling normalized the x- and y-axes to illustrate the superimposability of pharmacokinetic curves from different species. More recently, the x- and y-axes have been left in the common units of concentration and time, and individual pharmacokinetic variables have been adjusted to predict pharmacokinetic profiles in an untested species, usually humans.

Two approaches to interspecies pharmacokinetic scaling have emerged, an allometric approach and a physiologic approach. In the allometric approach, pharmacokinetic profiles in several animal species are described by a pharmacokinetic model (compartmental or noncompartmental), and the pharmacokinetic parameters of the model are scaled by the power equation $\mathbf{Y} = a\mathbf{W}^b$. An estimate for each pharmacokinetic parameter in humans is obtained by solving each power equation for 70 kg. In this approach, each species is viewed as a whole entity; no attempt is made to give physiologic meaning to the pharmacokinetic parameters because it is understood that the underlying anatomy, physiology, and biochemistry have contributed to the shape of the profile. In the physiologic approach, a physiologic flow model is established by reducing the pharmacokinetics of a drug in one animal species to physiologically, anatomically, and biochemically meaningful parameters, such as blood flow to eliminating organs; tissue and fluid volumes; blood-to-plasma and tissue-to-plasma drug concentration ratios; enzyme activities; and drug protein binding. Mass balance equations are written for each compartment, and the resultant differential equations are solved simultaneously. The value for each physiologic parameter in humans is then substituted into the equations, and a reasonable estimate for the pharmacokinetics of the drug in humans is thus obtained.

Interspecies pharmacokinetic scaling can be used to study the underlying similarities (and differences) in drug disposition among species, to predict drug disposition in an untested species, to define pharmacokinetic equivalence in various species, and to design dosage regimens for experimental animal models.

Physiologic Basis for Pharmacokinetic Scaling

Despite obvious differences in outward appearance, most land mammals have similar anatomy, physiology, biochemistry, and cellular structure. This similarity is most apparent when organ size and organ function are studied as a function of species body weight. Huxley[1] demonstrated that plots of organ size (Y) versus body weight (W) produce straight lines on log–log paper. The equation for this straight line is $\log Y = b \log W + \log a$, where b is the slope and $\log a$ is the y-intercept. The antilog of this equation is the power equation $Y = aW^b$, and it has come to be known as the allometric equation.

Adolph[2] compiled 33 equations which related quantitative physiologic properties in various animals to body weight (Table I). Since quantities that are related to a common quantity (i.e., body weight) are related to one another, he proposed that mathematical interrelationships could be developed that equate one physiologic property to another as follows:

$$Y_1 = a_1 W^{b_1} \quad (1)$$

$$Y_2 = a_2 W^{b_2} \quad (2)$$

$$\log W = (\log Y_1 - \log a_1)/b_1 = (\log Y_2 - \log a_2)/b_2 \quad (3)$$

$$\log Y_1 = \log a_1 + b_1/b_2 (\log Y_2 - \log a_2) \quad (4)$$

$$Y_1 = a_1 (Y_2/a_2)^{b_1/b_2} \quad (5)$$

Suppose one needs to calculate urine output as a function of water intake. Using the data in Table I for urine output (U) and water intake (I), one calculates $U = 0.46I^{0.93}$. The slope of the line, 0.93, gives the ratio of the exponential rate constant for the output of urine to the exponential rate constant for the intake of water. An exponent less than 1 means that the rate of urine production is less than the rate of water intake; in other words, water is being eliminated from the body by other pathways, for example, evaporation. The coefficient, 0.46, fixes the value of urine output when water intake is equal to 1 mL/h.

Stahl[3] compiled data on the weight of principal organs of primates, and he compared these data with the data from other mammals (Fig. 1). All primate data fell on a straight line that approximated the allometric relationship for the other mammals. These observations suggest that all mammals have in common a basic kind of "physiologic design" and can be compared as "physical systems."

Physical similarity, in the engineering sense, is defined specifically by sets of invariant dimensionless numbers or criteria of similarity which are obtained by forming quotients of allometric equations. For example, the quotient of renal blood flow as a percentage of cardiac output is determined as follows:

$$\text{renal blood flow/cardiac output} \times 100 = 43.06W^{0.77}/166W^{0.79} \times 100 = 25.9\% \quad (6)$$

where the units of renal blood flow and cardiac output are milliliters per minute and that of weight is kilograms. This relationship reveals that renal blood flow is approximately one-quarter of cardiac output regardless of mammalian spe-

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ble I—Equations Relating Physiologic Properties with Body eights among Mammals[a]

Physiologic Parameter	Allometric Equation[b]
ysiologic rates, mL/h	
Intake of water	$0.01\ W^{0.88}$
Urine output	$0.0064\ W^{0.82}$
Ventilation rate	$120\ W^{0.74}$
consumption, mL STP/h	
Basal	$3.8\ W^{0.734}$
Liver slices	$3.3\ W^{0.77}$
earance, mL/h	
Urea	$1.59\ W^{0.72}$
Inulin	$1.74\ W^{0.77}$
Creatinine	$4.2\ W^{0.69}$
Diodrast	$2.14\ W^{0.89}$
Hippurate	$5.4\ W^{0.80}$
ysiologic periods, h	
Heartbeat duration	$1.19 \times 10^{-5}\ W^{0.27}$
Breath duration	$4.7 \times 10^{-5}\ W^{0.28}$
Gut beat duration	$9.3 \times 10^{-5}\ W^{0.31}$
utput of nitrogen, g/h	
Nitrogen (total output)	$7.4 \times 10^{-5}\ W^{0.735}$
Nitrogen (endogenous output)	$4.2 \times 10^{-5}\ W^{0.72}$
Creatinine nitrogen output	$1.09 \times 10^{-6}\ W^{0.9}$
utput of sulfur, g/h	$1.71 \times 10^{-6}\ W^{0.74}$
mpartment weight, g	
Kidneys	$0.0212\ W^{0.85}$
Brain	$0.081\ W^{0.7}$
Heart	$6.6 \times 10^{-3}\ W^{0.98}$
Lungs	$0.0124\ W^{0.99}$
Liver	$0.082\ W^{0.87}$
Thyroids	$2.2 \times 10^{-4}\ W^{0.80}$
Adrenals	$1.1 \times 10^{-3}\ W^{0.92}$
Pituitary	$1.3 \times 10^{-4}\ W^{0.76}$
Stomach and intestines	$0.112\ W^{0.94}$
Blood	$0.055\ W^{0.99}$
scellaneous	
Tidal volume, mL	$6.2 \times 10^{-3}\ W^{1.01}$
Nephra number	$2\,600\ W^{0.62}$
Diameter renal corpuscle, cm	$8.1 \times 10^{-3}\ W^{0.08}$
Cytochrome weight, g	$1 \times 10^{-4}\ W^{0.84}$
Hemoglobin weight, g	$0.013\ W^{0.99}$
Myoglobin weight, g	$3.9 \times 10^{-5}\ W^{1.31}$

[a] From ref 2. [b] Body weight, W.

s.[4] The residual mass, $W^{0.77}/W^{0.79}$, is not significantly ferent from unity and is eliminated from the equation.

Boxenbaum[5] studied interspecies variations in liver ight and hepatic blood flow. Log–log plots of liver weight iver blood flow versus body weight produced straight lines g. 2), demonstrating the appropriateness of the power ation for describing these data. Additionally, hepatic od flow in all species was ~1.5 $L \cdot min^{-1} \cdot kg^{-1}$ of liver ight. To compare liver function, Boxenbaum selected a mpound that could serve as a measure of the ability of the er to alter exogenously administered substances. He se- ted antipyrine for this investigation for the following asons: (*a*) all known metabolic pathways are oxidative so as reduce confounding variables; (*b*) all available data indi- e first-order kinetics in usual doses; (*c*) the difference tween hepatic blood flow and hepatic clearance is suffi- ntly large so as to permit accurate determination of rinsic clearance; (*d*) the unbound fraction in the blood is entially unity in all species; (*e*) assay methods for antipy- e are essentially specific and accurate; (*f*) in those species

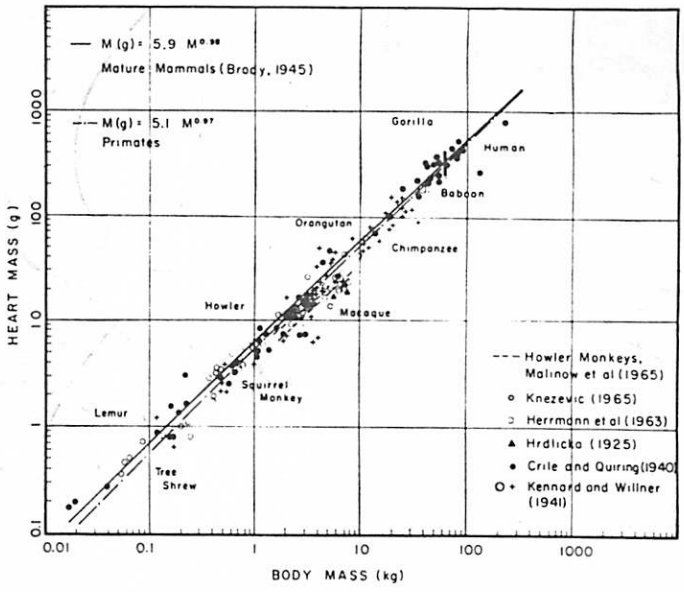


Figure 1—*Heart weights in primates. The points identify authors of data, not kinds of animals, and include a considerable range of body sizes for each kind of primate named. The solid line represents the allometric prediction equation for mammals in the mouse to steer or larger range (ref 52). The dashed line is a statistically fitted line based on 321 primates ranging in weight from ~10 g to 100 kg. The mammalian and primate lines are statistically indistinguishable. Reprinted with permission from ref 3. Copyright 1965 American Association for the Advancement of Science.*

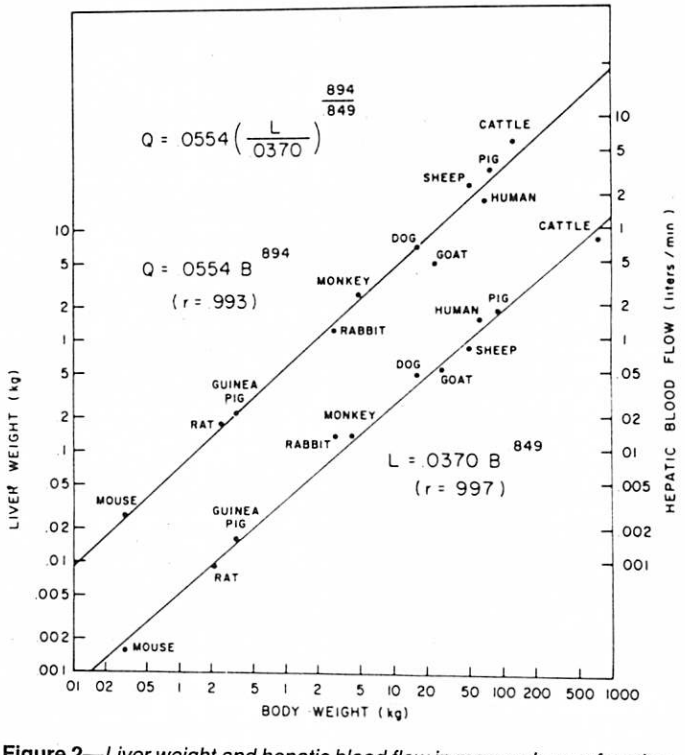


Figure 2—*Liver weight and hepatic blood flow in mammals as a function of body weight. Equations were fitted using the method of least squares on unweighted, logarithmically transformed data. Reprinted with permission from ref 5. Copyright 1980 Plenum Publishing.*

for which half-life was the only reported parameter, hepatic clearance could be calculated by assuming a volume of distribution equal to total body water; and (*g*) there existed in the literature an abundance of data for different species. When antipyrine intrinsic clearance (L/min) was plotted as a

function of body weight on log–log coordinates, the data for all species except humans fell on a straight line (Fig. 3). Boxenbaum concluded that the 7-fold difference between expected antipyrine clearance and reported antipyrine clearance for humans made them unique in that they "lacked the quantitative capacities of other mammalian species," a statement which has not been widely accepted.[6] When the data were replotted as unbound antipyrine intrinsic clearance per maximum lifespan potential (L/MLP) versus body weight on log–log coordinates (Fig. 4), superposition of the pharmacokinetic data from the different species was achieved.[7] Yates and Kugler[8] have presented an alternate hypothesis to explain why data for humans sometimes appear as outlying data points on simple allometric plots, specifically, the phenomena of neoteny. The effects of neoteny are manifest in both brain mass and lifespan. As a result of scaling antipyrine intrinsic clearance of unbound drug across species, using maximum lifespan potential[7] or brain weight,[9] the antipyrine data for humans were brought more closely in line with that of the other mammals.

For more information on the use of allometry in the biological sciences, the reader is referred to texts on interspecies scaling.[6,10–12]

Similarities in Pharmacokinetics

Small mammals can be regarded as true physical models of large mammals (in the engineering sense of the term), and a formal scheme to describe drug concentration might be suitable for either. Dedrick et al.[13] demonstrated that drug concentrations in several laboratory animals could be correlated as a function of dose and body weight. They plotted methotrexate plasma (or serum) concentrations from mice, rats, monkeys, dogs, and humans on one semilogarithmic plot (Fig. 5a). The pharmacokinetic profiles for the different species were strikingly different, with elimination most rapid for mice and rats, intermediate for dogs and monkeys, and least rapid for humans. When the y-axis (concentration) was normalized by dividing the observed plasma concentrations by the dose per unit body weight and when the x-axis (time)

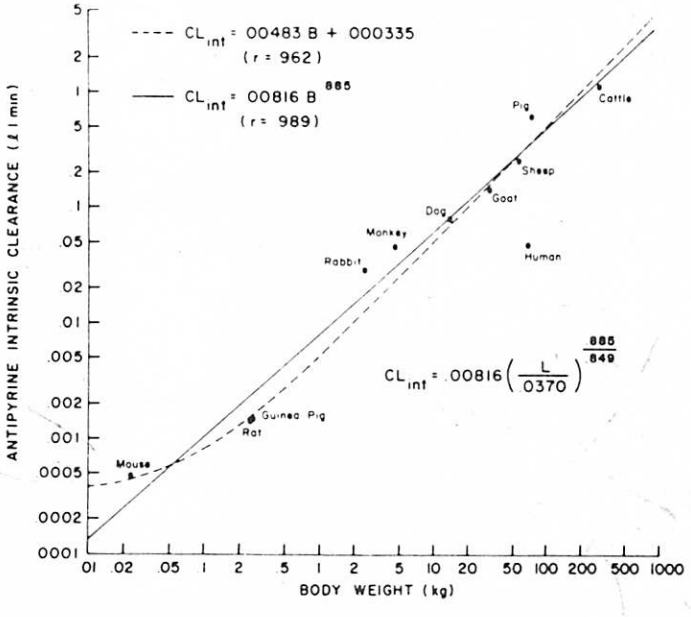


Figure 3—*Antipyrine intrinsic clearance in mammals as a function of body weight. Dashed line is the least-squares fit of nonlogarithmically transformed data weighted by the factor $1/y^2$. The solid line is from the equation fitted using the method of least squares on unweighted, logarithmically transformed data. Reprinted with permission from ref 5. Copyright 1980 Plenum Publishing Corp.*

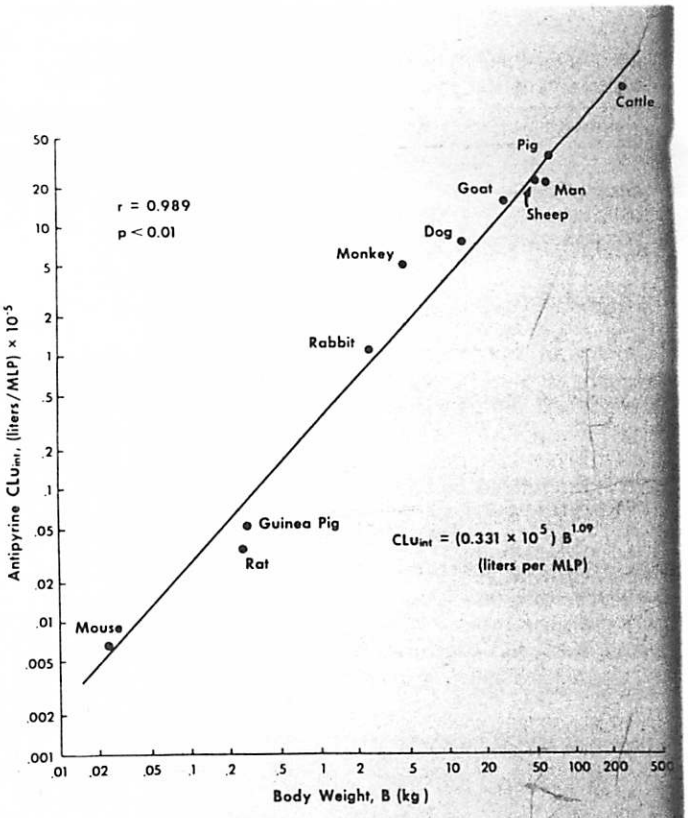


Figure 4—*Allometric relationship between intrinsic clearance of unbound antipyrine per maximum lifespan potential (MLP) and body weight. Reprinted with permission from ref 7. Copyright 1982 Plenum Publishing Corp.*

was normalized by dividing time after injection by $W^{0.25}$, the pharmacokinetic profiles were superimposable (Fig. 5b). The value $W^{0.25}$ was chosen empirically, and the selection was based on the concept that "equivalent time" between species correlates with weight to the 0.25 power.[14] In further investigation of the underlying relationships in methotrexate pharmacokinetics, the half-life of methotrexate in each species was plotted as a function of body weight on log–log coordinates (Fig. 6). The slope of the graph was 0.2 (i.e., the exponent of W), which is in reasonable agreement with the value of 0.25 chosen empirically.

These authors were the first to recommend the use of "equivalent time" in the analysis of pharmacokinetic data obtained from different species. They suggested that drug elimination could be correlated between species if one used an intrinsic biological property (creatinine clearance, blood circulation velocity, or mean residence time of blood components in the vascular system) as an equivalent time-scaling factor. This approach is advisable for dynamic systems because similarity in these systems does not occur as the comparison of simultaneous events. Instead, two dynamic systems are similar at corresponding (but different) instances of time.[15] In other words, two species obeying the same dynamics of drug elimination are in a similar temporal state at equal instances of intrinsic (biologic) time even though the events appear to transpire at unequal rates when measured with an extrinsic (chronological) time scale.

Boxenbaum[7] used data from the same sources as Dedrick et al.[13] to calculate the methotrexate plasma clearance (CL_{MTX}) and volume of distribution (Vd) in five species. When these pharmacokinetic parameters were plotted as a function of species body weight on log–log coordinates, both were linearly related to body weight. Boxenbaum demonstrated the use of engineering dimensional analysis by forming a quotient between the allometric equation for metho

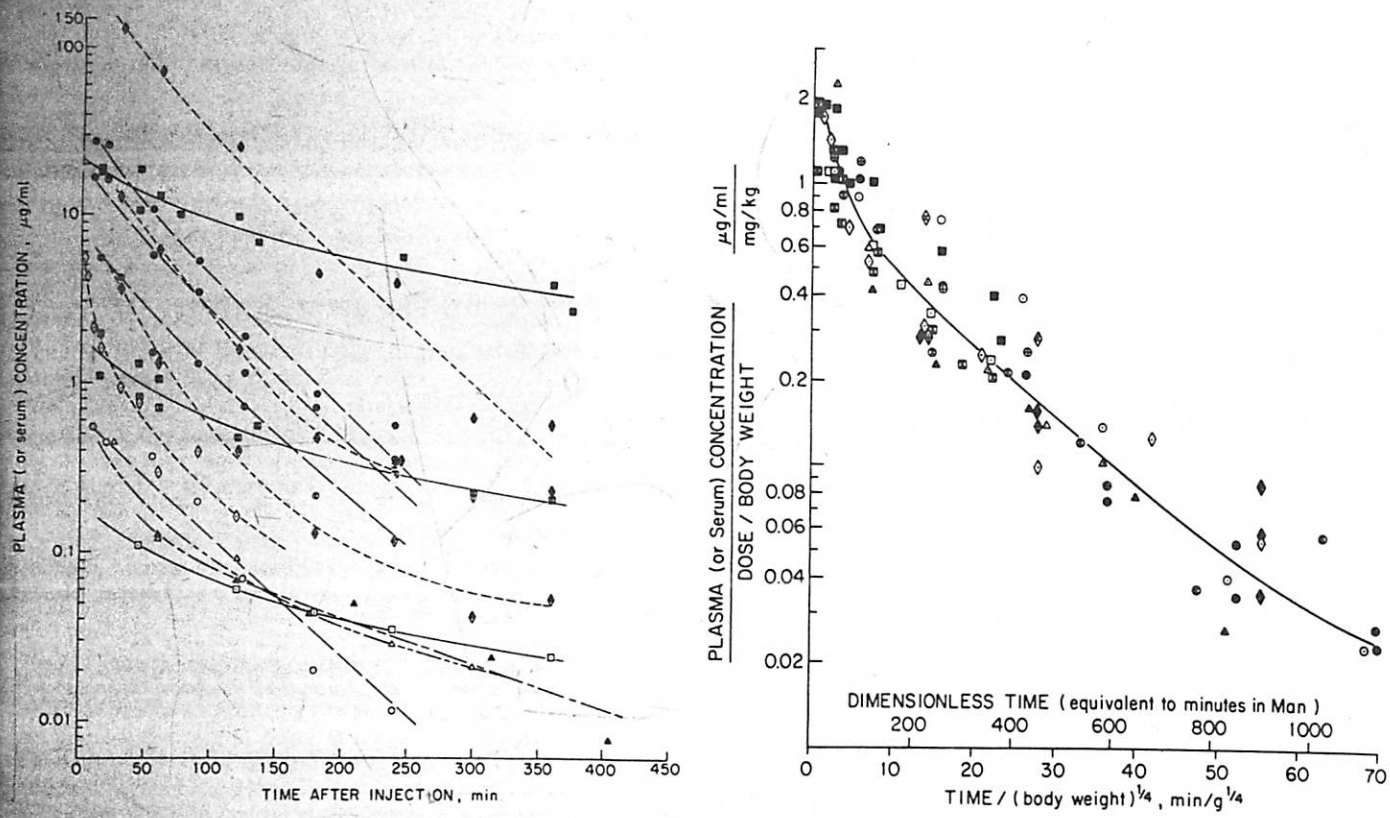


Figure 5—*Plasma (or serum) concentrations of methotrexate in the mouse (– – – –), rat (— — —), monkey (– – –), dog (– – – –), and human (——) after iv or ip injection (the symbols refer to different dose levels and routes of administration):* (a) *semilogarithmic plots of methotrexate concentration versus time and* (b) *semilogarithmic plot obtained after normalization of the axes. From ref 13.*

trexate clearance (CL_{MTX}) and the allometric equation for creatinine clearance (CL_{Cr}) as follows:

$$CL_{MTX}/CL_{Cr} = 10.9W^{0.69}/8.2W^{0.69} = 1.33 \quad (7)$$

where clearance is in milliliters per minute and W is in kilograms. Thus, CL_{MTX} is $1.33CL_{Cr}$, and this relationship is independent of species and species size. In a sense, all species are alike, excreting methotrexate from their bodies at a rate which correlates with their physiology. Similar analysis was performed for methotrexate volume of distribution (Vd) and total body water (TBW) as follows:

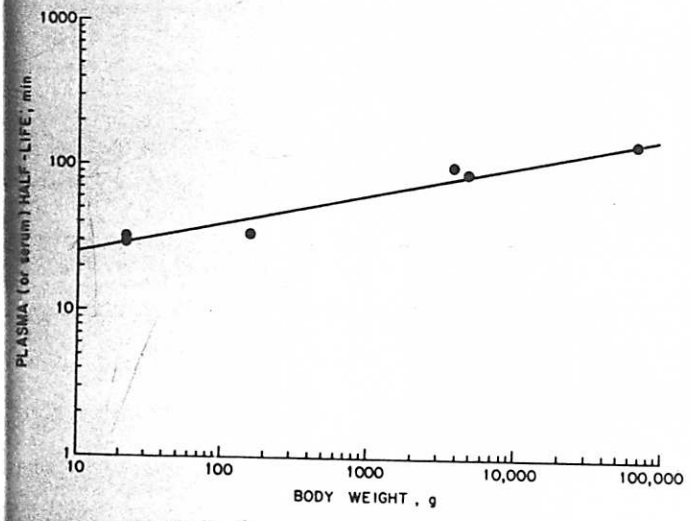


Figure 6—*Reported and calculated half-lives of methotrexate in plasma (or serum) of mouse, rat, monkey, dog, and human. From ref 13.*

$$Vd/\text{TBW} = 0.859W^{0.918}/0.703W^{0.963} = 1.22W^{-0.045} = 1.22 \quad (8)$$

where Vd and TBW are in liters and W is in kilograms. This analysis suggests that methotrexate Vd is 1.22 times larger than total body water in all species. The residual mass exponent in this calculation (−0.045) is small and essentially zero, indicating that body weight has little or no effect on this ratio.

Kallynochrons, Apolysichrons, Dienetichrons, Syndesichrons, and the Concept of Pharmacokinetic Time

Smaller, short-lived animals generally clear drugs from their bodies more rapidly (chronological time) per unit body weight than larger, long-lived animals. When drug removal is measured according to each species' own internal (biological) clock, animals tend to clear drugs at a similar pace.[7] Each species is endowed with a distinctive pharmacokinetic clock in accord with its own particular ideal space–time continuum. Since pharmacokinetic and physiologic events are correlated with body weight, it is possible to use body weight as part of a coordinate system on which to base a time function.

Consider antipyrine elimination in the human and the dog (Fig. 7a). The dog clears antipyrine 9 times faster than the human. The allometric equation for antipyrine clearance in this example is $CL = 77.1W^{-0.15}$. Boxenbaum and Ronfeld[16] introduced a new unit of time, the kallynochron, which they defined as t/W^{1-b}, in which b is the exponent from the allometric equation for clearance. In one kallynochron, species have cleared the same volume of plasma per kilogram of body weight. A semilogarithmic kallynochron plot was pro-

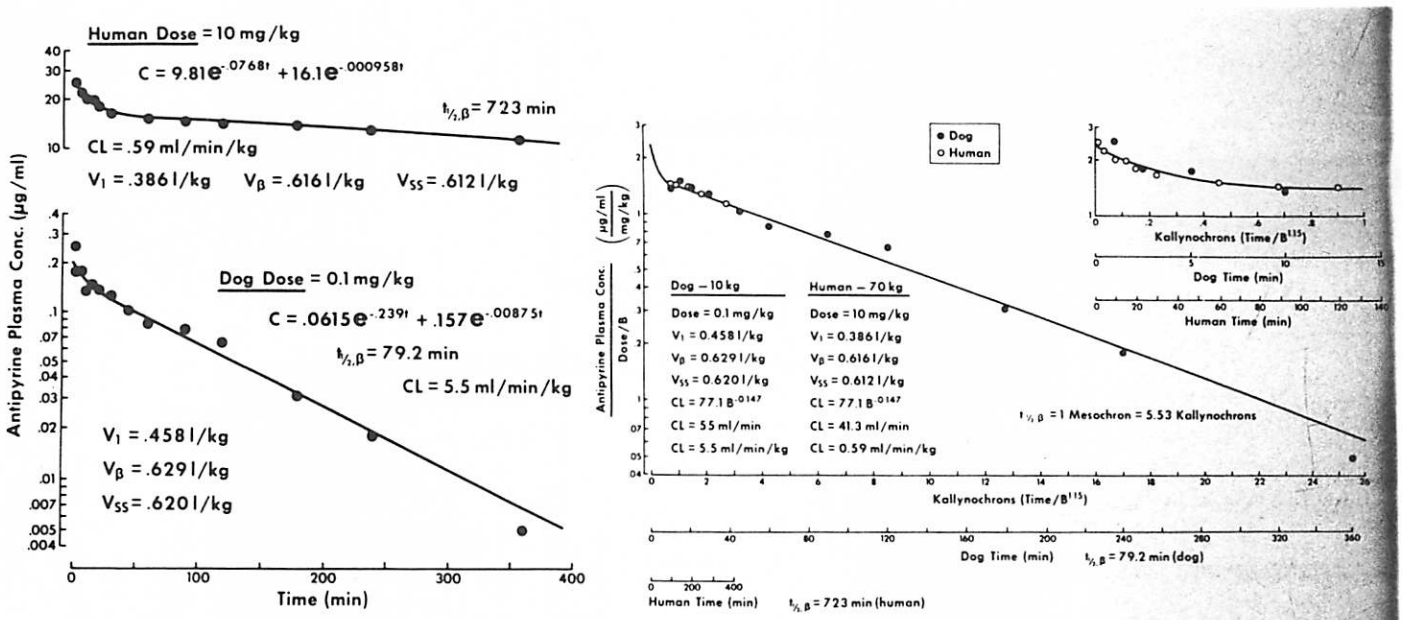


Figure 7—*Antipyrine disposition in dogs and humans after rapid iv injection:* (a) *biexponential antipyrine concentration–time curves and* (b) *elementary Dedrick plot of antipyrine data illustrated in Fig. 7a. "Kallynochron": The first element of this neologism is taken from the word "Kallyno," a transliteration of the classical Greek word meaning "to beautify, to look becoming, to make clean." The suffix "-chron" comes from "Cronus" ("Kronos"), a word for the Greek God of time. As such, this neologism refers to the time required to clear drug from the body. Reprinted with permission from ref 16. Copyright 1983 The American Physiological Society.*

duced by normalizing the antipyrine data as follows: The plasma concentrations were normalized by dividing each concentration by dose per unit body weight. And chronological time was transformed to pharmacokinetic time (kallynochrons) by dividing it by $W^{1.15}$. Boxenbaum called this transformation an elementary Dedrick plot in honor of Robert Dedrick's pioneering work in interspecies scaling. When viewed in this fashion, the antipyrine data were superimposable (Fig. 7b).

Similar transformation of chlordiazepoxide pharmacokinetic data obtained for a dog and a human did not produce superimposable profiles, indicating that these data are ill-conditioned for such a plot (Fig. 8a). Further analysis revealed that the dog has a greater relative volume of distribution than the human. To account for this difference, the allometric equation for volume of distribution ($W^{0.58}$) needed to be included in the transformation of each axis. The inclusion of $W^{0.58}$ in the transformation of the y-axis is straightforward (i.e., plasma concentration/dose per $W^{0.58}$). For the transformation of the x-axis, Boxenbaum and Ronfeld[16] introduced another unit of pharmacokinetic time, the apolysichron, which they defined as $t/W^{b'-b}$, in which b' and b are the allometric exponents relating volume of distribution and clearance to body weight, respectively. In one apolysichron, species have eliminated the same fraction of drug from their bodies and have cleared the same volume of plasma per kilogram $^{b'}$ of body weight. Obviously, the kallynochron and the apolysichron are equivalent when $b' = 1$ or

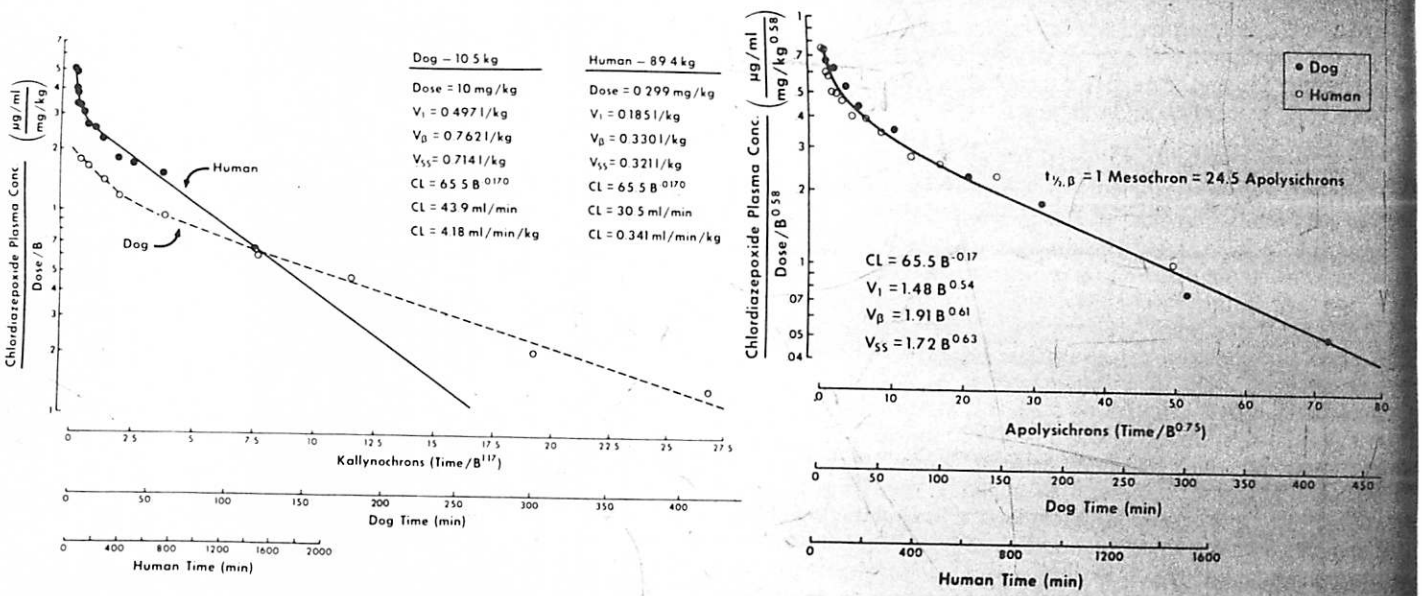


Figure 8—*Chlordiazepoxide disposition in dogs and humans after rapid iv injection:* (a) *elementary Dedrick plot of chlordiazepoxide plasma concentration–time curves and* (b) *complex Dedrick plot of chlordiazepoxide data illustrated in Fig. 8a. ("Apolysichron": The first element of this neologism is from the word "apolysis," a transliteration of the classical Greek word meaning "release or deliverance from (a thing)." The suffix "-chron" comes from "Cronus" ("Kronos"), a word for the Greek God of time. As such, the neologism refers to the time required to lose or release drug from the body.) Reprinted with permission from ref 16. Copyright 1983 The American Physiological Society.*

when the volume of distribution is directly proportional to body weight. This double transformation, or complex Dedrick plot, produced pharmacokinetic profiles that were superimposable (Fig. 8b).

Boxenbaum has defined two additional pharmacokinetic space–time continua: dienetichrons[17] and syndesichrons.[18] These units of pharmacokinetic space–time are similar to apolysichrons except that maximum life potential (MLP, Fig. 9) and brain weight (BW; Fig. 10) are incorporated in the scaling paradigms.

Interspecies Pharmacokinetic Scaling

The collapse of pharmacokinetic profiles from different animal species into a unique species-independent profile demonstrates the similarity of pharmacokinetics among species, introduces the concept of biologic (or equivalent) time in interspecies pharmacokinetic comparisons, and provides the foundation for interspecies pharmacokinetic scaling. Two approaches to interspecies pharmacokinetic scaling have emerged, an allometric approach (based on the formulation of allometric equations which represent individual pharmacokinetic parameters) and a physiologic (or reductionist) approach (based on the scale-up of physiologic flow models).

Allometric Approach

The allometric approach to interspecies scaling is a black box approach; that is, no attempt is made to determine the organ distribution of the drug or to give physiologic meaning to the pharmacokinetic parameters. Frequently, there is no need to know the details of drug distribution in many tissues. It is sufficient to know and be able to control the concentra-

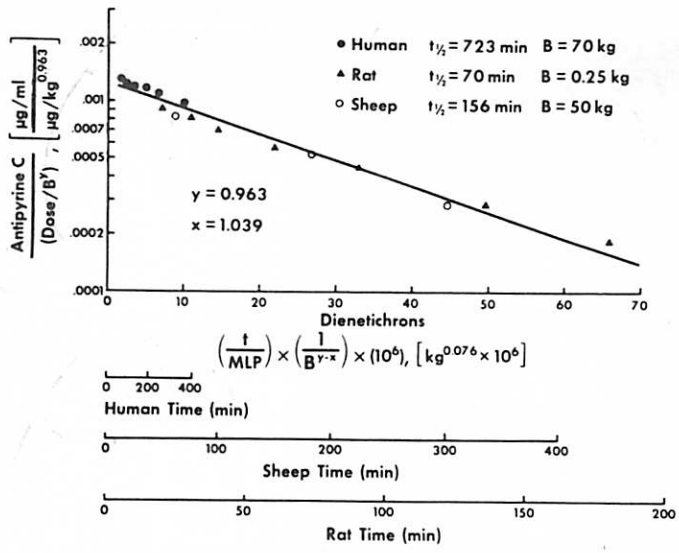


Figure 9—*Semilogarithmic dienetichron plot for antipyrine disposition in three mammalian species. ("Dienetichron": The first element of this neologism is from the word "dienec," a transliteration of the classical Greek word meaning "continuous, unbroken." The suffix "-chron" comes from "Cronus" ("Kronos"), a word for the Greek God of time. The prefix comes from the view that space experience and temporal sequence form an integrated continuum. According to this view, the entire organism is merely a section of a certain magnitude from birth to death [hence the maximum life potential component].) Reprinted with permission from ref 17. Copyright 1983 Marcel Dekker, Inc.*

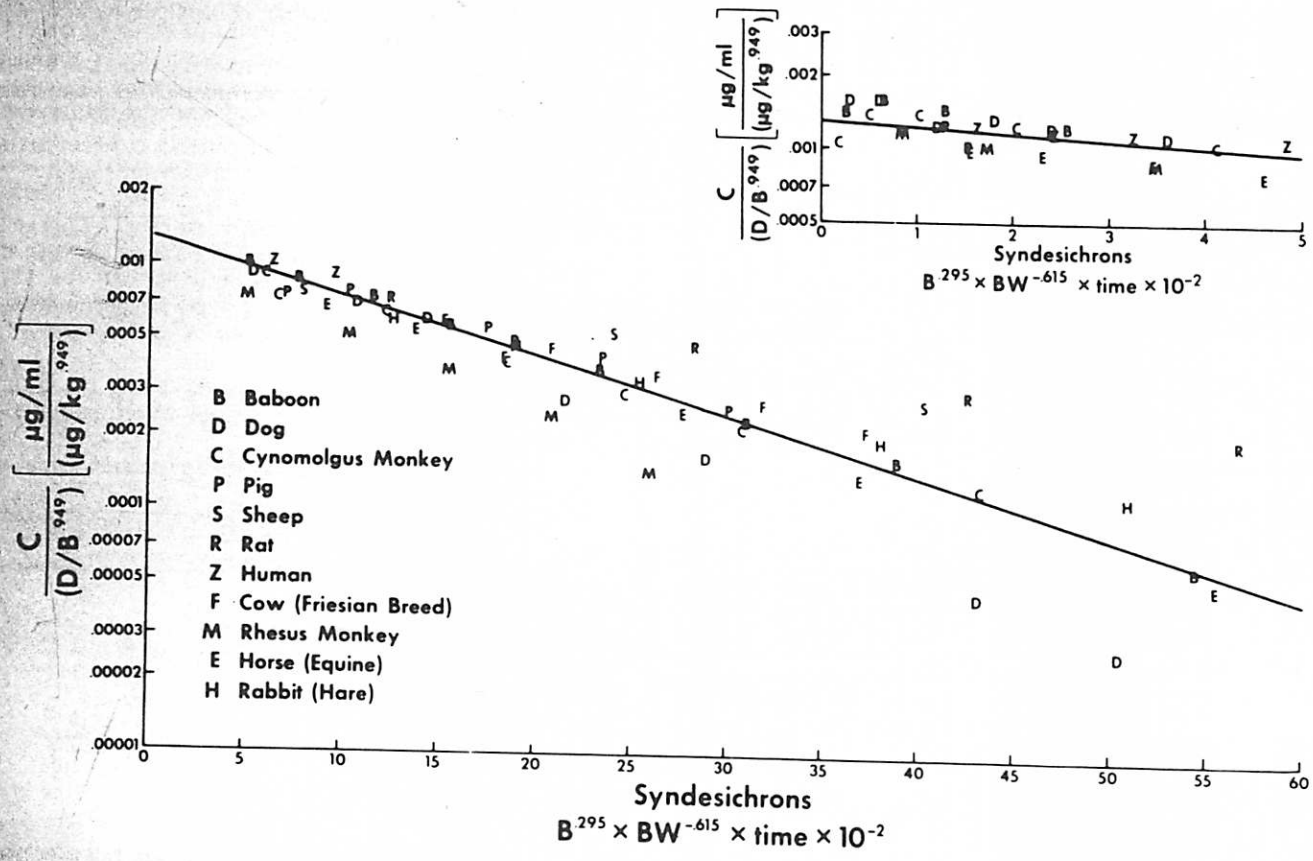


Figure 10—*Semilogarithmic syndesichron plot for antipyrine disposition in eleven mammalian species. ("Syndesichron": The first element of this neologism is from the word "syndes," a transliteration of the classical Greek word meaning "a binding together." The suffix "-chron" comes from "Cronus" ("Kronos"), a word for the Greek God of time. The prefix comes from the view that space experience and temporal sequence form an integrated continuum or are inextricably bound.) Reprinted with permission from ref 18. Copyright 1984 Marcel Dekker, Inc.*

tion of drug in the plasma. In these instances, the allometric approach is the method of choice and can be applied to the data, provided that the pharmacokinetics are first order in each species, the percentage of protein binding is similar and linear over the concentration range of interest, the elimination processes are physical (i.e., renal or biliary), and enough data are available for satisfactory linear regressions.

Numerous examples in the literature demonstrate the suitability of the allometric equation for predicting pharmacokinetic parameters in humans. Sawada et al.[19] predicted total body clearance, renal clearance, hepatic clearance, volume of distribution, intrinsic clearance of unbound drug, volume of distribution of unbound drug, and elimination half-life for six β-lactam antibiotics in humans. Data from mice, rats, rabbits, dogs, and monkeys were used in the extrapolations. Discrepancies between the observed and predicted values for volume of distribution and hepatic clearance were attributed to differences in the plasma-free fraction in each species and uncertain hepatic clearance (the observed hepatic clearance was calculated as the difference between plasma clearance and renal clearance, and it may have included some extrahepatic metabolism).

Sawada et al.[20] investigated the effect of species differences in the extent of protein binding of 10 basic drugs on the apparent volume of distribution (after distribution equilibrium) and the ratio of distributive tissue volume to unbound fraction in the tissue (V_T/fu_T). Small differences in tissue distribution of the drugs between animals and humans were detected, suggesting that uptake by the tissues and binding to tissue components did not display significant interspecies variation. Despite this similarity in the tissues, it was not possible to predict volume of distribution in humans from the animal data unless the plasma-free fraction was included in the analysis. Interspecies differences in binding to plasma proteins were variable and appeared to coincide with the variable distribution of binding constituents in plasma (i.e., albumin, α_1-acid glycoprotein, and β_1-lipoprotein).

The postdistribution half-lives ($t_{1/2}$) of 10 cephalosporin and 2 monobactam antibiotics in humans were predicted from data obtained from mice, rats, rabbits, monkeys, and dogs.[21] This forecasting was accomplished with the allometric equation $t_{1/2} = aW^b$ (Fig. 11). Only one antibiotic, cefotetan, did not scale well among the smaller animals and humans. The disparity between the predicted and observed half-life values for cefotetan may be the result of this antibiotic's existence in tautomeric forms.

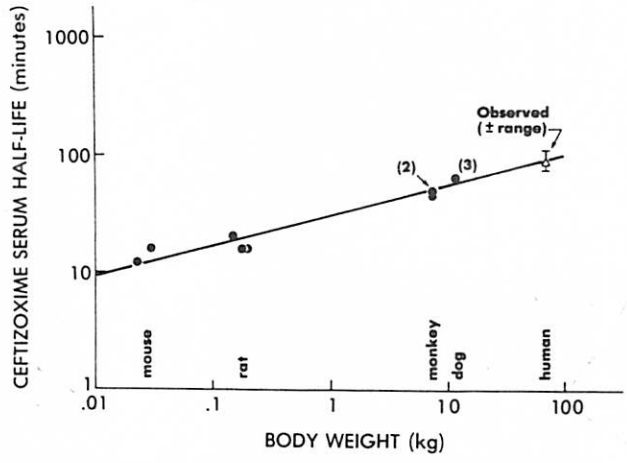


Figure 11—*Log–log plot of half-life versus body weight for ceftizoxime. The solid circles represent the values reported in the literature for each species. The solid line is the least-squares linear regression line for the animals, excluding humans. The prediction for antibiotic half-life in humans is read off the linear regression line at 70 kg. The triangle represents the reported antibiotic half-life in humans (mode), and the bars represent the range of values from the literature. Numbers in parentheses indicate number of data points. Reprinted with permission from ref 21. Copyright 1985 American Society for Microbiology.*

The allometric equation was used to establish an empirical relationship between the pharmacokinetic parameters of macrolide antibiotics (erythromycin, oleandomycin, and tylosin) and body weight.[22] Despite agreement between the observed and predicted human pharmacokinetic values for erythromycin and oleandomycin, the allometric model did not discriminate between the pharmacokinetics of these two antibiotics in humans. For some compounds, the usefulness of the allometric relationship may reside in predicting whether large interspecies differences in animal pharmacokinetics will translate to meaningful differences in humans.

Another area in which the allometric equation may prove valuable is the prediction of toxicologic endpoints. Although limited data are available, log–log plots of *minimally toxic dose* (lethal dose in 10% of small animals and maximum tolerated dose in large animals) versus *weight* for many anticancer agents are linear, meaning that these data are well described by the allometric equation[23] (Fig. 12). In general, small animals require larger doses to approximate the lethal dose in humans. If toxicity is due to a metabolite, the converse may be true[24]; however, without some information about the bioactivation and degradation process in each species, it is more difficult to extrapolate toxicity data for compounds that undergo metabolism.

The allometric approach can be used to predict entire pharmacokinetic profiles for humans from animal data. These predictions are obtained as follows:

1. Determine discrete pharmacokinetic parameters for the drug in young adult animals of four or more species (compartmental or noncompartmental methods can be used).
2. Perform linear regression analysis on the relationship log *pharmacokinetic parameter* versus log *weight* to obtain allometric equations for each parameter (if necessary, longevity, brain weight, or other significant physiologic parameters can be incorporated into the regression).
3. Solve each allometric equation for the average young adult human, that is, substitute 70 kg for weight to predict average pharmacokinetic parameters.
4. Use the predicted pharmacokinetic parameters to write pharmacokinetic equations for drug disposition in humans.
5. Check the prediction by administering the drug to young adult humans or obtain experimental data from the literature.

Swabb and Bonner[25] used a one-compartment model and

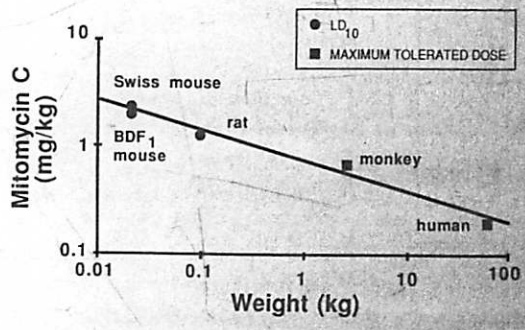


Figure 12—*Log–log plot of the minimally toxic dose of mitomycin C versus body weight for mice, rats, monkeys, and humans. Key: (●) LD_{10}; (■) maximum tolerated dose. Reprinted with permission from ref 23. Copyright 1986 American Pharmaceutical Assoc. Data taken from ref 53.*

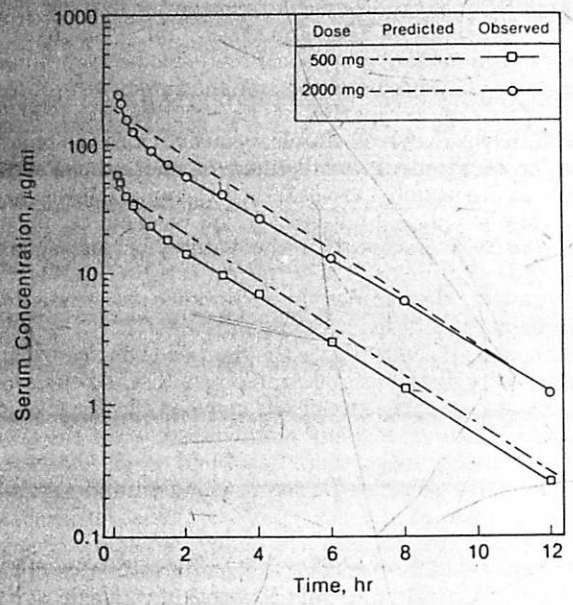


Figure 13—*Comparison between predicted and observed serum concentrations for aztreonam given as 500- and 1000-mg iv infusions over 3 min to healthy male subjects. Values are means for two groups of subjects. Reprinted with permission from ref 25. Copyright 1983 Plenum Publishing Corp.*

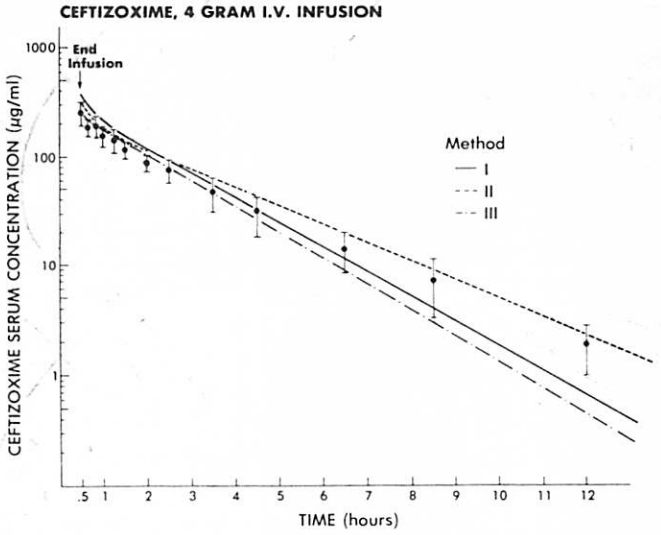


Figure 14—*Comparison between predicted and observed serum concentrations for ceftizoxime given as a 4-g, 30-min iv infusion to healthy male subjects. Key: (——) Method I; (– – –) Method II; (— · —) Method III. The symbols represent experimental data (mean ± SD) for four healthy volunteers taken from the literature. Reprinted with permission from ref 26. Copyright 1985 American Pharmaceutical Assoc.*

data from four species to predict aztreonam pharmacokinetics in humans (Fig. 13). These predictions were helpful in choosing doses and serum sampling times for the first kinetic study in healthy male volunteers and agreed well with subsequently measured concentrations in humans.

Mordenti[26] used three methods of pharmacokinetic scaling and data from mice, rats, monkeys, and dogs to predict biexponential disposition profiles for ceftizoxime in humans. Method I scaled the coefficients (A,B) and exponents (α,β) of the biexponential equation from each species; Method II scaled the microconstants (k_{12}, k_{21}, k_{10}) and volume of distribution (Vd_1) from the two-compartment model; and Method III scaled volume of distribution (Vd_1, Vd_{ss}, Vd_{area}) and clearance. Irrespective of the method chosen to produce the biexponential equations, there was close agreement between the predicted concentrations of ceftizoxime in human serum and the concentrations in serum reported in the literature (Fig. 14). This finding is important because it means that the pharmaceutical scientist is at liberty to choose any method of pharmacokinetic modeling and still obtain reasonable estimates in humans with the allometric approach.

Dimensionless criteria of similarity are obtained from the ceftizoxime data by allometric cancellation as follows:

$$\text{ceftizoxime half-life/time for heartbeat} = 30.1W^{0.248}/4.15 \times 10^{-3}W^{0.25} = 7253 \qquad (9)$$

where ceftizoxime half-life and time for heartbeat are measured in minutes. In other words, 50% of a dose of ceftizoxime is eliminated in ~7,300 heartbeats, regardless of animal

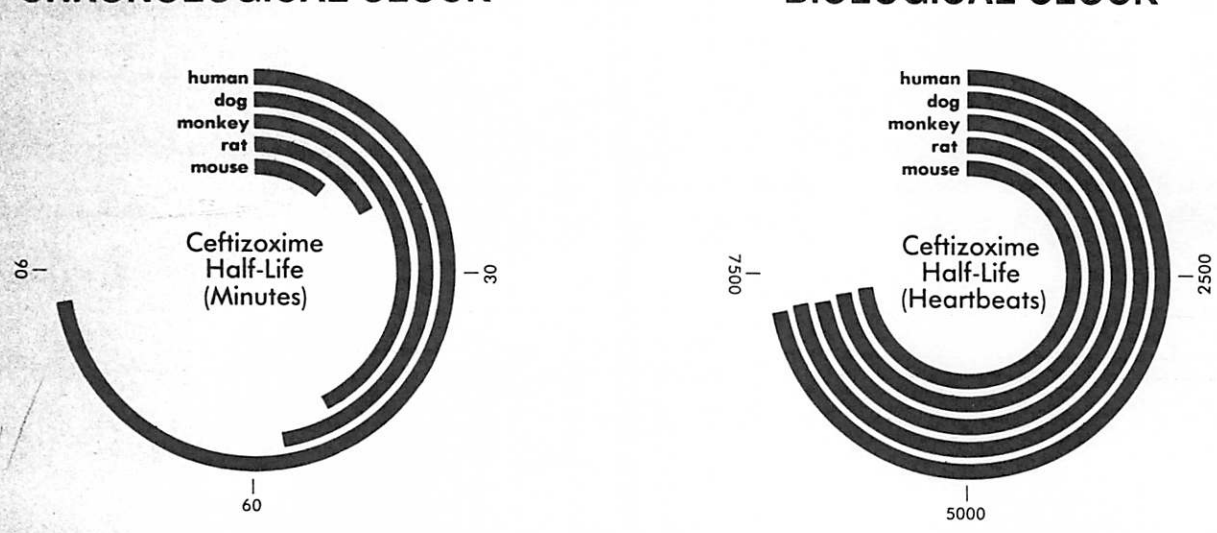


Figure 15—*Perceived differences in the half-life of ceftizoxime in various mammals depend on the reference system used to denote time:* (a) *When half-lives are reported in minutes, the smaller mammals eliminate 50% of the drug more rapidly than the larger species.* (b) *When half-lives are reported in heartbeats, all mammals eliminate 50% of the drug in an equivalent time. Adapted from ref 21 with permission. Copyright 1985 American Society for Microbiology.*

species. This quantity, ~7300 heartbeats, represents a unit of interspecies equivalent time. To forecast each half-life of ceftizoxime in other animal species, multiply the time for one heartbeat (in minutes) by 7300. The similarity in ceftizoxime half-life in different animal species is not apparent when the reference time is extrinsic, chronological time (minutes; Fig. 15a); however, the similarity is apparent when the reference time is intrinsic, biologic time (heartbeats; Fig. 15b).

Physiologic Approach

The physiologic approach is based on physiologic flow models which are anatomically, physiologically, and biochemically correct.[27-29] One must consider blood flow to eliminating organs; tissue and fluid volumes; blood-to-plasma and tissue-to-plasma drug concentration ratios; drug protein binding; and enzyme kinetics. The models are drawn as a flow scheme in which all the important compartments are connected via the circulatory system as in the body (Fig. 16).

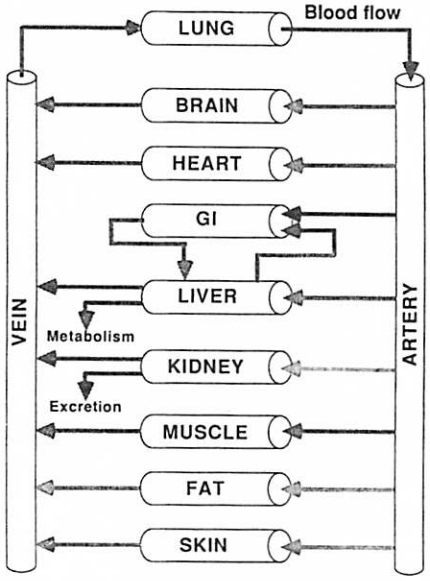


Figure 16—*Schematic of a physiologic flow model.*

The complexity of the scheme depends on the pattern of drug distribution, available data, and the insight of the investigator. The mathematical pharmacokinetic model is obtained by writing mass balance equations for the sum of the processes occurring in each compartment, and the resultant differential equations are solved simultaneously. Once the pharmacokinetics of the drug are defined in one animal species, predictions for humans are obtained by replacing the values for the physiological, anatomical, and biochemical parameters of the test species with the values for corresponding parameters of humans. These values can be obtained from the literature, determined from in vitro experiments, or estimated via interspecies extrapolations.

The physiologic approach is the method of choice when the details of drug distribution are important, when the central compartment is not the site of action, when the drug is highly lipid soluble and extensively metabolized, when the protein binding is strong and/or nonlinear, and when pharmacokinetic data can be obtained from only one animal species.

In formulation of a physiologic flow model for species for which few physiologic data are known, allometric relationships can be used to provide reasonable estimates of these data. In an illustration of this concept, physiologic parameters for seven animal species, representing a 10^3 range of weights, were taken from the literature[27] (Table II). Allometric equations were fitted to the physiologic data by using the method of least squares on unweighted, logarithmically transformed data (Table III). In all cases, statistically significant associations were obtained. Predictions of these physiologic parameters in an unlisted species can be obtained by substituting the weight of the unlisted species into the allometric equation. Allometric equations for tissue volumes and flow rates can be incorporated directly into the flow model.

Physiologic flow models are developed in laboratory animals, then scaled up (in the engineering sense) to make a priori predictions of drug disposition in humans. The anticancer agent methotrexate has been the most extensively studied drug, and details of the development of the physiologic model for methotrexate can be found in major review articles.[27-29] The physiologic model for methotrexate is multicompartmental and includes linear protein binding, strong saturable protein binding, and enterohepatic circulation.

Table II—Physiologic Parameters[a]

Parameter	Mouse	Hamster	Rat	Rabbit	Monkey	Dog	Human
Body weight, g	22	150	500	2330	5000	12000	70000
Compartment volumes, mL							
Plasma	1.0	6.48	19.6	70	220	500	3000
Muscle	10	—	245	1350	2500	5530	35000
Kidney	0.34	1.36	3.65	15	30	60	280
Liver	1.3	6.89	19.55	100	135	480	1350
Gut	1.5	12.23	11.25	120	230	480	2100
Gut lumen	1.5	—	8.8	—	230	—	2100
Heart	0.095	0.63	1.15	6	17	120	300
Lungs	0.12	0.74	2.1	17	—	120	—
Spleen	0.1	0.54	1.3	1	—	36	160
Marrow	0.6	—	—	47	135	120	1400
Plasma flow rate, mL/min							
Plasma	4.38	40.34	84.6	520	379	512	3670
Muscle	0.5	—	22.4	155	50	138	420
Kidney	0.8	5.27	12.8	80	74	90	700
Liver	1.1	6.5	4.7	177	92	60	800
Gut	0.9	5.3	14.6	111	75	81.5	700
Heart	0.28	0.14	1.6	16	65	60	150
Lungs	4.38	28.4	2.25	520	—	512	—
Spleen	0.05	0.25	0.95	9.0	—	13.5	240
Marrow	0.17	—	—	11	23	20	120

[a] Data from ref 27.

Table III—Equations Relating Physiologic Parameters with Body Weights among Mammals

Physiologic Parameter	Allometric Equation[a]	*t* value[b] (significance)[c]
Compartment volumes, mL		
Plasma	$0.0429W^{0.992}$	43.768
Muscle	$0.463W^{1.009}$	67.754
Kidney	$0.0218W^{0.843}$	58.184
Liver	$0.0859W^{0.885}$	28.128
Gut	$0.0865W^{0.909}$	14.952
Gut lumen	$0.0578W^{0.934}$	8.452 ($p < 0.01$)
Heart	$2.0 \times 10^{-3}W^{1.043}$	13.767
Lungs	$3.16 \times 10^{-3}W^{1.104}$	19.883
Spleen	$4.52 \times 10^{-3}W^{0.901}$	6.697
Marrow	$0.033W^{0.936}$	13.605
Plasma flow rate, mL/min		
Plasma	$0.601W^{0.778}$	10.832
Muscle	$0.0817W^{0.81}$	5.908
Kidney	$0.0845W^{0.802}$	13.502
Liver	$0.0944W^{0.792}$	5.89
Gut	$0.102W^{0.787}$	10.058
Heart	$5.77 \times 10^{-3}W^{0.965}$	6.189
Lungs	$0.215W^{0.82}$	2.138 ($p < 0.1$)
Spleen	$1.79 \times 10^{-3}W^{1.028}$	13.345
Marrow	$0.0164W^{0.804}$	12.394

[a] Body weight, W. [b] Null hypothesis: slope (b) = 0. When t value is not significant, accept the null hypothesis; that is, the parameter does not depend on weight. [c] Significance based on (n − 2) degrees of freedom; $p \leq 0.005$ unless otherwise noted.

Bischoff et al.[30] described the pharmacokinetics of methotrexate in mice by using a physiologic model. Scale-up of the mouse model to humans produced predictions of methotrexate concentrations in plasma that correlated well with experimental data.[31] The same mouse model, without intestinal reabsorption and with estimated parameters for the sting ray, was used to predict the disposition of methotrexate in the stingray,[32] demonstrating the versatility of physiologic models (Fig. 17). Bischoff et al. illustrated the concept of

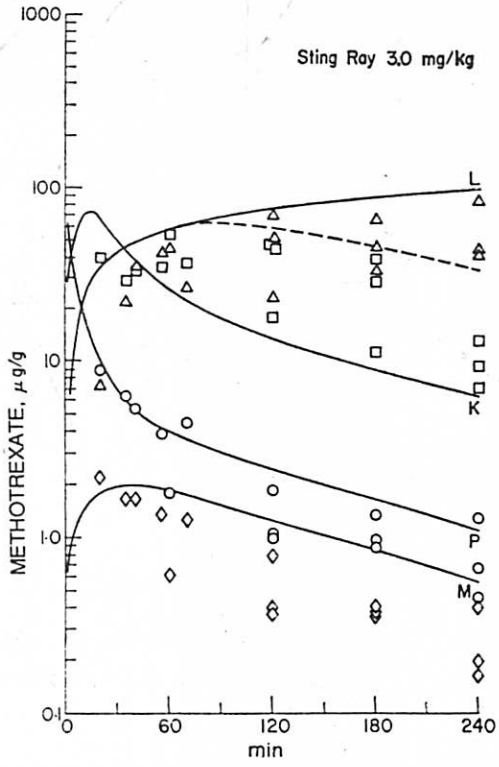
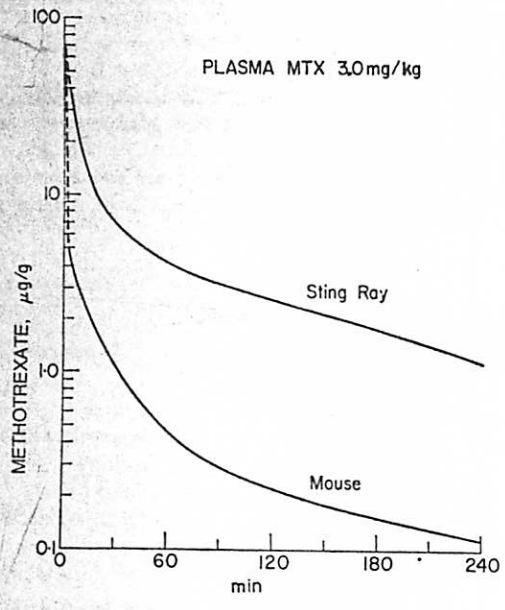


Figure 17—*Prediction of methotrexate tissue and plasma concentrations in stingrays based on scale-up of a mouse physiologic model. The symbols are observed serum concentrations following a 3-mg/kg iv dose and represent separate tissues from one stingray. Key:* (L, △) *liver;* (K, □) *kidney;* (P, ○) *plasma;* (M, ◇) *muscle. Reprinted with permission from ref 32. Copyright 1972 Pergamon Journals, Inc.*



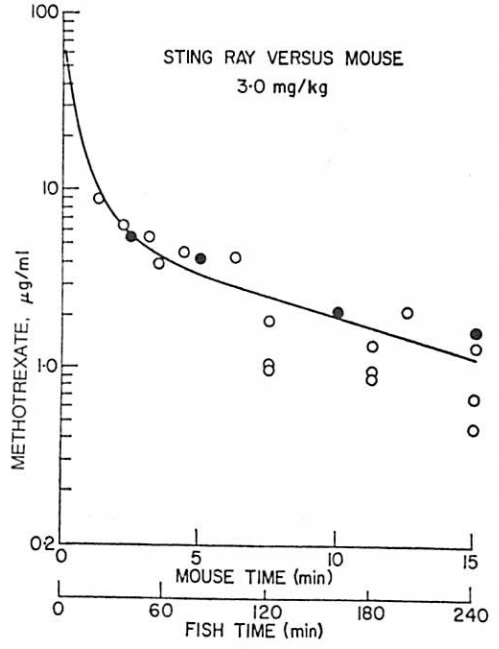


Figure 18—*Comparison of plasma methotrexate concentrations in the mouse and stingray with appropriate physiologic parameters used for each species (dose, 3 mg/kg iv):* (a) *When the time scale is an extrinsic time scale (min), the predicted plasma methotrexate concentrations appear dissimilar.* (b) *When the time scale is made proportional to the blood circulation velocity for each species (i.e., biological time), the plasma methotrexate concentrations in the mouse* (●) *and stingray* (○) *are superimposable. Reprinted with permission from ref 32. Copyright 1972 Pergamon Journals, Inc.*

equivalent time between species by viewing the methotrexate plasma concentrations for mice and stingrays in two ways. When the time scale (x-axis) was an extrinsic time scale (minutes), the concentration profiles appeared dissimilar (Fig. 18a). When the time scale was made proportional to the blood circulation velocity for each species, the concentration profiles were superimposable (Fig. 18b). These figures emphasize the importance of using intrinsic clocks for measuring pharmacokinetic events.

For drugs that are metabolized, physiologic models can be combined with in vitro estimates of intrinsic clearance[33] or in vitro estimates of enzyme activity (V_{max} and K_m) to obtain reasonable estimates of drug disposition in different species. The anticancer drug cytarabine hydrochloride (Ara-C) is converted to uracil arabinoside (Ara-U) by pyrimidine nucleoside deaminase. This enzyme is distributed differently in each species, and it is highly variable in kinetic characteristics (V_{max} and K_m). A physiologic model for Ara-C disposition was developed for humans by using in vitro values for enzyme activity and Michaelis constants.[34] The model predicted the plasma concentrations of Ara-C and Ara-U in humans after a single intravenous dose of the parent compound (Fig. 19). Using enzyme kinetics determined in vitro, this model was extended to mice, monkeys, and dogs to produce accurate pharmacokinetic profiles for each species.[35] The model was then expanded for the mouse to include the intracellular metabolism of the drug to the active metabolite, arabinoside cytosine triphosphate.[36] The variable distribution and kinetic activities of the deaminase enzymes make direct scale-up of Ara-C among species difficult unless in vitro data are available for each tissue.

The anticancer agent *cis*-dichlorodiammineplatinum (cisplatin) binds irreversibly to low molecular weight nucleophiles and macromolecules to form mobile and fixed metabolites at rates which are tissue specific. Biochemically, *cis*-dichlorodiammineplatinum is an unusual drug because the rates of its biotransformation do not appear to be enzymatically mediated. A physiologic flow model for the disposition of *cis*-dichlorodiammineplatinum and its biotransformation products was developed for female rats bearing Walker 256 carcinoma.[37] The model was scaled up to rabbits, dogs, and humans by using an interesting set of assumptions, approximations, in vitro estimations, and allometric extrapolations to provide the necessary biochemical and physiologic parameters.[38] Accurate predictions of the plasma concentrations of *cis*-dichlorodiammineplatinum, the total filterable platinum, and the total platinum in humans were obtained (Fig. 20).

Ethoxybenzamide is oxidized to salicylamide primarily by liver microsomal enzymes. A good correlation between in vitro and in vivo drug metabolism rates has been demonstrated for the rat.[39] The physiologic flow model for ethoxybenzamide in the rat was successfully scaled up for the rabbit[40] by incorporating the in vitro Michaelis–Menten constants for ethoxybenzamide de-ethylation into the model (Fig. 21).

The metabolism of diazepam in various rat tissues was determined in vitro using microsomal fractions from each tissue.[41] The resultant values were incorporated into a physiologic flow model and used to predict diazepam pharmacokinetics in a 10-compartment physiologic rat model. When the model was scaled up to humans by using literature values for the metabolism of diazepam in humans, an accurate assessment of diazepam plasma disposition was obtained.[42]

Other examples of the successful scale-up of animal physiologic models to humans include digoxin (rat to dog to human),[43] doxorubicin (rabbit to human),[44,45] lidocaine (monkey to human),[46] mercaptopurine (rat to human),[47] pentazocine (rabbit to human),[48] and hexobarbital, phenytoin, phenobarbital, and quinidine (rat to human).[49] Scale-up of

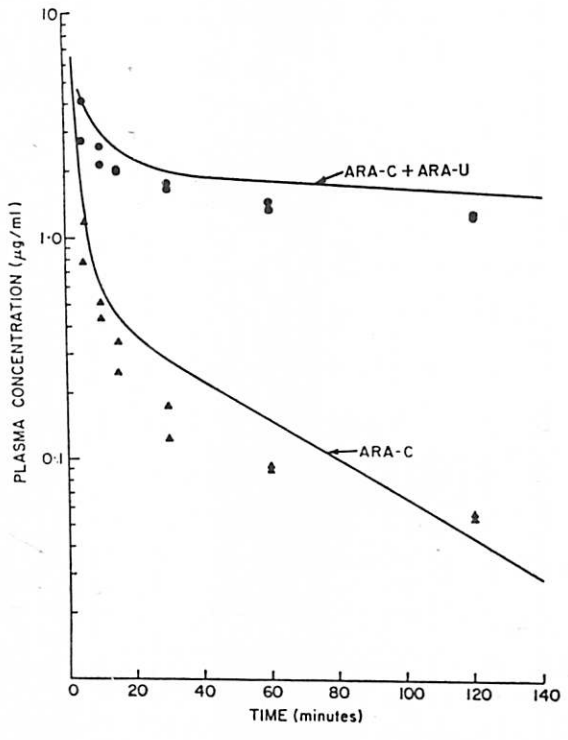


Figure 19—*Prediction of cytarabine (Ara-C) and uracil arabinoside (Ara-U) plasma concentrations in humans, using a physiologic model that included in vitro values for enzyme activity and Michaelis–Menten constants. The symbols represent observed serum concentrations in a 70-kg woman following two separate iv doses of 1.2 mg/kg. Reprinted with permission from ref 34. Copyright 1972 Pergamon Journals, Inc.*

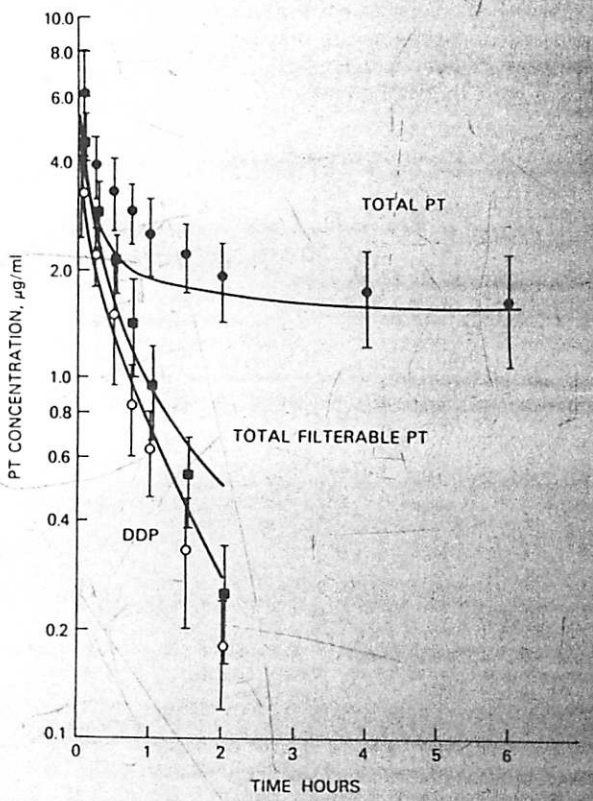


Figure 20—*Prediction of cisplatin (DDP), total filterable platinum (total filterable Pt), and total platinum (total Pt) in humans following an iv dose of 100 mg/m² of DDP. The symbols represent experimental data (mean ± SD) for 5 or 6 patients taken from the literature. Reprinted with permission from ref 38. Copyright 1986 Plenum Publishing Corp.*

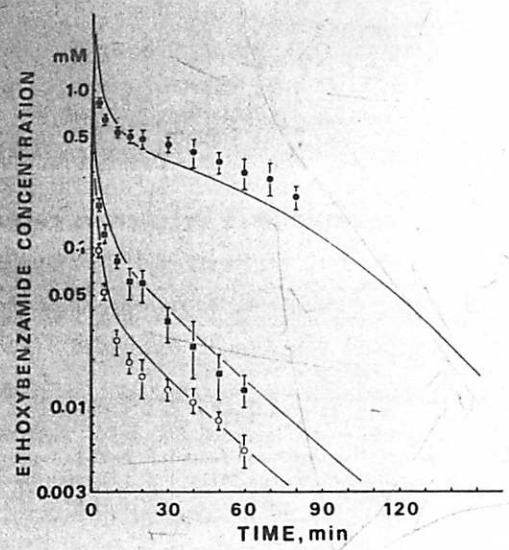


Figure 21—*Prediction of ethoxybenzamide plasma concentrations in rabbits based on scale-up of a rat physiologic model. The symbols represent observed serum concentrations following iv doses of 10 mg/kg (○), 20 mg/kg (■), and 80 mg/kg (●). Reprinted with permission from ref 40. Copyright 1982 Plenum Publishing Corp.*

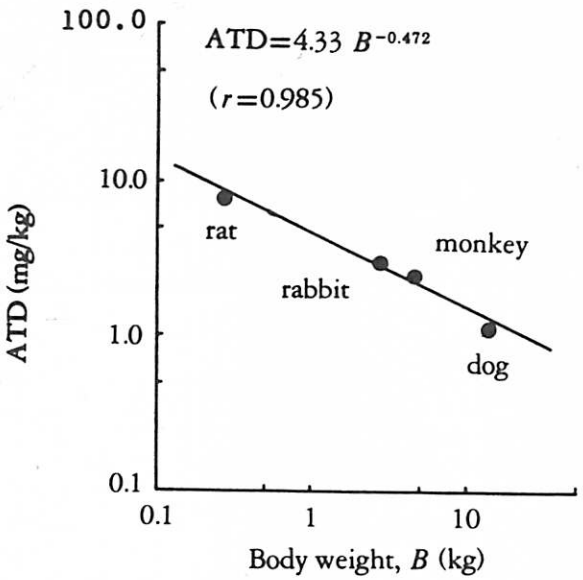


Figure 22—*Apparent threshold dose (ATD) of nipradilol in mammals as a function of body weight (B). Reprinted with permission from ref 50. Copyright 1985 Pharmaceutical Society of Japan.*

data for tolbutamide, valproate, and, in this instance, diazepam was not successful (rat to human).[49]

Oral Drug Administration

Although the prediction of intravenous pharmacokinetics has been successful, predicting the plasma concentration curves for humans after oral dosing is more difficult. One application of interspecies scaling that may prove useful for orally administered drugs is the estimation of the apparent threshold dose, that is, the dose of a high extraction ratio drug necessary to saturate elimination pathways, allowing drug to reach the systemic circulation. This application is illustrated by nipradilol, an antihypertensive and antianginal agent. Nipradilol is metabolized by different mechanisms and to different extents in the rat, rabbit, monkey, and dog.[50] In spite of complete absorption of orally administered doses, first-pass metabolism leads to low bioavailability, and the systemic availability for all species increases with dose. Marked species difference is seen in the apparent threshold dose, with the larger animals requiring smaller doses to saturate presystemic drug metabolizing enzymes (Fig. 22). The apparent threshold dose (ATD) of nipradilol relates to species body weight (B) as follows: ATD (mg/kg) = $4.33B^{-0.472}$.

Protein Binding

Although binding to plasma proteins seems unpredictable across species, interspecies scaling of the extent of camptothecin plasma protein binding is possible, using electrophoretically determined plasma protein fraction concentrations as independent variables.[51] Data from 24 species were used to produce the equation that describes the percent of camptothecin which is unbound in plasma [fu(%)]. This equation is written as follows:

$$\log fu\ (\%) = 2.12 + 0.0628 \log (\alpha_1) + 0.895 \log (\alpha_2) - 3.30 \log (\text{albumin}) - 0.651 \log (\text{albumin}) \log (\alpha_1) - 1.93 \log (\text{albumin}) \log (\alpha_2) \quad (10)$$

where albumin, α_1, and α_2 refer to albumin, α_1-globulin, and α_2-globulin protein fraction concentrations (g/100 mL), respectively. The β- and γ-globulin concentration terms did not significantly contribute to explaining the variance of the dependent variable and were not included in the equation. Equations such as this one may prove helpful when protein binding has a significant impact on interspecies pharmacokinetic scaling.

Conclusions

Animal data may be used to predict pharmacokinetic and toxicologic endpoints in humans. Two approaches are presented in this paper: the allometric approach and the physiologic approach. The approach that one selects to scale up animal data to humans depends on the nature of the compound and the desired mathematical output. The allometric approach is empirical, but easy, and best suited for renally excreted compounds or linear pharmacokinetic data. The physiologic approach is detailed, but difficult, and best suited for metabolized compounds or nonlinear pharmacokinetic data. Both approaches allow us to extrapolate outside the range of data with some confidence if the dominant mechanisms of transport are sufficiently well understood. A priori predictions are possible for many drugs, based on limited available data.

Animals live in different pharmacokinetic space–time continua. Use of an internal, or biological, clock in pharmacokinetic data analyses removes the superficial differences imposed by an external, or chronological, clock.

In general, small animals require more drug, administered more frequently, to mimic the human regimen. Interspecies scaling can guide us in selecting equivalent dosage regimens.

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