Use and Pitfalls of Allometry: A Valuable Tool in Comparisons and Extrapolations Between Species and in Ethical Considerations Concerning the Use of One Species to Model Another

James K. Kirkwood

Universities Federation for Animal Welfare, The Old School, Brewhouse Hill, Wheathampstead, Hertfordshire AL4 8AN, UK
E-mail: *Kirkwood@ufaw.org.uk*

Summary — Where research on one species is justified on the grounds that it will provide benefits to another, the strength of the ethical case depends critically on whether findings can be extrapolated meaningfully. Valid extrapolation depends on the species being sufficiently similar in respects critical to the research and on knowledge of the bases and effects of salient differences. Many biological parameters vary with body weight (W) between species. When species of small size are used to model larger ones, the influence of size on the rates of physiological, immunological and other processes must be taken into account. Between species, the rates of physiological processes tend to increase with $W^{0.75}$, and the durations of physiological events tend to increase with $W^{0.25}$. Providing potential pitfalls are understood, allometric scaling enables valid comparisons and extrapolations between species. Knowledge of these principles is crucial also in making predictions about many aspects of animals' biology and has application also in making sound ethical judgments about the justifiability of extrapolations between species concerning the wide range of processes linked to rates of metabolism.

Key words: *allometry, interspecies variation, laboratory animal care.*

Introduction

Many biological parameters (e.g. anatomical, physiological and life history parameters) have been found to vary in relation to functions of body weight between species. These patterns of variation can be described by allometric equations (e.g. 1), and these equations can provide a logical approach to the estimation of many aspects of the biology of species for which data may be lacking, for example, daily energy and nutrient requirements and appropriate drug dosage regimens. Where the correlation with some function of body weight between species is high, estimates of these characters derived from allometric equations may be reliable enough to preclude or reduce the need for detailed experimental measurements in other species. For example, Riviere *et al*. (2) have suggested that such approaches could have important consequences in avoiding the use of dose-titration studies in the development of some drugs for use in species in which they have not been used before.

As a powerful tool for prediction about many aspects of animals' biology, allometry may, as indicated above, be valuable in helping to avoid unnecessary use of animals in experiments in some circumstances. It can also be a powerful tool for prediction of matters relevant to the care and welfare of laboratory animals where specific data for the species are absent; for example, in predicting appropriate dose regimes for some drugs which offer therapeutic advantages, but for which no pharmacokinetic measurements have been made in the species. Allometry also enables a logical approach to the time-scaling of the duration of experimental procedures or their consequences, which may be helpful in providing insight into this aspect of the severity of these by allowing tentative comparisons with other species (e.g. humans).

The value of allometry for prediction of daily food requirements of a wide range of species of animals is well-established (3, 4). Although there has been skepticism in the past about the value of allometry for predictive purposes in pharmacology (for example, Baggot [5] discussing factors influencing pharmacokinetic variation wrote ". . . the only conclusion that can be drawn is that half-life should not be extrapolated from one species to another".), in recent years, there has been considerable enthusiasm for its use in drug dosage prediction in exotic animal and zoological medicine (e.g. 6) and in other fields (e.g. 7), perhaps at times (by some other authorities), with undue faith in its predictive power. Allometry is, indeed, a very valuable tool for interspecies comparisons and predictions, but it is important to be clear about its limitations.

Derivation of Allometric Equations

If the value of a biological parameter $\boldsymbol{p}$ (e.g. plasma half-life of a drug cleared by renal excretion, daily energy requirement, heart rate, kidney mass) is plotted against body weight ($\boldsymbol{W}$, kg) for a wide range of species of a similar body design (e.g. vertebrates), typically a curvilinear relationship becomes apparent. In the case of heart rate, for example, the larger the animal the lower the heart rate tends to be, but the gradient of the line becomes flatter with increasing size.

Plotting the same data using logarithmic scales (for both y and x axes — that is plotting $\log\boldsymbol{p}$ on $\log\boldsymbol{W}$), it is typically found that the data points are scattered about a straight line. Such lines can be described by the equation:

$$\log\boldsymbol{p} = \log c + b.\log\boldsymbol{W},$$

where b is the gradient (slope) of the line and c is the intercept on the y axis. This equation can be transformed, by taking antilogarithms, to the allometric form:

$$\boldsymbol{p} = a.\boldsymbol{W}^b,$$

where a is the antilog of c. Once values of a and b have been determined in this way, these allometric equations can be solved very easily, using a scientific calculator with exponent function, to generate predictions, from knowledge of $\boldsymbol{W}$, about $\boldsymbol{p}$ for species in which this parameter has not been measured.

In addition to their value in prediction in this way, allometric equations can be useful in other ways. For example, a) they summarise data, and b) determination of the value of b may be helpful in shedding light on the nature of the mechanisms that underlie patterns of variation with body weight. For example, if some parameter describing the rate of a physiological process is found to scale with $W^{0.67}$, this may be because it is constrained by a surface area effect (since surface area scales with $W^{0.67}$ between bodies of the same shape).

When using allometric equations to generate estimates, for example of appropriate drug dose intervals or daily food requirements, it is important to have some understanding of the reliability of the estimates produced. Allometric equations do not describe mathematical absolutes of the sort relating the circumference C of a circle to its radius r:

$$C = 2\pi r.$$

They are statistical summaries whose parameters depend on the quality and nature of the data on which they are based and the statistical method used to derive them. The limitations are outlined below.

Limitations of Allometric Predictions

There are a number of methodological problems that must be considered when analysing patterns of variation among species (8) and when basing predictions upon these patterns (9). Factors that limit the reliability and precision of estimates generated by allometric equations are outlined below.

Statistical methods of derivation of allometric equations

Allometric equations are derived, as outlined above, from regressions that describe the variation of one parameter in relation to another, typically body weight. There are several types of regressions (linear regression, major axis and reduced major axis) and, unless the correlation of $\boldsymbol{p}$ and $\boldsymbol{W}$ is very high, the values found for the gradients and intercepts may depend on which method is used (8). In short, allometric equations depend on the method used in their derivation — they are approximations, not mathematical certainties.

Taxonomic level of analysis

Allometric equations are often used to describe the variation in some parameter between species. In such cases, they should be derived by plotting the mean values for the parameter for each species against the mean body weight for each species, thus generating one, mean, data point for each species. Alternatively, analyses may be carried out to examine variation between individuals within a species, between mean values for families within an order, or between means for each order within a class. The regressions obtained are often dependent on the taxonomic level of the analysis (e.g. 8, 10–12). Bennett & Harvey (12) found, for example, that the allometric exponent in their equations relating resting metabolic rate to body weight in birds varied from > 0.9 between species within genera to < 0.7 between suborders within a class.

Unequal representation of taxa

Biases may be introduced into regressions as a result of unequal representation of taxa. This can occur if, for example, in a comparison between species, some species are represented by a data point from a single individual, whereas others are represented by species means. Or it may occur if the sample contains many representatives of one taxonomic group (e.g. many species from one family) and none or few from other taxa at the same (e.g. family) level (8, 9).

Taxonomic accuracy

Allometric equations for given taxa (e.g. describing variation in metabolic rate in, say, rodents or bats) are dependent on the correctness of the classification system defining the taxa. If a species has been incorrectly assigned to the wrong genus, or a family to the wrong order, or if a taxon has been taken to be a species when, more correctly, it should have been classified as a subspecies or genus, then biases may occur (8, 9). Not infrequently, taxa are re-classified in the light of new evidence on their phylogenetic position.

Data quality

The quality of data is frequently variable. Plasma half-lives can, for example, be difficult to measure, and the conditions under which measurements are made may not be standardised. Since it is not unusual for workers to concentrate on particular taxa (e.g. rodents, ungulates) there is potential for biases to occur in allometric equations derived, due to variation in methodology.

Range of data

When regressions are based on a group species that span only a narrow range of body weights, there is great potential for errors or chance biases in these data to lead to serious miscalculations if extrapolating beyond the range of body weights of the species for which data are available (13).

Precision of predictions

When linear regressions are calculated, the 95% confidence limits of the regressions are often calculated and presented also. These indicate the range within which there is a 95% chance that the regression line for the entire population (from which the sample used to derive the regression was taken) will pass. These limits do not indicate the range within which there is a 95% chance that the value of a parameter, $\boldsymbol{p}$, for an individual of body weight $\boldsymbol{W}$ will fall. The width of this range, between the upper and lower 95% *prediction* limits, is much greater (9). Even when the correlation co-efficient of the regression from which the allometric equation is derived is high, the range between the upper and lower 95% prediction limits tends to be quite wide. For example, even at the value for $\boldsymbol{W}$ at which the limits are narrowest (when $\boldsymbol{W}$ corresponds to the mean for the sample), for regressions relating energy metabolism to body weight, the upper and lower 95% prediction limits are typically about twice and half respectively the predicted $\boldsymbol{p}$ values (9).

Finally, allometric equations derived from analyses of variation in species means can only predict the species mean for an animal of given $\boldsymbol{W}$ (and within the same taxon — e.g. eutherian mammals, vertebrates). The species mean predicted provides no information about likely variation among individuals within a species.

Discussion

Allometric equations provide valuable summaries of the pattern of variation of various parameters ($\boldsymbol{p}$) with body weight ($\boldsymbol{W}$) between species. Where the regressions from which they are derived describe a high proportion of the total variation in $\boldsymbol{p}$, they can, with due regard to the caveats outlined above, be used to generate estimates of $\boldsymbol{p}$ for *similar* species in which $\boldsymbol{W}$ is known but $\boldsymbol{p}$ is not. Although, as discussed above, the reliability and precision of the estimates derived are significantly limited by methodological and other constraints, they can often be good enough to be very valuable in practise. Where no data are available for a particular species, predictions generated from allometric equations may, despite their limitations, provide the only logical approach to estimation of various biological characters and therapeutic needs.

There has been great interest for many years about why energy metabolism has been found quite consistently to scale with about the 0.75 power of body weight ($W^{0.75}$) between species, and several theories have been postulated. It has recently been suggested that it may be a reflection of a biological constraint consequent on the way substrates are transported through space-filling fractal networks of branching tubes, for example, by blood vessels in vertebrates (14). This supports the valuable “rule of thumb” that the rates of physiological processes tend to increase with $W^{0.75}$, and the durations of physiological processes tend to increase with $W^{0.25}$ (1, 3).

It can be useful in many contexts to scale the duration of physiological or other processes between species both for practical purposes, including therapeutics and experimental design, and also to inform ethical judgments about the validity of inferences about one species based on studies of another and in consideration of the possible impact of welfare harms. Such scaling may be valuable for example, a) to estimate appropriate intervals between injections of a therapeutic agent in one species based on knowledge of this in another; b) in considering what period without food in a human might correspond to a 3-hour fast in a mouse; and c) in calculating how often it might be necessary to dose a rat to mimic human exposure to some toxin of x mg/kg/day.

Such estimates can be derived using the following equation (after Kirkwood, 15):

$$t_u = t_k \times (W_u^{\,0.25}/W_k^{\,0.25}),$$

where t_u and t_k are the durations or intervals in the unknown and known species, respectively, and W_u and W_k are their body weights in kg. Thus, a three hour fast in a mouse weighing 0.03kg might, all else being equal, be expected to equate to a fast of 20.8 hours in an animal of similar design but weighing 70kg. Or, to provide another example, if an interval of 12 hours between doses of x mg/kg of a certain drug whose clearance is related to metabolic rate has been found to be appropriate for a species weighing 100kg, all else being equal, it would be logical to make a first estimate that the corresponding dose interval in a similar species weighing 0.1kg would be 2.1 hours. Given the limitations about using allometry for predictions, it would be inappropriate to place undue trust in the precision of such estimates but, as first estimates, they do nevertheless have a rational basis.

Conclusion

In many fields of science, animals of one species are used as models of others. Most commonly, laboratory rodents are used to model human disease or therapeutic processes. However, animal models are also used in veterinary medicine because, for example, it can be simpler and less costly to study principles of physiology, immunology, pharmacology and other aspects of biology in small rodents than in large species (e.g. cattle and horses), or because it may be judged appropriate to investigate diseases of endangered species using non-endangered species as models. Frequently, the animal being used as the model differs in size from that being modelled and usually, because of logistical and economic considerations, the model species is the smaller.

Many agree (e.g. 16) that ethical justification for the use of live animal models should depend upon consideration of the balance of the welfare cost to the animals used against the benefits arising from the study. The strength of the ethical case for the use of one species for studies aimed at benefiting animals of another depends upon, among other factors, the validity of extrapolating results from the one to the other. Extrapolation depends upon there being sufficient similarity between the species with respect to the system under study and being able to account adequately for the effects of whatever differences there may be.

Body size influences many anatomical, physiological and life history parameters between species (1), and when one species is used to model another or when extrapolating therapeutic regimens between species, it is essential to properly take this into account. Allometry, which can be used to describe the ways in which various biological characters scale with body size between species, is a valuable tool for this process. However, there are fundamental limitations as to the reliability and precision of estimates derived from allometric equations, and it is important to be aware of these and not to place undue faith in the predictions.

References

1. Calder, W.A. III. (1984). *Size, Function and Life History*. Cambridge, Massachusetts, USA: Harvard University Press.
2. Riviere, J.E., Martin-Jiminez, T., Sundlof, S.F. & Craigmill, A.L. (1997). Interspecies allometric analysis of the comparative pharmacokinetics of 44 drugs across veterinary and laboratory animal species. *Journal of Veterinary Pharmacology and Therapeutics* **20**, 453–463.
3. Kleiber, M. (1975). *The Fire of Life,* second edition. New York, USA: Robert E. Kreiger.
4. Kirkwood, J.K. (1996). Nutrition of captive and free-living wild animals. In *BSAVA Manual of Small Animal Nutrition and Feeding (*ed. N. Kelly & J. Wills), pp. 235–243. Cheltenham, UK: British Small Animal Veterinary Association.
5. Baggot, J.D. (1982). Disposition and fate of drugs in the body. In *Veterinary Pharmacology and Therapeutics* (ed. N.H. Booth & L.E. Macdonald), pp. 36–69. Ames, Iowa, USA: Iowa State University Press.
6. Sedgwick, C.J. (1986). Scaling and anaesthesia for primates. In *Primates: the Road to Self-Sustaining Populations* (ed. K. Benirschke), pp. 816–822. New York, USA: Springer-Verlag.
7. Mordenti, J. (1985). Forecasting cephalosporin and monobactam antibiotic half-lives in humans from data collected in laboratory animals. *Antimicrobial Agents and Chemotherapy* **27**, 887–891.
8. Harvey, P.H. & Mace, G.M (1982). Comparisons between taxa and adaptive trends: problems of methodology. In *Current Problems in Sociobiology* (ed. King's College Sociobiology Group), pp. 343–361. Cambridge, UK: Cambridge University Press.
9. Kirkwood, J.K. & Bennett, P.M. (1992). Approaches and limitations to the prediction of energy requirements in wild animal husbandry and veterinary care. *Proceedings of the Nutrition Society* **51**, 117–124.
10. Hayssen, V. & Lacy, R.C. (1985). Basal metabolic rates in mammals: taxonomic differences in allometry of BMR and body mass. *Comparative Biochemistry and Physiology* **81A**, 741–754.
11. Heussner, A.A. (1982). Energy metabolism and body size. I. Is the 0.75 mass exponent a statistical arti-

fact? *Respiration Physiology* **48**, 1–12.

12. Bennett, P.M. & Harvey, P.H. (1987). Active and resting metabolism in birds: allometry, physiology and ecology. *Journal of Zoology* **213**, 327–363.
13. Blaxter, K.L. (1989). *Energy Metabolism in Animals and Man*. Cambridge, UK: Cambridge University Press.
14. West, G.B., Brown, J.H. & Enquist, B.J. (1997). A general model for the origin of allometric scaling laws in biology. *Science, New York* **276**, 122–126.
15. Kirkwood, J.K. (2001). Dose estimation from body weight. In *The Veterinary Formulary* (ed. Y. Bishop), fifth edition, p.644. London, UK: The Pharmaceutical Press.
16. House of Lords Select Committee (2002). *Select Committee Report on Animals in Scientific Procedures, Vol. 1*, 81pp. London, UK: The Stationery Office Limited.