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Forecasting Cephalosporin and Monobactam Antibiotic Half-Lives in Humans from Data Collected in Laboratory Animals

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The postdistribution half-lives of 10 cephalosporin and 2 monobactam antibiotics in humans were predicted from data obtained in other mammals. This forecasting was accomplished with the allometric equation $t_{1/2} = aW^b$, where a is the y intercept and b is the slope obtained from the log-log plot of antibiotic half-life ($t_{1/2}$) versus body weight (W). Dimensionless similarity criteria were used to produce a biological clock for ceftizoxime elimination. The creation of the biological clock, which measured physiologic time (heartbeats) rather than chronologic time (minutes), demonstrated that ceftizoxime half-life was identical in five mammals. This methodology will contribute to infectious disease research through a greater understanding of pharmacokinetic scaling in mammals.

During the preclinical evaluation of antimicrobial agents, extensive pharmacokinetic studies are conducted in laboratory animals. Although we have come to recognize that smaller animals eliminate drugs more rapidly than do larger animals, the potential clinical significance of the animal studies is customarily overlooked.

Physiologists have shown that physiologic and anatomical variables can be expressed as a function of body weight (W) by the allometric equation $Y = aW^b$, where Y is the physiologic variable, a is the allometric coefficient, and b is the allometric exponent (1, 13, 14, 15, 27, 31). This allometric equation expresses the relationship of W to physiologic properties such as cardiac output, renal function, hepatic function, and blood flow (1, 8, 10, 17, 28, 32); in fact, any body process that includes external time as a dimension is size and weight dependent (17) and is amenable to allometric analysis.

The logarithmic transformation of the equation is $\log Y = \log a + b\log W$, where a is the y intercept and b is the slope obtained from the log-log plot of Y versus W. If weight is expressed in kilograms, a is the value of Y for a theoretical 1-kg animal. The exponent b denotes the proportionality between Y and W.

An interesting concept to evolve from allometric analyses has been the identification of an interspecies, weight-dependent time scale. The new time scale, called physiologic time (6), is measured by biological clocks (13) which use internal, physiologic parameters such as heartbeats, breath cycles, or blood circulation velocities as units of measurement. When physiologic events in different mammals are measured by biological clocks, they occur in equivalent physiologic time. This equivalence, called synchronism of time between species (27), is demonstrated by the observation that each mammal lives for approximately the same number of heartbeats or breath cycles (13). Thus, the life span of an elephant and a mouse is the same when measured with a biological clock (i.e., heartbeats), although their life spans vary significantly when measured in years. (Primates live longer than predicted on the basis of W; for instance, humans live three times longer than other mammals of the same size.) By amassing and analyzing numerous physiologic indices, it has been shown that the biological time scale relates uniformly to W to the power 0.25 (1, 6, 8, 12, 13, 17, 27).

Animals are commonly used in preclinical infectious disease research. To demonstrate the potential clinical significance of animal pharmacokinetic studies, the terminal half-lives of renally excreted cephalosporins and monobactams in various animal species were collected from the literature. These data were fitted by the allometric equation $t_{1/2} = aW^b$. (Half-life data were chosen for analysis because drug half-life is customarily reported in mammals, and the hybrid nature of drug half-life contributes to its successful use in allometry [2].) Human antibiotic half-life values were predicted with each equation and compared with reported half-life values to evaluate this method of pharmacokinetic forecasting.

MATERIALS AND METHODS

Terminal half-life data for cephalosporin and monobactam antibiotics were taken from studies published in scientific journals, from proceedings of infectious disease conferences, and from pharmacokinetic data available from drug companies. Antibiotics that met the following criteria were included in the data analysis: (i) all available data indicate first-order kinetics in usual doses; (ii) protein binding is linear in the concentration range of interest; (iii) assay methods for plasma or serum antibiotic determinations are essentially specific and accurate; (iv) all elimination pathways are renal, with only small amounts of intact drug excreted in the bile (physical elimination, such as glomerular filtration, scales to W, whereas metabolic elimination scales to both brain weight and W [3]); and (v) there exists in the literature an abundance of data on different species.

Adequate information was obtained on 10 cephalosporin and 2 monobactam antibiotics in 5 animal species (mouse, rat, rabbit, monkey, and dog). Both W in kilograms and the reported half-life ($t_{1/2}$) in minutes were transformed logarithmically and fitted by the equation $\log t_{1/2} = \log a + b\log W$ with linear least-squares analysis. Actual reported animal weights were employed whenever possible; otherwise, weight estimates were based on the age of the animal (as reported by the investigator) or standard adult animal weights. The allometric equations that were generated from

TABLE 1. Prediction of terminal antibiotic half-life in humans by the equation $t_{1/2} = aW^b$ and data collected on mice, rats, rabbits, monkeys, and dogs

Antibiotic (reference)	a	b	Correlation coefficient	Half-life (min) in humans	
				Prediction	Published (reference)
Aztreonam[a]	32.6	0.186	0.999	72	96 (29)
Carumonam[a]	31.5	0.258	0.974	94	106[b]
Cefamandole (20)	23.5	0.198	0.990	54	52 (22, 24)
Cefazedone (25)	69.4	0.115	0.966	113	108 (7)
Cefazolin (9, 16, 18)	27.8	0.238	0.962	77	108 (24)
Cefmetazole (16, 20)	23.8	0.234	0.918	64	65 (7)
Cefoperazone (18)	15.9	0.444	0.980	105	114 (23)
Cefotetan (16)	30.0	0.283	0.901	100	192 (11, 33)
Cefotiam (20, 30)	27.6	0.233	0.969	74	60 (5)
Cefpiramide (18)	45.6	0.385	0.931	235	264 (21)
Ceftizoxime (20, 26)	30.3	0.252	0.974	89	84 (23)
Cefuroxime (19, 26)	27.6	0.198	0.901	64	72 (22)
Mean ± SD		0.252 ± 0.084			

[a] Kita, Y., T. Fugono, and A. Imada, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, p. 5616–5619, 1983.
[b] Weidekamm, E., K. Stoekel, and W. H. Ziegler, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, p. 56/10–56/13, 1983.

the animal data were used to predict the terminal half-life for each antibiotic in a 70-kg human.

RESULTS

Table 1 lists the allometric equations that were derived from the log-log relationship of terminal half-life to W for each antibiotic. The a and b parameters were used to predict the terminal half-life of each antibiotic in a 70-kg human. The half-life value for each drug as reported in the literature is included in Table 1 for comparison.

The ceftizoxime data were plotted on log-log paper to illustrate the methodology for predicting human half-life values from animal data (Fig. 1). The a value (or y intercept [1 kg]) denotes the half-life of each drug in a theoretical 1-kg animal. The b value (or slope) demonstrates that the half-life is not proportional to W; if it were proportional, b would be 1. An exponent greater than 0 but less than 1 means that the larger mammals eliminated the drug more slowly than did the smaller ones. The mean value for b was 0.252.

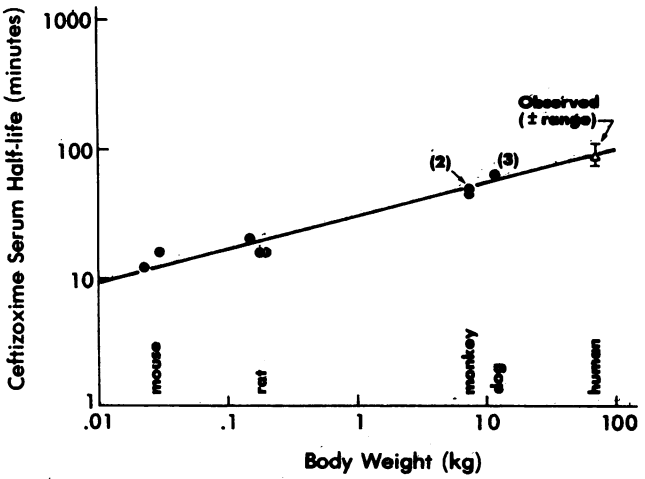

FIG. 1. Log-log plot of ceftizoxime half-life versus W. The solid circles represent the half-life of ceftizoxime in various animal species. The solid line is the least-squares linear regression line. The prediction of ceftizoxime half-life in humans is read off the regression line at 70 kg. The triangle represents the reported ceftizoxime half-life in humans (mode), and the bars represent the range of values from the literature. Numbers in parentheses indicate numbers of data points.

DISCUSSION

Knowledge of the terminal half-lives of 12 renally excreted antibiotics in laboratory animals proved adequate for accurately predicting the half-lives of most of the compounds in humans. The cefotetan half-life data did not scale well between the smaller animals and humans although a good correlation coefficient was observed for the fitted data. The disparity between predicted and observed values may be the result of cefotetan existing in tautomeric forms. Although a good correlation coefficient certainly implies an interconnectedness of variables, one should not assume that it proves that such a relationship exists. Allometric relationships are not biological laws; they merely describe patterns as well as identify animals (and compounds) that differ from the patterns (17).

The theory of pharmacokinetic similarity (4) states that different species dispose of drug molecules at rates correlatable with internal physiologic processes such as creatinine clearance, blood circulation velocities, and mean residence time of blood components in the vascular system. Allometric equations for several physiologic processes are shown in Table 2. The value of b is used to compare these allometric equations with those for antibiotic elimination. The similarity of b for inulin (0.27), *para*-aminohippuric acid (0.22), and cephalosporins (0.252) suggests a relationship in the elimination rates of these compounds that is consistent with our

TABLE 2. Equations relating mammalian biological periods (Y) to W (kilograms) by the allometric relationship $Y = aW^b$ (17)

Biological period (min)	a	b	Correlation coefficient
Life span in captivity	6.10×10^6	0.20	0.77
Time for circulation of blood volume	3.5×10^{-1}	0.21	0.98
Blood volume turnover time for inulin	6.51	0.27	0.98
Blood volume turnover time for *para*-aminohippuric acid	1.70	0.22	0.98
Cardiac cycle	4.15×10^{-3}	0.25	0.88

knowledge of their elimination pathways. The closeness of the values of the exponents to 0.25 also supports the principle that biological events or cycles transpire as constant multiples of each other in a time proportional to body mass to the power 0.25. The parallelism of these allometric equations is illustrated in Fig. 2 and 3. (When the slopes are compared, the shallow nature of these curves and the lack of information regarding the error that is contained in the allometric equations should be borne in mind.)

Engineering dimensional analysis and modeling theory compare mammals as physical systems (28). Physical similarity, in the engineering sense, is defined specifically by invariable sets of dimensionless numbers, or criteria of similarity. Dimensionless criteria of similarity are obtained by forming quotients of allometric prediction equations; for example, the quotient of renal blood flow as a percentage of cardiac output reveals that renal blood flow is approximately one-quarter of cardiac output regardless of mammalian species (10):

$$\frac{\text{Kidney blood flow}}{\text{cardiac output}} \times 100 = \frac{43.06W^{0.77}}{166W^{0.79}} \times 100 = 25.9\%,$$

where kidney blood flow and cardiac output are measured in milliliter per minute. The residual mass, $W^{0.77}/W^{0.79}$, is not significantly different from unity and is eliminated from the expression.

Similar equations may be derived from the antibiotic data; for instance,

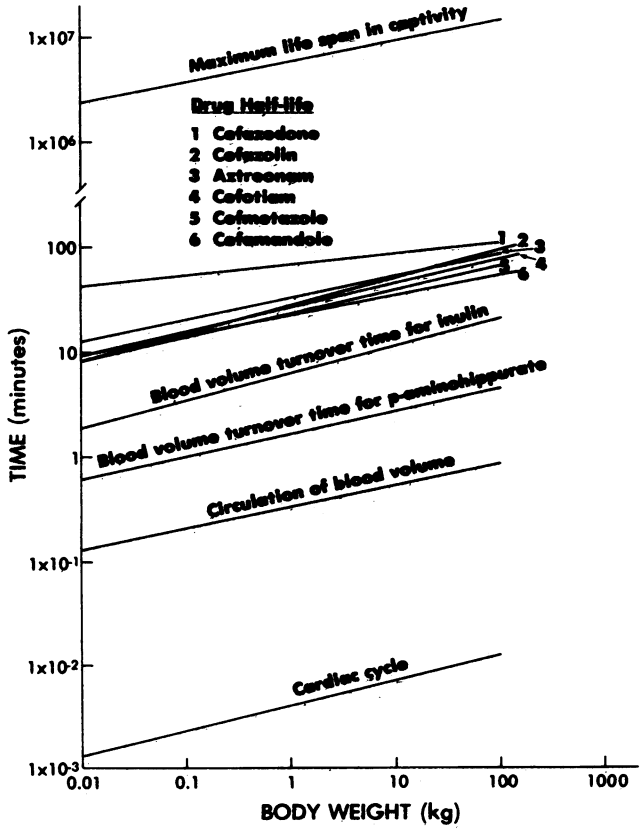

FIG. 2. Log-log plot of antibiotic half-life versus W for cefazedone, cefazolin, aztreonam, cefotiam, cefmetazole, and cefamandole. The log-log relationship of several physiologic indices to W are indicated.

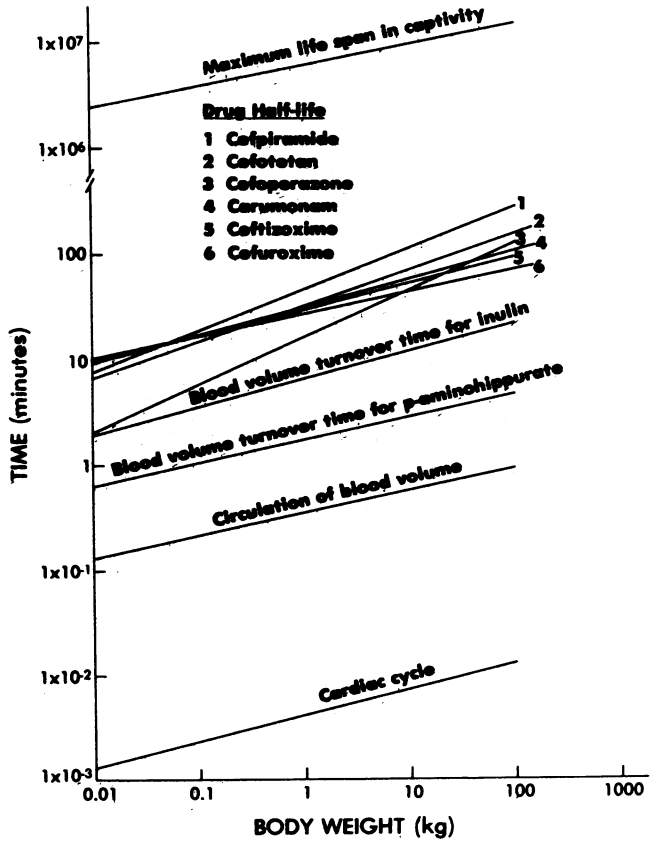

FIG. 3. Log-log plot of antibiotic half-life versus W for cefpiramide, cefotetan, cefoperazone, carumonam, ceftizoxime, and cefuroxime. The log-log relationship of several physiological indices to W are indicated.

$$\frac{\text{Cefmetazole half-life}}{\text{blood volume circulation time}} = \frac{27.8W^{0.206}}{0.35W^{0.21}} = 79.4,$$

where cefmetazole half-life and blood volume circulation time are measured in minutes (Human data are included in the allometric equation.). In other words, 50% of the cefmetazole dose is eliminated in approximately 79 blood circulation cycles regardless of the animal under study. This invariant, dimensionless number, 79, is used to forecast the half-life of cefmetazole in any animal by simply multiplying the blood circulation time (in minutes) of that animal by 79. (The error in estimates formed in this manner is not known because the variance and error in the experimental data are not known.)

A dimensionless criterion of similarity for ceftizoxime can be formed in a similar manner:

$$\frac{\text{Ceftizoxime half-life}}{\text{time for heartbeat}} = \frac{30.1W^{0.248}}{4.15\times10^{-3}W^{0.25}} = 7{,}253,$$

where ceftizoxime half-life and time for heartbeat are measured in minutes. (Human data are included in the allometric equation.) In other words, 50% of a dose of ceftizoxime is eliminated in approximately 7,300 heartbeats regardless of the animal species. This invariant, dimensionless number, 7,300, is used to forecast the half-life of ceftizoxime in any animal in a manner analogous to that of the cefmetazole example. Similar quotients can be obtained from all of the antibiotics in Table 1 and the physiologic indices in Table 2.

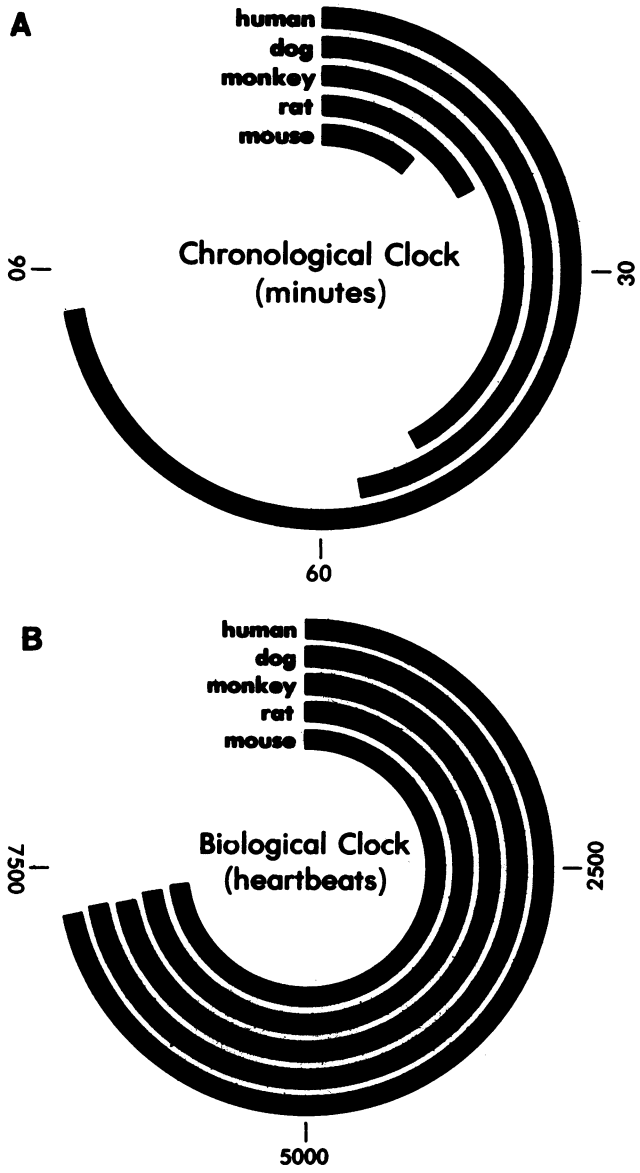

FIG. 4. Ceftizoxime half-life in various mammals depends on the reference system used to denote time. (A) Chronological clock for ceftizoxime half-life based on chronologic time. Half-lives are reported in minutes. (B) Biological clock for ceftizoxime half-life based on physiologic time. Half-lives are reported in heartbeats.

Dimensionless criteria of similarity embody the natural physical properties of the system under study because they rely on internal rather than imposed standards of measurement (27). Dimensionless numbers provide a convenient means of making interspecies comparisons and can be used to construct biological clocks for drug pharmacokinetics. For example, the half-life of ceftizoxime in different mammals appears quite different when it is measured by an external time scale (chronologic time) such as the U.S. standard of time, which is based on the coupling of magnetic moments in the cesium atom (Fig. 4a). When ceftizoxime half-life in these same mammals is measured by an internal parameter (physiologic time) such as heartbeat, the ceftizoxime half-life becomes invariant (Fig. 4b). The successful normalization of chronologic time to physiologic time creates a biological clock and alleviates the problems of interspecies variation in pharmacokinetics.

Physiological dimensionless numbers, such as those obtained in the above examples, define the extent of physical similarity between mammalian species. The disclosure of dimensionless numbers in mammals indicates that well-established quantitative relationships exist among all organs and functions, irrespective of the size and nature of the models (12). These relationships are the basis for successful interspecies pharmacokinetic scaling.

Conclusion. The extrapolation of cephalosporin half-life data from animals to humans demonstrates the methodology employed in interspecies pharmacokinetic scaling and illustrates the relevance of pharmacokinetic studies conducted in animals. In general, care must be taken when interpreting the results of an allometric analysis. There are circumstances when allometric equations might incorrectly forecast drug half-lives: for instance, when the equations are applied to nonlinear elimination data (where half-life has no meaning), when there is great variability in the experimental measurements, when the terminal elimination phase is incompletely characterized or when experimental stress in the animals modifies their renal hemodynamics and subsequently the clearance of the drug.

The practical utility of interspecies pharmacokinetic scaling is governed by the needs of the investigator and the nature of the mathematical output. Successful allometric analyses of pharmacokinetic data obtained in animals can have tremendous impact during the preclinical assessment of newly synthesized antibacterial compounds by providing reasonable estimates of human antibiotic pharmacokinetic parameters. This knowledge will allow research and development teams to decide the pharmacokinetic positioning of new antimicrobial compounds before human studies. Conversely, allometric relationships can be employed to select the proper dose and dosage interval for antibiotic therapy in experimental animal models of infection (J. Mordenti, Proc. Int. Congr. Chemother. 19th, Kyoto, Japan, p. S85–86, 1985.). This type of pharmacokinetic scaling will ensure that the antibiotic treatment the animals receive is both adequate (same peak) and comparable (same area under the curve for each 24-h therapy interval) to the treatment administered to humans. Proper scaling of doses and dosage intervals in animal models will increase the acceptance of antibiotic efficacy trials conducted in animals. Finally, veterinarians can use similar methods of interspecies scaling to select antibiotic dosing regimens for animal species in which antibiotic studies are rarely conducted.

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