Allometric Scaling in Pharmacokinetic Studies in Anesthesiology

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Nearly everyone recognizes that larger individuals usually require larger doses (in mass units) to achieve the same drug effect as in smaller individuals—hence, the common practice of defining drug doses on a per-kilogram basis. Clinicians in anesthesia learn that refinement of this principle is necessary at the extremes of individual size.[1] Children typically require greater doses (per kilogram) compared to adults,[2] whereas doses are often lower (per kilogram) for larger individuals, but without strict fragmentation into discrete subgroups. Clinicians may rightly wonder whether these principles apply only to anesthetic drugs or whether it is a broader biologic phenomenon supported by theory. Are these principles useful within a restricted population of nonobese adults, where sizes of the individuals are similar? What about studies in adults and children? What about larger obese individuals? Clinicians may also wonder whether these principles have a role in the pharmacokinetic models that appear in the scientific literature touted to predict drug responses and help guide drug dosing. Do they influence model accuracy, applicability, robustness, or clinical safety?

Looking further than the differences in drug dosing between children and adults, many clear patterns and interrelationships can be found across the incredible diversity of biology. For example, larger animals have slower heartbeats and lead longer lives, which raises questions about how these characteristics may be related. The study of allometry focuses on understanding biologic processes across a diversity of sizes. Allometric theory is a cohesive system of ideas based on general principles intended to explain the relationship between body size and diverse characteristics. The advantage of a theory is that it can make predictions about observations and their interrelationships.

Pharmacokinetic Model Development

Pharmacokinetic models predict drug concentrations from the time of drug administration until elimination from the body. They are useful for understanding the biologic process of drug transport and elimination, and to guide drug dosing. Model development starts with an initial model, and modifications are proposed and evaluated for their evidence in the data. A modification is "accepted" into the model if it provides a better description of the data. This propose–evaluate–accept/reject cycle is repeated until no further improvement can be found. This is data-driven analysis.

The choice of initial model is not data-driven because it is defined before consideration of the data. Its justification can come from a theoretical basis, information obtained from previous studies, or other considerations. Allometric theory can be useful to guide the choice of initial model with respect to size scaling, but does not address other sources of variability. As data-driven analysis proceeds, the final model can deviate from allometric theory if the evidence supports that.

Allometric Scaling

The term *allometry* originated from Huxley and Teissier[3] as a way to unify nomenclature in the study of relative growth (*i.e.,* the relationship between proportions and size). Allometric equations are often exponential functions where Y is some characteristic of interest, a is a derived constant, b is the scaling exponent, and *size* is a measure of body size, usually total body weight, with $size_{ref}$ as a comparator.

$$Y = a \cdot \left(\frac{\text{size}}{\text{size}_{\text{ref}}} \right)^{b}$$

The counterpart to allometry is isometry, where a proportion of interest remains constant while size varies. In other words, $b = 1$.

Allometric scaling is used widely in the biologic sciences and in diverse applications (*e.g.,* quantifying tumor growth).[4] In pharmacokinetics, it is used for extrapolation of the results of animal research across species[5] and for the estimation of model parameters in humans.[6] The justification is that there are anatomical, physiologic, and biochemical similarities across species that can be applied for a general mathematical analysis. It has found increasing application to pharmacokinetic modeling; however, this has not been without controversy.[7,8]

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West–Brown–Enquist Allometric Model

The compelling contribution of West *et al.*[9] was a mathematical model of cardiovascular and respiratory systems that we now refer to as the *West–Brown–Enquist model*. The assumptions of the model are quite technical and focus on its hierarchical space-filling nature, energy efficiency, and exchange surface limited to the terminal branches. These are examined in detail by Savage *et al.*[10] Based only on these assumptions, a mathematical derivation can be performed that—while unfortunate in its requirement of a strong mathematical background for understanding—can produce easily interpretable results. Body size can be defined to scale linearly (exponent = 1) with body weight and blood volume. Metabolic rate and cardiac output (mass · time^{-1} or volume · time^{-1}) scale to a 0.75 exponent of body size, and circulation time scales to a 0.25 exponent of body size. Of course, this presents an extremely simplified model of biologic processes, and there is considerable debate regarding its consistency[11] and assumptions.[12] It is also not clear whether the theory may be useful under perturbed physiologic conditions (*e.g.,* rapid changes in blood pressure or cardiac output).

Allometric Scaling in Pharmacokinetic Models

Pharmacokinetic modeling uses compartmental models of volumes of distribution and clearances that are not directly addressed by the West–Brown–Enquist model. Total body weight (indicated as *WGT* in the equations that follow) can be used as a body size measure because of its wide availability. It seems appropriate to scale compartmental volumes linearly (exponent = 1) with blood volume (and thus, body size). Elimination and intercompartmental clearances (volume · time^{-1}) may scale to a 0.75 exponent, similar to metabolic rate and cardiac output. Time constants may scale to a 0.25 exponent, similar to circulation time, or equivalent rate constants (time^{-1}) may scale to the −0.25 exponent, provided the process involved is determined by material (mass) transport through the distribution network. Equations for a simple allometric compartmental pharmacokinetic model would be

$$size = \frac{WGT}{WGT_{ref}} \qquad V = V_{ref} \cdot size^{1} \qquad CL = CL_{ref} \cdot size^{0.75}$$

$$k = k_{ref} \cdot size^{-0.25}$$

where WGT_{ref} is the weight of a hypothetical reference individual and functions as a comparator. These equations are illustrated in figure 1. If reference values are estimated from data, it does not matter what weight is used for the reference individual. Often it is 70 kg, which makes interpretation more meaningful and differences in drug properties between studies easier to discern.[13] Other body size measures may be used, such as estimates of lean body weight or fat-free mass,[14] appreciating that differences in body composition may allow for a better match between the model and biology. Interpolation is also possible using normal fat mass.[15]

The equations in this section and the Allometric Scaling section assume a fixed proportion of "physiologically active" to "excess" weight. This may not be true for obesity, which is an issue of body composition,[16] and may or may not be reflected in the pharmacokinetic model. This likely depends on physiochemical drug properties, such as fat solubility. Allometric models do not provide an explanation for pharmacokinetic changes with obesity; they do, however, reduce drug dose (per kilogram) for larger obese individuals, which is likely clinically appropriate.[17] For example, the remifentanil models developed by Eleveld *et al.*[18] and Kim *et al.*[19] applied in severely obese individuals both result in dosing close to recommendation (with minor exceptions) when targeting about 4 ng/ml plasma concentrations.[20] This is illustrated for steady state infusion rates in figure 2. This is an extrapolation for the allometric Eleveld model because few obese individuals were used in model development, but it behaves similarly to the Kim model, where many obese individuals were included in model development.

Allometric scaling equations are, by definition, focused on the influence of size and do not address other factors. For pharmacokinetics, some potential confounding factors are maturation, aging, disease, and differences in body composition, among many others. The presence of these confounding factors makes it difficult to determine whether some observational data are or are not consistent with allometric scaling theory. No theoretical framework is available for these factors, and the modeling approaches are empirical.

Pharmacokinetics usually involves multiple processes, and current models use multiple compartments. Each compartment is considered to be comprised of different tissues with similar pharmacologic properties and treated as a single mathematical entity. The interactions of a drug with the structural and physicochemical properties of the tissues represented by the compartments define the associated reference values. From this perspective, the compartmental volumes and clearances can be seen as properties of those tissues and not of the body as a whole. Using V/V_{ref} as a size descriptor is referred to as *compartmental allometry*[21] because it applies allometric scaling at the compartment level. It seems most applicable to peripheral compartments where clearances are intrinsic properties of the tissues represented by the compartments.

Evidence from the Literature

Sinha *et al.*[22] examined lean liver volume (*LLV*) in humans using computerized tomography and found two equations consistent with the data: (1) $LLV = k \cdot WGT^{0.75}$, and (2) $LLV = k \cdot FFM^{1} \cdot (1.21\ if\ female)$, where k is a proportionality constant and *FFM* is the fat-free mass predictor of Janmahasatian *et al.*[14] If hepatic drug clearance is proportional to lean liver volume,[22] then this result supports the practice of using the West–Brown–Enquist model theoretic 0.75 exponent of body weight to scale hepatic drug clearance in pharmacokinetic models. Alternatively, predicted fat-free mass could be used with a correction factor for females. The justifications for

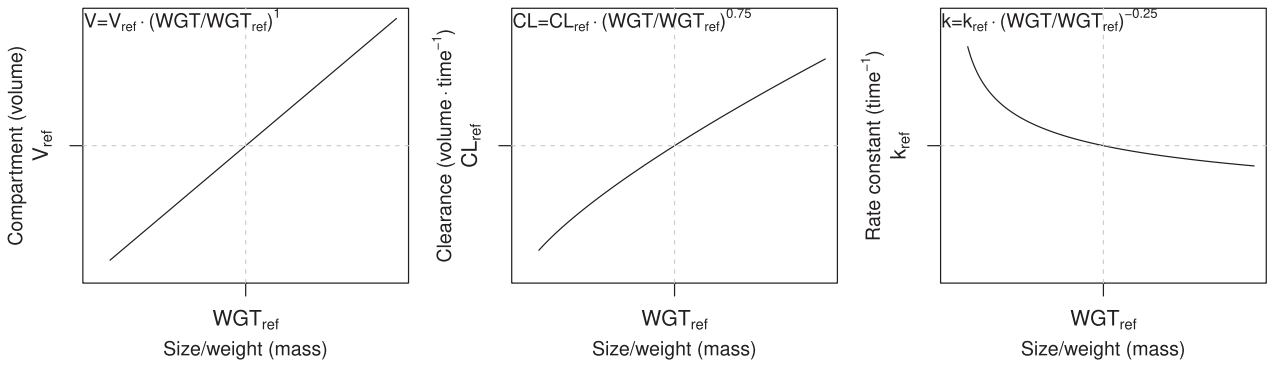

Fig. 1. Example allometric scaling equations. CL, drug clearance; k, rate constant; V, compartmental volume; WGT, body weight. Subscript *ref* indicates a reference value that functions as a comparator.

each equation for scaling drug clearance are different, and it is not clear which is "better" and under which circumstances.

The idea that hepatic drug clearance is proportional to lean liver volume suggests that one or more of the West–Brown–Enquist assumptions must not be valid for human livers, specifically, the assumption of minimal energy loss of fluid flow seems likely incorrect for organs in isolation because of their specialized role within the body as a whole. The application of allometric scaling theory at the organ level needs further exploration, and many questions remain (*e.g.,* terminal elimination may scale with body size differently than intercompartmental clearances, but this has not yet been examined in the literature).

For pharmacokinetics, the West–Brown–Enquist model theoretic scaling exponents of 1 for volumes and 0.75 for clearances do appear adequate in many situations provided maturation is complete. Eleveld *et al.* developed a pharmacokinetic model for remifentanil[18] that included data from children and adults with fat-free mass[23] as a body size measure. The supplementary documents of that study show that when only weight scaling is used, the estimated weight-scaling exponents differ from theoretical exponents.

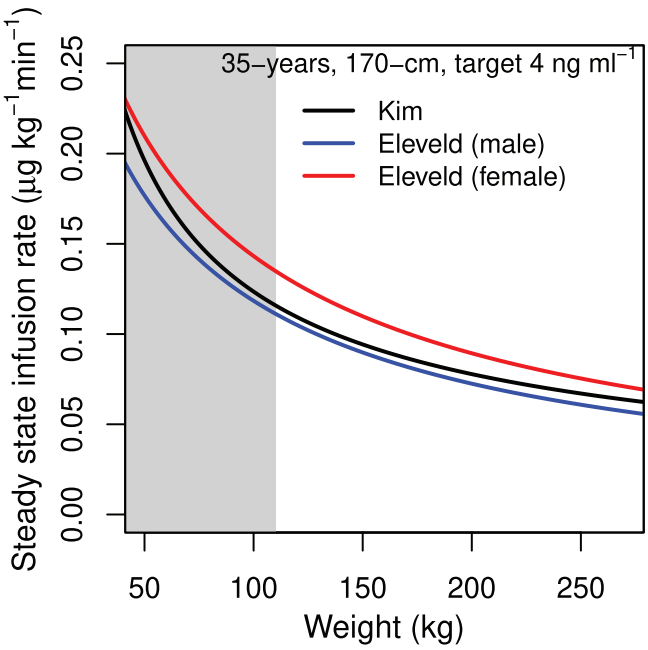

Fig. 2. Steady state infusion rates targeting 4-ng/ml remifentanil concentrations for the Kim and Eleveld models. The allometric Eleveld model behaves similarly to the Kim model for obese individuals, even though model development for the Eleveld model considered few obese individuals (as shown in the *gray shaded area*).

However, when other covariates were considered, the best performing final model used theoretical exponents. Calvier *et al.*[24] studied a physiologically based pharmacokinetic simulation and found that a 0.75 allometric-scaling exponent is suitable for predicting drug clearance in children older than 5 yr. Liu *et al.*[25] found the 0.75 exponent adequate for designing pediatric studies based on adult data for children older than 2 yr, although this obviously does not remove the need for pediatric studies. Mahmood *et al.*[26] recognized that a 0.75 scaling exponent is useful for predicting mean drug clearance for children older than 5 yr. Two other studies[27,28] suggest that it is reasonably useful for extrapolating dosing from adults to children older than 5 to 6 yr. Models for propofol[29] and vancomycin[30] developed for very broad populations, including neonates, children, adults, elderly individuals, and obese individuals, used the theoretical weight-scaling exponents for individuals older than 6 months and 2 yr, respectively.

Cella *et al.* found that a 0.75-scaling exponent for midazolam clearance resulted in poor extrapolation between the infants/toddlers and children groups.[31] It should be noted that they did not use a full West–Brown–Enquist model, did not consider maturation,[32] and did not ensure smooth covariate relationships across group boundaries. It is not clear whether they would have reached the same conclusion if they addressed these issues.

Knibbe *et al.*[33] developed an allometric model to predict propofol pharmacokinetics in rats, children, and adults. They estimated allometric exponents and found theoretical values close to those of West–Brown–Enquist for both volumes and clearances. Bae *et al.*[34] also estimated allometric-scaling exponents in their study of fentanyl pharmacokinetics in 95 adults. The 95% CI for the exponent for the compartmental volumes did include the theoretical value of 1; however, the estimated exponent for clearance was 0.313 (95% CI, 0.037 to 0.583), lower than the theoretical value of 0.75. The influences of age and body composition do not seem to have been part of the analysis, so it may not be possible to resolve their roles in an unambiguous way. Sinha *et al.*[35] found that more than 100 adults must be included to discriminate scaling exponents with low bias and adequate false-positive rates. With normal or high between-subject variability, it is almost impossible to differentiate scaling exponents with fewer than 200 individuals. Therefore, estimating allometric-scaling exponents does not reliably defer the selection of scaling exponents to data-driven analysis.

Disproving Allometric Scaling

A theory is disproven if observations are made that are logically impossible if the theory is true. Mahmood suggests that the West–Brown–Enquist model is disproven if estimated weight scaling exponents do not match theoretical values.[36] This conclusion requires that (1) the correct size measure be known with certainty; and (2) no confounding processes significantly influence the observation. These are unlikely to be true for pharmacokinetic studies. As an illustration, the fentanyl clearance function found by Bae *et al.*[34] $CL = CL_{ref} \cdot (WGT / 70)^{0.313}$ is identical to $CL = CL_{ref} \cdot ((WGT / 70)^{-0.417})^{0.75}$, which would be interpreted as theoretical allometric-scaling exponents with an empirical size measure. Also identical is $CL = CL_{ref} \cdot (WGT / 70)^{0.75} \cdot (WGT / 70)^{-0.437}$, which would be interpreted as theoretical allometric scaling exponents with an additional empirical covariate relationship. The covariate relationship could also be with age or body composition, which are often correlated with weight. If these alternatives cannot be excluded, then the estimated exponent does not disprove the West–Brown–Enquist model. This also shows that an estimated exponent is a data-derived, covariate relationship and should be handled with an appropriate threshold of evidence. In contrast, using theoretical exponents enables size scaling without additional parameters. This likely creates more useful models compared to those without size scaling.

If a theory is disproven, it may still be possible to modify to account for new evidence. Should evidence be found that disproves the West–Brown–Enquist model, it is prudent to examine which assumptions are violated and whether or not they can be corrected. Modified assumptions considering finite network size[10] or asymmetry[37] may lead to an improved theory that matches new evidence. This is better than rejecting the theory in its entirety and using empirical models without explanatory power.

Ontogeny and Maturation

The physiologic structures and processes underlying some pharmacokinetic characteristics such as drug clearance may not be present in unchanged form and function from conception to adulthood. These changes are outside of the scope of allometric theory and must be addressed by some other model.

Peeters *et al.*[38] found that a propofol pharmacokinetic model that predicted propofol pharmacokinetics in rats, children, and adults overestimates propofol clearance in neonates and infants when theoretical or estimated allometric exponents are used. This is consistent with the idea that the physiologic processes underlying propofol clearance are immature in neonates and infants, and are less functional for drug clearance compared with adults.

Anderson and Holford[39] suggest the use of an empirical maturation model as a function of postmenstrual age to adjust the allometric overprediction smoothly from premature neonates to adults. An example is shown in figure 3. This approach has been proposed by Germovsek *et al.*[40] as a pharmacokinetic standard for drug clearance and has been shown to perform as well as other methods.[26,41] Hybrid allometric–physiologic-based pharmacokinetic models have also been investigated to describe drug-specific maturation functions.[42]

Fixing allometric scaling exponents to theoretical values is recommended by the European Medicines Agency

(Amsterdam, The Netherlands) when analyzing pediatric data with maturation models.[43] Otherwise, the correlation between age and weight typical for pediatric studies is likely to cause numerical issues.[44]

Some researchers eschew the maturation model and prefer varying weight scaling exponents across the population with body weight[45] or age. Some functional forms[26,46] are illustrated in figure 3. These behave similarly to maturation models provided the exponents are greater than 0.75 for younger/smaller individuals, and this is true for published models. Krekels *et al.*[47] used a physiologic-based pharmacokinetic workflow and found that for scaling clearance from adults to young children, an exponent of 1 was useful for children older than 1 month for drugs undergoing glomerular filtration and for children older than 2 yr for most hepatically cleared drugs. Mahmood *et al.*[26] advocate for an age-dependent exponent for the selection of first-in-children dose during drug development that also shows exponents greater than 0.75 for children younger than 5 yr. The age-dependent exponent method is not objective as it is based on the authors' previous experiences, observations, and data analyses, and uses discrete age groups.

Criticism

A number of criticisms of the West–Brown–Enquist model for pharmacokinetics have appeared in the literature, although the theory is often faulted for things outside of its scope. It lacks an ontogenetic perspective,[36] but this should probably not be expected from a theory of size. Another criticism is that allometric scaling is intended for extrapolation across species, not within species. The concept of species (however defined) is not part of the West–Brown–Enquist model, and it is not clear how it would be invalid within species.

Fisher and Shafer suggest that linear scaling should be assumed unless the data better support allometric scaling,[7] with their focus on improving model usability by facilitating mental calculation of drug doses. Our view is that allometric equations are not problematic because of the ubiquity of computing power. If computers are not available, then nomograms, tabulations, or approximating equations may be helpful. The fact that most pharmacokinetic studies examine restricted populations and cannot differentiate allometric from linear scaling demonstrates a lack of evidence; this cannot be used as evidence for either approach.

It is sometimes claimed that allometric scaling is inherently empirical. This is true when an estimated- weight *versus* -parameter relationship is used; however, the West–Brown–Enquist model does have a theoretical derivation.

The limitations of the West–Brown–Enquist model and the practical difficulties with conclusively evaluating the theory should certainly be viewed as weaknesses compared with other theories of size of equal utility. However, no alternative theories are presented based on a system of ideas and general principles, and neither quantitative corrections nor refinements appear in the pharmacokinetics literature.

Clinical Aspects of Allometric Scaling

Allometric scaling primarily concerns the expectations and decisions made at the start of a clinical case because size does not change intraoperatively. Of course, it is only one of the many factors influencing pharmacokinetics and optimal drug dosing.

Models developed and applied in restricted populations (*i.e.*, in adults only) are unlikely to strongly differ in predictive performance between allometric and nonallometric methods, and therefore may appear to have equal utility. However, clinicians are not always aware, and do not understand the limitations, of a development population, and model developers are not able to restrict the populations to which their

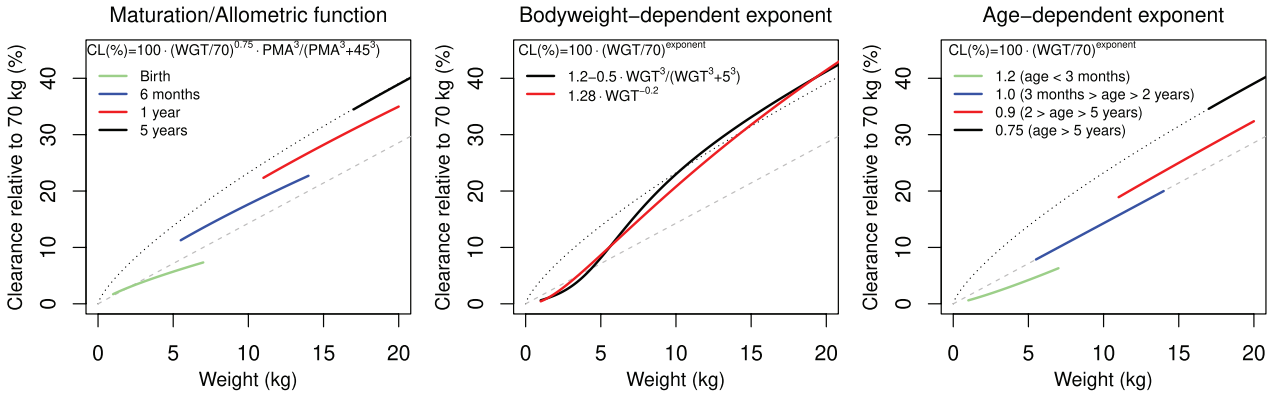

Fig. 3. Illustration of three different functions proposed for scaling of drug clearance in young children: maturation/allometric, body weight–dependent, and age-dependent scaling. All three methods predict reduced clearance for young/small children compared with CL = 100 · (WGT/70)$^{0.75}$ (*dotted black line*). A linear model, CL = 100 · (WGT/70)^{1} (*dashed gray line*), extrapolates reasonably from adults to young/small children but underpredicts drug clearance for older/larger children. CL, drug clearance (relative to 70-kg adult); PMA, postmenstrual age (in weeks); WGT, body weight (in kg).

models are applied. Therefore, it is a clinical reality that pharmacokinetic models are sometimes extrapolated with caution outside of their development population. Model extrapolation can also occur by accident *via* user error. Figure 4 illustrates the misprediction of drug clearance when the incorrect model is selected in children and adults and a 0.75 scaling exponent is approximated by weighted linear scaling. If drug clearance is over- or underpredicted, then initial dosing decisions are likely to be nonoptimal, in need of systematic corrections and increased clinician workload. The consequences of misapplication can be minimized by enabling reasonable model behavior outside the development population. The 0.75 scaling exponent of the West–Brown–Enquist model is consistent with evidence in the literature for extrapolating drug clearance from adults to children. The model does not address obesity, but does what clinicians are likely to expect: decreases the dose per kilogram for larger individuals. Clinicians are likely to benefit from allometric models because of their reasonable model behavior across broader populations compared with other scaling methods.

The risks of model extrapolation can be substantially prevented by developing the model from data from very broad, diverse populations. Current models developed in this way uniformly incorporate some form of allometric scaling and scale drug clearance by an exponent less than 1. When these allometric models are used, clinicians benefit from a reduced burden of understanding the limitations of multiple models and a reduced risk of selecting an incorrect model.

Summary

The West–Brown–Enquist model is no exception to the "all models are wrong" aphorism,[48] but it does provide a quantitative explanation for the clinical observation that children typically require greater doses (per kilogram) than adults; this is consistent with experimental results. Allometric scaling concerns the expectations and decisions made at the start of a clinical case, and clinicians benefit from a reduced risk of selecting an incorrect pharmacokinetic model to guide drug dosing.

The theoretical scaling exponents of the West–Brown–Enquist model appear useful, especially for adults and children older than 2 to 5 yr. Given its support in the literature, its theoretical foundations and lack of alternative theories, and its practical advantages for clinicians, it should be used in the absence of contradicting information. This indicates its use as an initial model for pharmacokinetic model development. Data-driven analysis can result in models that deviate from theory, provided evidence is given and the observations cannot be reasonably explained by other sources of

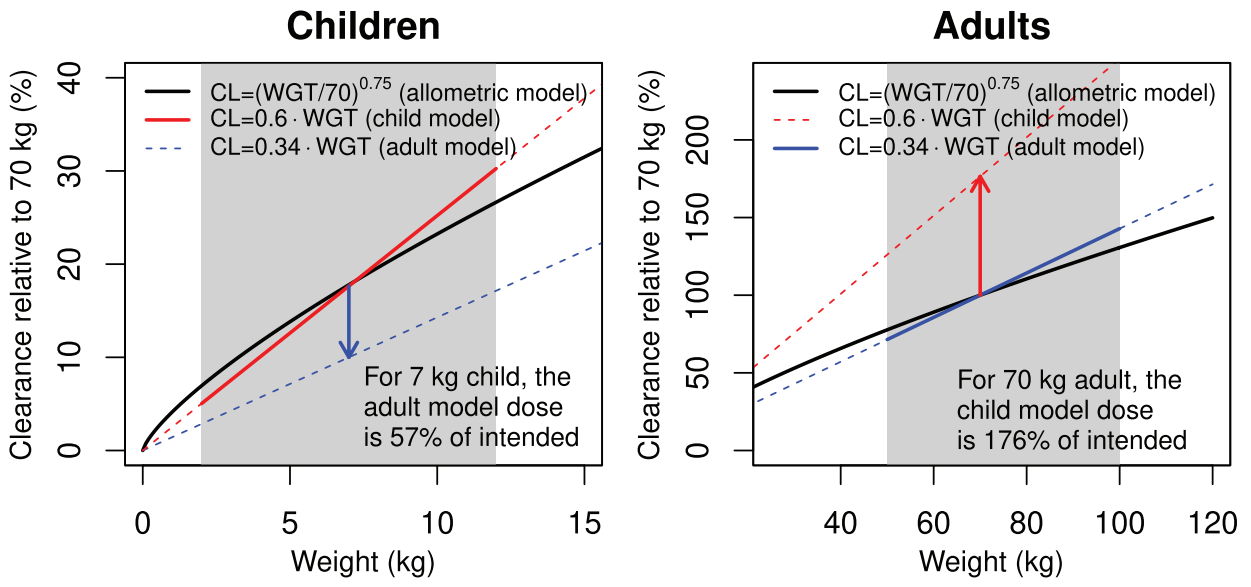

Fig. 4. Clearance predictions for linear weight scaled adult and children models *versus* an allometric model. The *black lines* are the allometric model; *straight lines* are weight linear models developed for children (*red*) and adults (*blue*). *Dotted lines* indicate extrapolated predictions. *Gray shaded area* indicates the weight range of the children and adult populations. Within the children or adult populations, the allometric model is closely approximated by the linear model. If an error is made and the incorrect model is chosen, the predicted clearance will be 57% of intended in children and 176% in adults and will likely result in nonoptimal initial dosing. This error cannot be made with the allometric model. CL, drug clearance (relative to 70-kg adult); WGT, body weight (in kg).

variability. This results in models consistent with the data and, as much as possible, with widespread clinical experience. The limitations of the West–Brown–Enquist model should be a stimulus for improvements and corrections, not abandonment for empiricism lacking general principles.

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Competing Interests

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Anesthetic Safety Was No Mystery for Paul M. Wood, M.D.

In her quintessential detective novel *Green for Danger* (1944, *left*), Christianna Brand composed a riveting who-done-it amidst the backdrop of a rural British World War II hospital. The local postman was rushed to surgery, but his delivering days were done after a mislabeled medical gas tank spelled the end. Drawing directly upon her volunteer experiences in the military hospitals during the war, Brand illuminated the safety hazards in amassing non-standardized gas cylinders (*right*). Already investigating this polychromatic puzzler in the United States, Paul M. Wood, M.D., Founder of the Wood Library-Museum of Anesthesiology and Secretary of the American Society of Anesthetists, led a coalition of physicians, hospitals, and industry groups who petitioned the United States National Bureau of Standards to recognize uniform color coding of medical gases in 1941. Providing wartime anesthesia in a military hospital was notoriously chaotic and complex with heterogeneous supplies. Thankfully, safety super-sleuth Wood was on the case. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology, Schaumburg, Illinois.)

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