A REVIEW OF ALLOMETRIC SCALING WITH CONSIDERATIONS FOR ITS APPLICATION TO REPTILE THERAPEUTICS

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The principals of allometric scaling and the consideration of metabolic size in therapeutics have been introduced in a number of forums[1,3,4,6,7,8] in recent years. The purpose of this discussion is simply to review these concepts and discuss the potential application of these theories to reptile therapeutics.

The use of allometric scaling for the calculation of drug doses is a practice with which most practitioners are familiar through the use of chemotherapeutic agents in cancer therapy. Treatment protocols involving these highly toxic chemicals often use a mg/square meter (m^2) basis for calculating doses rather than the mg/kg basis traditionally used for most other drugs. The meter squared variable is derived using Meeh's formula ($K(W_{kg}^{0.66})/10^2$) which relates the body surface area of an animal to its metabolic rate. This formula was originally derived by physically attempting to measure the external surface area of a variety of mammals. The rationale for using this relationship is that as an animal decreases in size, the ratio of surface area to body mass increases as does the animal's metabolic rate. Conversely, as size increases, the ratio of surface area to body mass and the metabolic rate decrease. Thus, changes in surface area more accurately reflect changes in metabolic rate (and therefore drug metabolism) than does simple body mass. Using a metabolic basis for determining doses of these drugs has been found to allow maintenance of blood levels of drug within the same therapeutic range in a variety of patients. As expected, the implications of this phenomena are even more profound when dealing with animals of highly disparate body sizes, as are routinely encountered in exotic animal medicine.

A more accurate assessment of metabolic rate as it applies to pharmacokinetics is based on a formula which determines the minimum energy cost (MEC) of a animal. This allows an assessment of an animal's metabolic machinery at the level of capillary beds, glomeruli, alveoli, etc., the level in the body at which the uptake, distribution, biotransformation and clearance of any drug occurs. This therefore provides a method of incorporating these metabolic parameters into therapeutic considerations.

In order to compare animals across different "metabolic taxa," five different energy classes have been designated based on groups of animals which have the same mean core body temperature range. Constants (K) have been identified by Hainsworth for each of these groups and are used in all extrapolations.

Energy Group	Constant (K)
Passerine bird	129
Non-passerine bird	78
Placental mammal	70
Marsupial mammal	49
Reptile	10

Minimum Energy Cost (MEC) is calculated by raising the lean body mass of the animal to the three-quarter power and multiplying this quotient by the appropriate energy group constant $K(W_{kg}{}^{0.75})$. When dealing with reptiles and other poikilotherms, it is important to remember that standardization of body temperature is necessary for legitimate extrapolations. Therefore, poikilotherms must have their environmental temperature adjusted so as to achieve an optimal core body temperature of approximately 37°C.

With these principles in mind, it is a simple matter then to apply them to specific therapeutic regimes by employing a few arithmetic calculations, all of which can be rapidly performed on a pocket calculator. In order to scale a dose of a particular drug for a patient animal, it is first necessary to extrapolate from a known effective dose in a model animal. Optimally, this model dose would be based on pharmacokinetic studies in the same or similar species to your patient; however, with drugs that are metabolized by similar physiologic phenomena at the cellular level in all species, it is possible to extrapolate across taxonomic lines.

First, it is necessary to convert your model animal's dose and treatment frequency from a mg/kg basis to a metabolic basis. Note that once this step is completed for a given drug, the metabolic dose and freqency can be recorded in a formulary and used in future calculations for other patients.

The following steps will allow you to extrapolate a metabolic, or MEC dose:

-- Calculate Minimum Energy Cost (MEC) of the model animal. $MEC=K(W_{kg}{}^{0.75})$

-- Calculate a Treatment Dose (the mg/kg dose) for your model animal.

-- Divide this Treatment Dose by the MEC of the model animal to obtain the MEC Dose.

The next step is to extrapolate a frequency of administration. This again is alculated from your model animal dose:

-- Calculate the Specific Minium Energy Cost (SMEC) of the model animal. $MEC=MEC/W_{kg}$ or $K(W_{kg}{}^{-.25})$.

-- Calculate a Treatment Frequency by dividing 24 hours by the hourly treatment interval of the model animal; e.g., for a model TID treatment, calculate the treatment Frequency by dividing 24 hours by 8 hours to obtain 3.

-- Divide the Treatment Frequency calculated above by the model animal's SMEC to obtain the SMEC Frequency of this drug.

(Remember that the calculated MEC Dose and SMEC frequency can now be used to calculate doses for future patients in which this drug will be used).

Now calculate the dose and treatment frequency for your patient animal:

-- Calculate the MEC for your patient

-- Multiply the patient MEC by the MEC Dose for this drug as calculated above. This equals the mg of drug per treatment.

-- Calculate the SMEC for your patient.

-- Multiply the patient SMEC by the SMEC Frequency for this drug as calculated above. This equals the number of treatments per 24 hours.

It is sometimes desirable to alter the frequency of administration from the calculated rate; e.g., in an animal in which the calculated frequency is six times/day, the stress of handling this frequently for treatment may outweigh the benefits of the therapy. To calculate a new frequency:

-- Multiply the mg/treatment by the treatments/24 hours to obtain the mg/24 hours.

-- Divide this by the frequency you wish to use to obtain a new mg/treatment.

As a caution, remember that by changing the frequency of administration and thereby changing the amount of drug given at each dose, it is possible to create peaks and troughs in serum concentration which either exceed safe levels or fall below the effective therapeutic range of the drug.

As with any dosing regime, including those derived using the traditional mg/kg dose, a knowledge of the pharmacology of the drug, and in particular the pharmacokinetic differences between species, must be taken into account, especially when extrapolating across taxonomic lines. This appears especally important in treatment regimes involving extrapolations from homeoterems to poikilotherms. As previously mentioned, a body temperature within the optimal metabolic range must be maintained in order for results to be predictable. For some reptiles, especially those that spend a portion of their natural life cycle in a state of torpor, merely warming the animal may not be enough to reach a metabolically active state. An assessment of heart rate as a metabolic indicator may be more useful than cloacal temperature in these cases.[5] An apparent paradox to the allowmetric principles was noted by Mautino and Page[2] When they reported that higher doses of some drugs were needed to achieve effective serum levels in large tortoises than were seen to be effective in smaller animals. It is possible that differences such as absorption rates, which may be extremely slow in the larger animals, could result in partial metabolism of the drug before effective blood levels are attained, thereby increasing the clinically effective dose.[5] Another speculation, based on clinical observation, is the possible existence of hyperosmotic states which may be achieved as natural phenomena in certain species, such as as desert or marine animals, which normally experience very different environmental conditions from other species.[5] Differences in serum osmolarity would naturally influence the pharmacokinetics of a drug introduced to this system. Clearly more exploration of these issues along with further pharmacokinetic studies will greatly enhance the usefulness of the principles of allometric scaling in regard to therapeutics in reptiles.

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