Allometric Scaling

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You will eventually be confronted with having to treat a species with which you are not familiar. This will always happen, and you should always be prepared for it. Determine a treatment protocol. This can be the most difficult hurdle. Some of the treatments which are administered to "exotic" animals:

a. may be effective;
b. may be ineffective, because the animal has been:
    (i) underdosed;
    (ii) recovers regardless of treatment; or
    (iii) the treatment is ineffective and the animal becomes sicker
c. may be harmful due to overdose or toxicity.

The members of the animal kingdom differ in appearance, speed of movement and size. The Table shows the size ranges of various living organisms, in increments of 10^3 between each step.

Organism	Mass	
Mycoplasma	<0.1 pg	$<10^{-13}$ g
Average Bacterium	0.1 ng	10^{-10} g
Average ciliate	0.1 ug	10^{-7} g
Amoeba	0.1 mg	10^{-4} g
Bee	100 mg	10^{-1} g
Guinea pig	100 g	10^{2} g
Human	100 kg	10^{5} g
Blue whale	>100 tons	10^{8} g

The difference between the smallest and the largest is 10^{21}. It is difficult to appreciate these numbers, but if you imagine an organism 10^{21} times the size of the blue whale, it would be 100 times the volume of the earth. The mass of the universe is estimated to be 10^{80} grams. In clinical practice we encounter animals of different sizes, and these have a range of resting-state metabolic sizes, body sizes, and morphologies. This creates a problem when you must extrapolate drug doses from one clinical subject to another.

Traditionally, veterinary medicine has calculated drug doses based upon either weight or mass. This is practical when one compares animals grouped under similar metabolic weights and sizes. When differences in size and metabolic weight are great (e.g., when comparing animals having several hundred-fold differences in weight, and, therefore, energy levels (metabolic rates), dose rates can vary greatly. The possibilty of under-

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dosing, over-dosing or poisoning is always present.

The use of Unregistered ("extra-label") Drugs or Devices in Non-food-producing Animals

It is not uncommon to encounter the concept that "if permission is obtained from the client to use unregistered drugs or devices on the client's animal, then the veterinarian will be absolved from responsibility in relation to those drugs". No client can make an administrative decision relating to veterinary procedures. In law, a client cannot absolve a veterinarian from the consequences of any actions that the veterinarian may make in relation to animals owned by the client. Thus, if a client signs a form absolving a veterinarian from untoward consequences in relation to therapy of an animal owned by the client, it could be used in evidence against the veterinarian.

If the veterinarian uses a registered therapeutic or device and an untoward reaction develops that can be attributed to an absence, a deficiency, a defect or an excess in the therapeutic or device, then as long as the veterinarian adhered to the storage and administrative instructions for that therapeutic, then the manufacturer and the registering authority will investigate. If a veterinarian uses a therapeutic agent or device in or on an animal, and that agent or device is not registered for use in that animal, and if an untoward reaction eventuates, and if the client institutes legal proceedings, then the veterinarian will have to defend all actions performed on the client's animal. In short, in the latter case, the buck stops with the treating veterinarian, irrespective of whether the veterinarian has a "permission document" signed by anyone. A veterinarian is responsible for any actions taken in respect of animals under the veterinarian's care.

Extrapolation of Drug Doses

Many veterinarians extrapolate drug doses from questionable data, hearsay, serendipity and trial-and error. If you work with birds, fish, reptiles or small mammals, you know instinctively that they will have different metabolic rates than dogs, cats or horses. Birds need to eat more food per unit mass and need that food more often during the day than large mammals. A group of mice weighing 100 kg will heat up a room more rapidly than a human weighing 100 kg, because the former has a much greater surface area per unit of mass and so uses more oxygen and releases more carbon dioxide, water vapour and heat into the atmosphere. A small animal has a specific basal metabolic rate (expressed in kcal/kg) that is greater than that of a large animal, provided both have the same core body temperature range. Smaller animals have more surface area per unit of body size, a more rapid mean circulation time, higher densities of capillaries per unit of tissue, more respiratory gas exchange surface area, higher glomerular filtration rates, more hepatic elements, and higher intracellular densities of mitochondria and cytochrome C (tissue metabolic equipment) per unit of body size than a larger animal (Schmidt-Nielsen, 1984).

The scaling of physiological parameters between animals of different sizes can be quantified by the following formula:

Specific metabolic rate (SMR) = Body Weight (kg) to the minus 0.25 multipled by 70.

ie: $SMR = 70[BW(kg)^{-0.25}]$

Mouse weighing 0.02 kg - $70(0.02^{-0.25})$ = 186.1 kcal/kg body weight
Man weighing 100 kg - $70(100^{-0.25})$ = 22.13 kcal/kg body weight

The ratio of these two values (186.1/22.13) is 8.4, showing that 100 kg of mice have 8.4 times the SMR of a human weighing 100 kg, and so would use 8.4 times as much oxygen, and output 8.4 times as much carbon dioxide, heat and water.

In the 1930's physiologists investigated the basal metabolic rates of a range of animals. They soon realised that when the mass of animals in a taxonomic group was plotted against metabolic rate, the result is a straight line (Kleiber's line). When the lines of various taxa were compared, they formed almost parallel lines having a slope of 0.75, differing only in their Y intercepts.

The Minimum Energy Cost (MEC) is the resting animal's energy output (in kilocalories) during a 24 hour period. The only differences in the MEC between different animal species are:

a. the taxonomic energy group and
b. the weight or mass of the given animal.

The taxonomic energy group is one of 5 distinct groups which is a constant that is based on the typical body temperature set point. The 5 groups or taxa are the following:

1. Passerine Birds
2. Non-passerine Birds
3. Placental mammals
4. Non-placental mammals (ie marsupials)
5. Reptiles

With this information, the formula was derived as follows:

$$Y = K(W_{kg}^{0.75})$$

where:

Y = the resting animal's MEC in kcal/24 hours.
K = taxonomically dependant constant based upon average core body temperature
W = animal's body mass in kilograms.

Since MEC represents the energy output during a 24 hour period in a resting animal, the MEC must be multiplied by a maintenance factor. This maintenance factor represents the animal's clinical appearance or body condition at presentation. The maintenance factors are the following:

1.5 = Low metabolic rate/neutered
2.5 = Normal activity
3.0 = Convalescent/In lactation
3.5 = Debilitated/Poor body condition

EXAMPLE: The maintenance factor for a lethargic ostrich would be 3.5.

The values of K were derived from all this research and are for 1 kg representatives of each group (Hainsworth, 1981):

Group	(K) Constant
passerine birds	129
non-passerine birds	78
placental mammals	70
marsupial mammals	49
reptiles (at preferred temperature)	10

You must remember that when you allometrically scale a drug dose from a warm-blooded animal to a cold-blooded animal, you must adjust the core body temperature of the latter to 35-37°C.

After all this, you must be aware that allometric scaling is valid for some drugs, but not for others. The half-life of chloramphenicol in a budgerigar is twice that of a macaw, despite a 30- to 60-fold difference in body weights. Thus if you scaled the dose for a macaw to a budgerigar, you would administer a toxic dose to the latter, whereas scaling the dose from a budgerigar to a macaw would result in subtherapeutic or ineffectual dosage. The half-life of doxycycline hydrochloride is 10 hours in orange-winged Amazons, but 20 hours in a Goffin's cockatoo, despite their having the same body size.

Thus what is the MEC of a 20 g mouse and a 100 kg human?

$$\text{MEC} = 70(0.02^{.75}) \qquad \text{MEC} = 70(100^{.75})$$

$$= 3.72 \text{ kcal/day} \qquad = 2213.6 \text{ kcal/day}$$

From MEC the energy costs for any individual can be estimated. Since the uptake, dissemination and elimination of drugs are a function of metabolic size ($W_{kg}^{0.75}$), MEC can therefore be used to extrapolate drug doses from an animal of one body size to another and from one species to another as long as the pharmokinetic axes for the drug are the same for the different animals.

Thus if you have a model animal for which you have drug data that correlate with therapeutic serum levels (e.g., antibiotics) or clinical response (e.g., anaesthetics), calculate its MEC and then divide the total dose by the MEC to obtain an MEC-dose rate (mg/kcal). Then multiply the subject animal's MEC by the MEC-dose-rate to obtain the dose rate for the subject animal. Extrapolate the frequency of treatment by comparing the model and subject's specific metabolic rates (of course, you need to know the frequency of treatment for the model animal).

This provides a uniform and scientific basis for scaling drug doses.

MEC-Dose Rate Scaling Worksheet

Date: Clinician:
Control Species: Patient Species:
Drug Scaled: Reference Source:

Serum Minimum Inhibitory Concentration (MIC):

CONTROL SPECIES

1. $Species_{cont}$:
   $Weight_{cont}$: kg
   $Dose\ Rate_{cont}$: mg/kg ⌊ $Interval_{cont}$ q h.
   Route (circle) : po sc im iv it

2. Treatment $Dosage_{cont}$ (W_{kg} x dosage rate): mg.

3. Minimum Energy Cost (MEC_{cont}) = $K^{*}(W_{kg}^{0.75})$ kcal/day

4. Specific Metabolic Energy Cost ($SMEC_{cont}$) = $K^{*}(W_{kg}^{-0.25})$ kcal/kg

5. MEC DOSE (item 2 divided by item 3 - Treatment $Dose_{cont}/MEC_{cont}$ = mg/kcal

PATIENT SPECIES

6 $Species_{pat}$: $Weight_{pat}$: kg

7. Minimum Energy Cost (MEC_{pat}) = $K^{*}(W_{kg}^{0.75})$ kcal/day

8. Specific Minimum Energy cost ($SMEC_{pat}$) = $K^{*}(W_{kg}^{-.25})$ kcal/kg

9. Treatment Dosage (item 5 x item 7 - MEC dose x MEC_{pat}) = mg.

10. Treatment $interval_{pat}$:

    $[(SMEC_{pat}/SMEC_{cont})/Interval_{cont}]^{-1}$ = $Frequency_{pat}$ (in hours).

11. Divide 24 hours by treatment interval (item 10) to obtain treatments/day.

12. Divide dosage per treatment (item 9) by patient weight (item 6) mg/kg

13. **Treatment instructions for Subject Species**

(from item 12) mg/kg (from item 10) q h. Route: po sc im iv it

* K - factors:

passerines	129
non-passerines	78
Placentals	70
Marsupials	49
Reptiles (at 37°C ambient)	10

References

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