FORMULARY FOR LABORATORY ANIMALS

THIRD EDITION

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PREFACE TO THE FIRST EDITION

SEVERAL YEARS AGO while we were at the University of Alabama at Birmingham, it became evident that a formulary for use in laboratory animal medicine would be extremely useful. While there are many excellent references available, few contain a comprehensive list of drugs. This formulary grew out of the need to make drug dosages available in a single publication that can be carried in the coat pocket by the laboratory animal veterinarian, and to also serve as a resource for the private practitioner and the scientific investigator. It is our hope that we have succeeded in our effort. Our intent is to constantly collect drug dosages and other useful information to include in subsequent editions. With this in mind we solicit our reader's input. All comments and suggestions to improve this book will be appreciated. Send your comments to Dr. C. T. Hawk, Division of Laboratory Animal Resources, Duke University Medical Center, Box 3180, Durham, NC 27710-3180, or you may send comments via electronic mail to Dr. Hawk: thawk@acpub.duke.edu.

The drug dosages listed in this formulary were derived from hundreds of journals and textbooks. We recommend that the references be consulted to determine the circumstances under which the stated dosages were used. We believe that professional judgment is necessary to select the proper dose.

PREFACE TO THE SECOND EDITION

SINCE THE PUBLICATION of the first edition, several new drugs have been approved for use in the United States that are a welcome addition to the laboratory animal care profession, especially analgesics, anesthetics, and anti-infectives. This new edition includes a new chapter describing how to estimate drug dosages between species using allometric scaling methodology. Dr. Tim Morris was kind enough to author the scaling chapter and we greatly appreciate his effort. We thank Dr. Stan Lindstedt for reviewing the chapter and making helpful suggestions. Finally, we thank many of our readers who made suggestions on how we could improve upon the first edition. As we stated in the first edition, it is our intent that this formulary continuously evolve and, for this reason, we continue to solicit our reader's input. Send comments to Dr. C. T. Hawk, Division of Laboratory Animal Resources, Duke University Medical Center, Box 3180, Durham, NC 27710-3180.

PREFACE TO THE THIRD EDITION

THE FIELDS OF laboratory animal science and medicine are international disciplines. The most notable aspect of this third edition is its international involvement. It is produced in association with not only the American but also the European Colleges of Laboratory Animal Medicine. We thank the following people for their contributions to this new edition: Dr. Margarete Arras (Switzerland), Dr. Nati Ezov (Israel), Dr. Dolores García-Olmo (Spain), Dr. Yona Grunfeld (Israel), Professor Adrian Smith (Norway), and Dr. Octavio Villanueva (Mexico). We have updated not only drugs and dosages, but also several tables and the chapter on dose estimation by Dr. Tim Morris. Finally, we thank our readers for sending us their comments, which help improve each new edition. As before, we continue to solicit your input. Send comments to Dr. C. T. Hawk, GlaxoSmithKline Pharmaceuticals, 709 Swedeland Rd. UW 2630, King of Prussia, PA 19406.

ABBREVIATIONS

Species

Am	Amphibians	Fi	Fish	N	Nonhuman primates
Bi	Birds	G	Gerbils	R	Rats
Bo	Bovine	Go	Goats	Rb	Rabbits
C	Cats	Gp	Guinea pigs	Rc	Raccoons
Ch	Chinchillas	H	Hamsters	Re	Reptiles
D	Dogs	M	Mice	Sh	Sheep
F	Ferrets	Mi	Mink	Sw	Swine

Dosages, Measures, and Methods

bid	twice daily
BW	body weight
cu ft	cubic feet
d	day
g	grams
G	gauge
gal	gallons
h	hours
IA	intaarterially
IC	intracoelomically
IM	intramuscularly
in.	inches
IP	intraperitoneally
IPP	intrapleuroperitoneally
IT	intratracheally
IU	international units
IV	intravenously
kcal	kilocalories
kg	kilograms
l	liters
lb	pounds
m	meters
mg	milligrams
min	minutes
ml	milliliters
mm	millimeters
ng	nanograms
O/D	outside diameter
PO	by mouth (per os)
ppm	parts per million
ppt	parts per trillion
prn	as needed
pt	pints
q	every
qid	four times daily
qod	every other day
s	seconds
SC	subcutaneously
sid	once daily
t	tons
Tbs	tablespoons (approximately 15 ml)
tid	three times daily
tsp	teaspoons (approximately 5 ml)
U	Units
%	g/100 ml

DOSE ESTIMATION AMONG SPECIES

Timothy H. Morris

VETERINARIANS TREATING common farm and companion species can use a wide range of drugs with regulatory approval. These drugs are specifically formulated and supplied with information on indications, dose, dose frequency, routes of administration, and safety. In many clinical situations, laboratory animal veterinarians do not have available approved drugs with this information. In addition, they may be asked to assist investigators in the dose selection of experimental drugs. This need for "off-label" drugs is recognized in legislation (European Commission, 1990; Federal Register, 1996). Even with clinical experience and information such as that supplied in this formulary, knowledge of the principles of dose extrapolation among species is needed both to assess published doses and to estimate doses when no information is available. A simple introduction to dose extrapolation is presented, with relevant citations to aid further understanding.

Although it may be possible to predict drug dosage on a milligram/kilogram basis in closely related species of similar body size, when there are large differences in size, this assumption has quite literally been described as an "elephantine fallacy" (Harwood, 1963). This comment was prompted by the dramatic and tragic consequences in a behavioral study (West and Pierce, 1962) that estimated the dose for an elephant of the psychotomimetic drug LSD, using the milligram/kilogram dose from a study in cats. The error was to fail to appreciate that the much slower metabolic rate of the elephant would result in gross overdosage. The scientific and animal welfare concerns that such errors raise are clear, and by more accurately calculating clinical doses, laboratory animal veterinarians can also assist investigators in planning effective studies.

Understanding dose estimation across species first requires knowledge of how doses are calculated and how species differ.

In producing a commercially available drug, the mechanism of action is investigated; the pharmacokinetics are measured; the mechanisms of disposition, metabolism, and excretion (ADME) are understood; it is safety tested; and its efficacy is assessed in clinical trials (Martinez, 1998a,b,c,d,e). For a particular species, the calculated milligram/kilogram dose is influenced by all these factors and also by drug formulation.

Differences between species relative to drugs can be size independent or size dependent. Species differences in biotransformation do occur (Morris, 2000a), and are size independent. For example, dogs are deficient acetylators, pigs are deficient in sulphation capacity, only birds and reptiles form ornithurate conjugates, cats are deficient in glucuronidation, and N-acetylglucosamine is an uncommon conjugate in rabbits (Morris 2000a; Riviere et al., 1997; Van Miert, 1989).

To understand the effect of size, some background is required. Studies have shown that many anatomical and physiological factors are mathematical functions of body weight. The history of such studies has been described by Calabrese (1991). Adolph (1949), and Soviet scientists after him in an even wider manner, found that in species spanning a wide weight range, over a hundred diverse biological parameters are linearly related to body weight. The equation that describes this relationship is $\log P = \log a + b \log W$, where P is the parameter of interest, W is the body weight, a is the intercept fixing P when body weight equals 1 kg, and b is the exponents (the slope of the line) (illustrated by Kirkwood, 1983). This equation can be simplified to $P = aW^b$ Morris, 1995). The exponent varies with the parameter, but Lindstedt and Calder (1981) provided a useful classification. The exponent for volumes of organs (heart, lung, etc.) is about 1, because relative to each other and the body as a whole they are indispensable; thus, they increase in proportion directly to increased size. The skeleton, by contrast, is required to be stronger in larger animals; thus, the exponent is greater than 1. However, returning to the issue of drug dosage, the principal sized-dependent species difference is metabolic rate, of which the exponent is 0.75. To understand this, one first accepts the generalization that as anatomical features and biochemical reactions are similar across the same order such as mammals (Davidson et al., 1986), there are consequences as organisms increase in size. The body surface area in relation to body weight falls as animals get larger, and thus the ability to lose heat also falls. Metabolic processes are optimized for a particular temperature. Evolutionary pressure, with increasing size, is to choose between controlling this inability to lose heat by a fundamental change in metabolic processes, or reducing metabolic rate. The selected adaptation, reducing metabolic rate, explains the observations made by Huxley (1932) and Adolph (1949), and has been confirmed by many studies since then (e.g., Bartels, 1982; Riviere et al., 1997), that in species spanning a wide weight range, physiological parameters such as oxygen consumption, ventilation rate, renal clearance, and nitrogen output only correlate linearly when plotted across body weight on a log:log scale with an exponent of about 0.75. Interestingly, the mechanisms behind biological scaling may be better described and understood from a perspective of the impact of fractal patterns in biology (Morris 2000b; Wolfram 1994), rather than using mathematical equations (Banavar et al., 2003). Hence, as body size increases, these physiological parameters are relatively reduced; for example, 1g of shrew tissue has a metabolic rate 1000 times greater than 1g of blue whale tissue (Kirkwood, 1983). Durations of processes such as cardiac cycle, life span, and drug half-life, when plotted against body weight, also correlate linearly when a log:log scale is used, with the exponent being

0.25. As body size increases durations increase; for example, compare the life span of the shrew and blue whale. A general model for the origin of scaling in biology has been proposed and suggests that these adaptations are based on fractal geometry (West et al., 1997; Willis, 1997).

A simple summary would be that since time parameters are related to weight to the power of about 0.25, and volumes are related linearly to the power of about 1.0, volume-rates (volume divided by time, e.g., cardiac output) must be related to weight to the power of about 0.75 (see Lindstedt and Calder, 1981, equation 7):

$$\frac{\text{Volume}}{\text{Time}} \propto \frac{M^{1.0}}{M^{0.25}} = M\,0.75$$

With an understanding of the effect of size on metabolic rate, dose estimation across species can then be considered. It is actually less accurate to compare the actual doses across species because doses are derived from pharmacokinetic modeling (Riviere, 1997). It is better to compare a drug's pharmacokinetic parameters, since these depend on physiological parameters that vary according to $P = aWb$ (Ritschel et al., 1992). This can be demonstrated using the straightforward explanation of pharmacokinetics from Riviere (1997), which explains the importance of knowing the clearance and half-life of a drug. Clearance is calculated as follows:

$$Cl = \mathrm{K} \times V_d$$

Where clearance (Cl) = slope of the semi-log drug concentration/time plot (K) ;TS volume of distribution (V_d). Thus, as the slope of the semi-log drug concentration/time plot (K) depends on the ADME of the particular drug, and as described previously these metabolic processes scale to $W^{0.75}$, and volumes scale to W^1, it follows that drug clearance scales to $W^{0.75}$. (A broader mathematical explanation is given by Weiss et al., 1977, equations 2–7.)

By contrast, for half-life ($T_{1/2}$):

$$T_{1/2} = \frac{\ln 2}{K} \text{ and as } K = \frac{Cl}{V_d} \text{ thus } T_{1/2} = \ln 2 \times \frac{V_d}{Cl}$$

(ln 2 is the natural logarithm of 2.) This explains why (as noted previously) the half-life scales to $W^{0.25}$, as it is related to the reciprocal of Cl (which scales to $W^{0.75}$). (A broader mathematical explanation is given by Boxenbaum, 1984, equation 17.)

Thus, a major source of error in extrapolation of dose across species on a milligram/kilogram basis is that it fails to take into account the effect of differences in metabolic rate on drug pharmacokinetics.

How can metabolic rate be taken into consideration? Dose can be solely extrapolated on a milligram/kilogram$^{0.75}$ basis (Kirkwood, 1983; Mahmood and Balian, 1996a; Morris, 1995). Reports that assess this approach have shown variable efficacy (Mahmood and Balian, 1996a; Mizen and Woodnutt, 1988; Riviere et al., 1997), supporting anecdotal concerns of clinicians who use this method regularly. What detailed methods have been used, and what are their accuracy and limitations?

Scaling describes methods used to increase or decrease the size of any operation. It has its roots in engineering, and an example is moving synthesis of a chemical from the laboratory to an industrial plant. When used in engineering, four generic types of scaling are recognized: (1) increasing the numbers of units working in parallel, (2) maintaining design and function while increasing size, (3) altering the flow scheme of the basic system, and (4) choosing another type of equipment (Boxenbaum, 1984). From a biological perspective, the kidneys can be used as an example of scaling. When body size increases, they increase in size (type 2); glomerular capillary length remains similar (type 1); blood supply per unit time decreases (type 3); and although methothrexate is excreted via the kidney in most species, the biliary system is used in the rat (type 4).

Allometry is the study of size and its consequences (Boxenbaum, 1984); thus, it concentrates on scaling factors related to the influence of size on metabolism, and excludes type 4 factors such as different metabolic routes. The basic allometric principle is expressed in the equation $P = aW^b$ (described previously), and has been used to extrapolate pharmacokinetic parameters across a wide range of species (Mordenti, 1986; Riviere et al., 1997; Travis and Bowers, 1991; Weiss et al., 1977). Variable applicability has already been noted above and in other studies (Van Miert 1989). Most recently when 44 compounds were assessed, only 11 showed significant allometric correlations (many of these were antibiotics) and 13 showed less-robust correlations (Riviere et al., 1997).

The principal reason for this lack of universal applicability is that allometry deals only with size; specifically, it does not address metabolic differences among species. As well as the qualitative differences among species described above in general, those drugs with hepatic metabolism, especially those with low extraction (Riviere et al., 1997) rather than renal clearance, those drugs in which protein binding varies among species, and those drugs that do not have first-order pharmacokinetics are less applicable to allometric scaling. The accuracy of allometric scaling for compounds with hepatic metabolism has been improved by incorporating in vitro data from liver microsomes and hepatocytes (Lave et al., 1995).

There have been a number of variations to this basic allometric approach. Although dosage based on body surface area can be inaccurate, the formulae can be modified to incorporate a scaled size factor (Van Miert, 1989). More complex allometric equations that incorporate brain weight or maximum life span (Mahmood and Balian, 1996a, b) or add secondary analysis (Mahmood et al., 2003) have shown promise in increasing the range of drugs in which clearance can be better predicted across species. Another approach is to normalize the time in pharmacokinetic calculations to equivalent pharmacokinetic time or "biological time" as compared to "chronological time" (Lindstedt and Calder, 1981; Mordenti, 1986).

A fundamentally different approach to pharmacokinetic scaling, and thus dose prediction, across species is physiological modeling (Mordenti and Chappel, 1989). A flow scheme of body compartments and their associated processes (e.g., protein binding, enzyme kinetics, etc.) is drawn up for each drug on a particular species and described mathematically. Then physiological data from another species are substituted to obtain the drug information for that species. These methods can be quite accurate, can account for metabolic differences, and are well within the capabilities of modern computers. The two main limitations are the need for much physiological data and the fact that, even with a powerful computer and user-friendly interface, a detailed understanding of pharmacokinetics is required.

What are the consequences of all this information for the laboratory animal veterinarian?

1. When determining dose extrapolations among species of widely varying body weights, metabolic rate should be taken into account; hence, calculations based on milligram/kilogram dose may be less accurate than those based on milligram/kilogram$^{0.75}$.
2. If a drug is formulated for a large species, the dose volume will be relatively much larger when this formulation is used in a smaller species.
3. Dose frequency will increase in smaller species, even becoming impractical in very small species.
4. Simple allometric scaling does not account for metabolic differences, which can override the effects of size on metabolic rate. In vitro hepatic metabolism data may aid analysis.

In practical terms, if the literature suggests that metabolic differences will not confound your estimation, it is prudent to calculate drug dosages with a consideration of metabolic rate. This method has been illustrated (Morris, 1995; Timm et al., 1994) and is used in a commercially available electronic formulary (Vetbase, Hajeka Informatie & Advies, Graafschap 7, 3524 TL Utrecht, The Netherlands, http://vetinfo.demon.nl). It can be calculated from the worksheet in Figure 1.1 (worked example is shown in Fig. 1.2), or the calculations can be transferred to a computer spreadsheet. In some cases, it may be best to alter the dose; in other cases, it may be best to alter the dose frequency; and, in still other cases, if the dose frequency or dose volume is too high, it may be best to compromise, by estimation, between both changes.

Figure 1.1. Allometric dose and interval scaling worksheet

1) Convert reference drug dose into **total dose** and **interval** format (use a calculator for x^y/x^{-y}):
   Control animal species name$_{cont}$ __________ Body weight$_{cont}$ __________ kg
   Dosage rate$_{cont}$ __________ mg/kg (Route: PO SC IM IV)
   Frequency __________ times/day

   Treatment dose$_{cont}$ (W_{kg} × dosage rate) = __________ mg
   Dosing interval$_{cont}$ (24h/frequency) = __________ h

2) Now calculate parameters that express metabolic size (MEC) and metabolic rate (SMEC) in a format that can be compared between animals of very different body sizes using allometric scaling to compare dose quantity.

   Minimum energy cost$_{cont}$ (MEC$_{cont}$) = $k(W_{kg}^{0.75})$ = __________
   or dose frequency.

   Specific minimum energy cost$_{cont}$ (SMEC$_{cont}$) = $k(W_{kg}^{-0.25})$ = __________

   W = body weight, k = factors: passerines 129, nonpasserines 78, placentals 70, marsupials 49, reptiles (at 37°C ambient) 10 (It is preferable to only scale *within* groups.)

3) Then calculate the dose and interval in terms that can be used for conversion between species, using the data from (1) and (2) above:

   MEC DOSE (Treatment dose$_{cont}$/MEC$_{cont}$) = __________

   SMEC INTERVAL (SMEC$_{cont}$ × Dosing interval$_{cont}$) = __________

4) Now you can use this *MEC dose* and *SMEC interval* for this drug to derive an allometrically scaled dose for subject animal species, with a very different body weight.

   Species of subject animal($_{subj}$) __________ Body weight$_{subj}$ = __________ kg

   Minimum energy cost$_{subj}$(MEC$_{subj}$) = $k(W_{kg}^{0.75})$ = __________

   Specific minimum energy cost$_{subj}$ (SMEC$_{subj}$) = $k(W_{kg}^{-0.25})$ = __________

5) Treatment dose$_{subj}$ = (*MEC DOSE* × MEC$_{subj}$) = __________ mg

   mg/kg dose = treatment dose/subject weight = __________ mg/kg

   Treatment interval$_{subj}$ = (*SMEC INTERVAL*/SMEC$_{subj}$) = __________ h

   Frequency (24 h/interval) = __________

Source: Developed from a worksheet, produced by Charles Sedgwick, and modified by Karen Timm, Oregon State University.

Figure 1.2. Example of use of allometric dose and interval scaling worksheet for dose or dose frequency for oxytetracycline injection administration to a rat, using data from cattle dosage

1) Convert reference drug dose into total dose and interval format
Control animal species name$_{(cont)}$:Cow Body weight$_{cont}$: 500 kg
Dosage rate$_{cont}$: 10 mg/kg (Route: IM) Frequency: 1 time/day

Treatment dose$_{cont}$ (W_{kg} × dosage rate)	=	5000 mg
Dosing interval$_{cont}$ (24 h/frequency)	=	24 h

2) Minimum energy cost$_{cont}$ (MEC$_{cont}$) = $k(W_{kg}{}^{0.75})$ = 7402

Specific minimum energy cost$_{cont}$(SMEC$_{cont}$) = $k(W_{kg}{}^{-0.25})$ = 14.8

w = body weight, k = factors: placentals 70

3) Dose and interval in terms for conversion between species

MEC DOSE (Treatment dose$_{cont}$/MEC$_{cont}$)	=	0.675
SMEC INTERVAL (SMEC$_{cont}$ × dosing interval$_{cont}$)	=	355

4) Subject animal species
Species of subject animal$_{subj}$: rat Body weight$_{subj}$: 0.3 kg

Minimum energy cost$_{subj}$(MEC$_{subj}$) = $k(W_{kg}{}^{0.75})$	=	28.4
Specific minimum energy cost$_{subj}$ (SMEC$_{subj}$) = $k(W_{kg}{}^{-0.25})$	=	94

5) Treatment dose$_{subj}$ = (*MEC DOSE* × MEC$_{subj}$) = 19.17 mg

mg/kg dose = treatment dose/subject weight	=	63.9 mg/kg
Treatment interval$_{subj}$ = (*SMEC INTERVAL*/SMEC$_{subj}$)	=	3.7 h
Frequency (24 h/interval)	=	6

Note: Either the relative dose needs to be increased from 10 mg/kg in the cow to 63.9 mg/kg in the rat, or the cow dose needs to be given 6 times a day to the rat. Note also that the dose volume, using a 100 mg/ml presentation, is 0.19 ml/rat (0.63 ml/kg), relatively much higher than for the cow: 50 ml/cow, 0.1 ml/kg.

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