

A simple practice guide for dose conversion between animals and human

Abstract

Understanding the concept of extrapolation of dose between species is important for pharmaceutical researchers when initiating new animal or human experiments. Interspecies allometric scaling for dose conversion from animal to human studies is one of the most controversial areas in clinical pharmacology. Allometric approach considers the differences in body surface area, which is associated with animal weight while extrapolating the doses of therapeutic agents among the species. This review provides basic information about translation of doses between species and estimation of starting dose for clinical trials using allometric scaling. The method of calculation of injection volume for parenteral formulation based on human equivalent dose is also briefed.

Key words:

Calculation, clinical trials, experiment, extrapolation, parenteral, species, starting dose, translation

Introduction

Safe and effective drug dosing is necessary, regardless of its purpose of administration. There are several instances, wherein the initial dose of a particular drug is unavailable in a specific species. Therefore, choosing starting dose of such drugs for research, experiments, or clinical trials in animals and humans is a concern. It should be emphasized that the common perception of scaling of dose based on the body weight (mg/kg) alone is not the right approach. This is primarily because the biochemical, functional systems in species vary which in turn alter pharmacokinetics. Therefore, extrapolation of dose from animals to humans needs consideration of body surface area, pharmacokinetics, and physiological time to increase clinical trial safety. There are four different methods namely dose by factor, similar drug, pharmacokinetically guided, and comparative approaches are described in literature to assess the initial dose.^[1] The dose by factor method is an empirical approach and use the no observed adverse effect levels (NOAEL) of drug from preclinical toxicological studies to estimate human equivalent dose (HED).^[2] Here, the dose selection is based on minimum risk of toxicity, instead of choosing one with minimum pharmacologic activity in humans. In similar drug approach, the existing pharmacokinetics data for

another drug of the same pharmacological category may be used.^[3] On the other hand, pharmacokinetically guided approach utilizes the drug activity instead of scaling of dose among species.^[4] In case of comparative approach, different methods are utilized to determine initial dose, and the data are compared and optimize to get an initial dose.

Allometric scaling is an empirical approach where the exchange of drug dose is based on normalization of dose to body surface area. This approach assumes that there are some unique characteristics on anatomical, physiological, and biochemical process among species, and the possible difference in pharmacokinetics/physiological time is accounted by allometric scaling.^[5,6] This method is frequently


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used in research for experimental purpose to predict an approximate dose on the basis of data existing in other species. Drugs with lesser hepatic metabolism, low volume of distribution, and excreted by renal route are ideal candidates for scaling of dose by this approach. The US Food and Drug Administration's current guidance is based on dose by factor approach where the NOAEL of drug is scaled by making use of allometry to derive the maximum recommended starting dose (MRSD) for clinical studies.^[7] This simple empirical approach considers the sizes of individual species based on body surface area which is related to metabolic rate of an animal that is established through evolutionary adaptation of animals to their size.^[8,9] Moreover, the MRSD is usually scaled well across animal species when normalized to body surface area (mg/m²). Typically, MRSD is calculated from preclinical toxicology studies and applying a factor.^[10] Figure 1 depicts the five steps to calculate MRSD in entry into human studies. Briefly, determine NOAEL's in animal species, then convert NOAEL to HED, select appropriate animal species, apply safety factor, and finally, convert to pharmacologically active dose. NOAEL, the highest dose level that does not cause significant adverse effects, is a typical index for safety obtained from proper animal experiments to determine a safe starting dose.^[7] In step 2, the NOAELs value is converted to HED on the basis of the body surface area correction factor (i.e., $W^{0.67}$, which depends on the animal weight), using appropriate scaling factors from animal species.^[11] Table 1 summarizes the factors for converting doses. The next step is selection of most appropriate species to use in calculation of MRSD. In general, animal species with the lowest HED is considered most sensitive species for determining human risk and is usually selected.^[12] However, one can be more accurate by considering the change in pharmacokinetic parameters of drug between species. On the other hand, a specific animal that is more sensitive toward adverse effect can also be a suitable species. In step 4, the HED is divided by a factor value of 10, to increase safety of first human dose. This safety factor is accountable for differences in physiological and biological processes between human and animal species. In the final step, the value obtained is converted to pharmacologically active dose in humans.

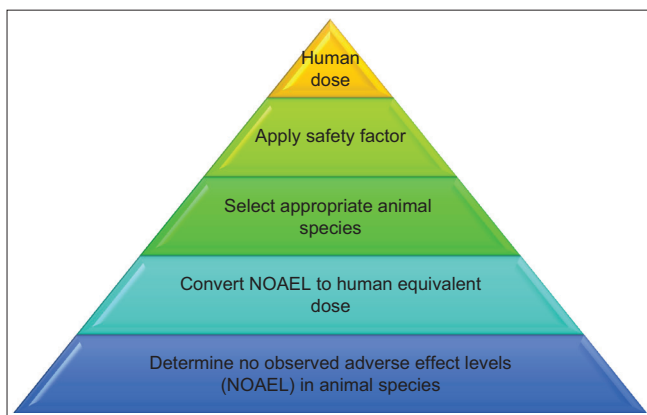


Figure 1: Schematic representation of five steps to estimate starting dose in human studies

Key Points in Scaling of Dose

- Larger animals have lower metabolic rates
- Physiological process of larger animals is slower
- Larger animals required smaller drug dose on weight basis
- Allometry accounts the difference in physiological time among species
- Do not apply allometric scaling to convert adult doses to kids.

Dose Calculations and Examples

The dose by factor method applies an exponent for body surface area (0.67), which account for difference in metabolic rate, to convert doses between animals and humans. Thus, HED is determined by the equation:

$$\text{HED (mg / kg)} = \text{Animal NOAEL (mg / kg)} \times (\text{Weight}_{\text{animal}} [\text{kg}] / \text{Weight}_{\text{human}} [\text{kg}])^{(1-0.67)} \quad \text{Eq. (1)}$$

For example, for a newly developed drug molecule, the NOAEL value in rat weighing approximately 150 g is 18 mg/kg. To calculate the starting dose for human studies, use Equation 1.

$$\text{HED (mg / kg)} = 18 \times (0.15 / 60)^{(0.33)} = 2.5 \text{ mg / kg}$$

Thus, for a 60 kg human, the dose is 150 mg. This HED value is further divided by a factor value of 10; thus, the initial dose in entry into man studies is 15 mg.

Dose is equally related to body weight although it is not the lone factor which influences the scaling for dose calculation. The correction factor (K_m) is estimated by dividing the average body weight (kg) of species to its body surface area (m²). For example, the average human body weight is 60 kg, and the body surface area is 1.62 m². Therefore, the K_m factor for human is calculated by dividing 60 by 1.62, which is 37 [Table 1]. The K_m factor values of various animal species [Table 1] is used to estimate the HED as:

$$\text{HED (mg / kg)} = \text{Animal does (mg / kg)} \times (\text{Animal } K_m / \text{Human } K_m) \quad \text{Eq. (2)}$$

As the K_m factor for each species is constant, the K_m ratio is used to simplify calculations. Hence, Equation 2 is modified as:

$$\text{HED (mg / kg)} = \text{Animal does (mg / kg)} \times K_m \text{ ratio} \quad \text{Eq. (3)}$$

The K_m ratio values provided in Table 1 is easily obtained by dividing human K_m factor by animal K_m factor or vice versa. For instance, the K_m ratio values for rat is 6.2 and 0.162, obtained by dividing 37 (human K_m factor) by 6 (animal K_m factor) and vice versa, respectively. Thus, usually to obtain the HED values (mg/kg), one can either divide or multiply the animal dose (mg/kg) by the K_m ratio provided in Table 1. For example, for a particular drug, the NOAEL in rats is 50 mg/kg. Using Equation 3, HED is calculated either by multiplying or dividing the animal dose with the K_m ratio values given in Table 1. Accordingly, divide the

Table 1: Human equivalent dose calculation based on body surface area*

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m ²)	To convert dose in mg/kg to dose in mg/m ² , multiply by K _m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.09	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.^[7] FDA: Food and Drug Administration, HED: Human equivalent dose

rat dose (50 mg/kg) by 6.2 or multiply by 0.162, the HED is 8.1 mg/kg.

However, it must be borne in mind that the k_m factor varies across animal species and increases proportional to W^{2/3} within a species as body weight increases. For example, the k_m value in rats varies from 5.2 (100 g rat), 6 (150 g rat), and 7 (250 g rat). Therefore, calculation of HED for a drug of NOAEL in rats is 50 mg/kg with an average weight of 250 g is as below:

$$\text{HED (mg / kg)} = 50 \text{ (mg / kg)} \times \left(\frac{7}{37}\right) = 9.5 \text{ mg / kg in humans}$$

Using the standard k_m factor value of 6 for rats with average weight of 150 g [Table 1], the dose varies accordingly as seen below:

$$\text{HED (mg / kg)} = 50 \text{ (mg / kg)} \times \left(\frac{6}{37}\right) = 8.1 \text{ mg / kg in humans}$$

Interchange of unit (mg/kg to mg/m²) of dose of animals or human is carried out using the K_m factor [Table 1] as:

$$\text{mg / m}^2 = K_m \times \text{mg / kg} \quad \text{Eq. (4)}$$

However, conversion between species based on mg/m² is not supported for drugs administered by topical, nasal, subcutaneous, or intramuscular routes as well as proteins administered parenterally with molecular weight >100,000 Daltons.

Similar to the HED estimation, the animal equivalent dose (AED) can also be calculated on the basis of body surface area by either dividing or multiplying the human dose (mg/kg) by the K_m ratio provided in Table 2. AED is calculated by minor modification of Equation 3 as:

$$\text{AED (mg / kg)} = \text{Human does (mg / kg)} \times K_m \text{ ratio} \quad \text{Eq. (5)}$$

For example, if the maximum dose of a particular drug in human is 10 mg/kg, the AED is calculated by multiplying the HED by 6.2 or dividing by 0.162; AED is 62 mg/kg.

Table 2: Animal equivalent dose calculation based on body surface area*

Species	Reference body weight (kg)	To convert dose in mg/kg to dose in mg/m ² , divide by K _m	To convert human dose in mg/kg to AED in mg/kg, either	
			Multiply human dose by	Divide human dose by
Human	60	37		
Mouse	0.02	3	12.3	0.081
Hamster	0.08	5	7.4	0.135
Rat	0.15	6	6.2	0.162
Ferret	0.30	7	5.3	0.189
Guinea pig	0.40	8	4.6	0.216
Rabbit	1.8	12	3.1	0.324
Dog	10	20	1.8	0.541
Monkeys (rhesus)	3	12	3.1	0.324
Marmoset	0.35	6	6.2	0.162
Squirrel monkey	0.60	7	5.3	0.189
Baboon	12	20	1.8	0.541
Micro pig	12	27	1.4	0.730
Mini pig	40	35	1.1	0.946

*Data adapted and modified from FDA draft guidelines.^[7] FDA: Food and Drug Administration, AED: Animal equivalent dose

For parenteral administration, HED conversion (mg/kg) is also based on body surface area normalization. The conversion can be made by dividing the NOAEL in appropriate species by the conversion factor. Guidelines for maximum injection volumes, by species, site location, and gauge size are summarized in Table 3. Injection volume of parenteral formulation is calculated by following equation.

$$\text{Injection volume (ml)} = \frac{\text{Animal weight (kg)} \times \text{Animal does (mg / kg)}}{\text{Concentration (mg / ml)}}$$

Table 3: Guidelines for maximum injection volume, by species, site location, and gauge size*

Species	Route														
	Subcutaneous			Intramuscular			Intraperitoneal			Intravenous			Intradermal		
	Maximum injection volume-ml	Gauge size	Site	Maximum injection volume-ml	Gauge size	Site	Maximum injection volume-ml	Gauge size	Site	Maximum injection volume-ml	Gauge size	Site	Maximum injection volume-ml	Gauge size	Site
Human	< 2	25-31	Upper arm, abdomen, thigh, buttock	2-5	21-23	Deltoid, vastus lateralis	2-5	Peritoneum	-	< 250	18-20	Vein	< 0.10	25-26	Dermis
Mouse	1-2	< 20	Back (scruff)/lower abdomen	< 0.1	25	Quadriceps, posterior thigh	2-3	Lateral tail vein	25	< 0.2	25	Lateral tail vein	< 0.05	-	Lateral abdomen
Hamster	3-4	< 20	Dorsum between scapula	< 0.1	25	Lind limb, caudal thigh	2-3	Lower left quadrant	25-26	< 0.2	26	Lateral tarsal vein, cephalic/lingual vein	< 0.05	-	-
Rat	5-10	< 20	Back (scruff)/lower abdomen	< 0.3	25-26	Quadriceps, hamstring	5-10	Lower left quadrant	24	< 0.5	24-27	Lateral tail/ saphenous vein	< 0.05	-	Lateral abdomen
Dog	100-200	22	Dorsum between scapula	2-5	22-25	Hind limb, caudal thigh	100-200	Cephalic, saphenous	22-25	< 100	21	Cephalic/ saphenous vein	-	-	-
Guinea Pig	5-10	25	Dorsum between scapula	0.3	25	Lind limb, caudal thigh, lumbar muscles	10-15	Lower left quadrant	25	10-15	26-27	Lateral saphenous vein	-	25	Dorsum along flank
Rabbit	10-50	22-25	Dorsum	< 0.5	22-25	Hind limb, caudal thigh	50-100	Lower left quadrant	22	< 5	25	Marginal ear vein	< 0.10	25	Dorsum along flank
Monkey (rhesus)	10-30	22-23	Dorsum	1-3	22-23	Hind limb, caudal thigh	25-50	Peritoneum	20	5-10	22-23	Saphenous vein	-	-	-
Squirrel monkey	5-10	20	Scuff	1-3	20	Quadriceps, posterior thigh, triceps	25-50	Peritoneum	20	0.5-1	21	Femoral vein	-	-	-

* Data from guidelines for injection methods^[13]

Suppose the concentration of the formulation (say nanoparticles) is 10 mg/mL, its AED is 62 mg/kg, the rat weight is 250 g and is administered through intraperitoneal route, and then the injection volume is calculated as

$$\text{Injection volume (ml)} = \frac{0.25 (\text{kg}) \times 62 (\text{mg / kg})}{10 (\text{mg / ml})} = 1.55 \text{ ml}$$

The injection volume observed here (1.55 mL) is well below the maximum injection volume (5–10 mL) for rat through intraperitoneal route and the injection site is lower left quadrant [Table 3].

Conclusion

Dose estimation always requires careful consideration about the difference in pharmacokinetics and pharmacodynamics among species. Allometric scaling assists scientists to exchange doses between species during research, experiments, and clinical trials. Different equations described in this review could be used for dose extrapolation among species. Allometric scaling is generally used to convert doses among the species and is not preferred within species.

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Conflicts of interest

There are no conflicts of interest.

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