Posological review of dose extrapolation methodologies in animal studies, early-phase clinical trials and special populations

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ABSTRACT
Identifying the right dose is arguably an essential step in the design of experiments related to drug discovery and development. Often, dose extrapolation is done to scale the doses of a drug from one species to another. However, posological literature is replete with cases that warrant against the careless and inadequate application of dose-extrapolation methodologies. Increasing costs of research and the development and ethical considerations of experimentation in animals and humans do not condone injudicious design of experiments. This call to caution forms the essential premise of the current review, which focuses on the methodology of the interspecies dose extrapolation and its place in early-phase clinical trials and animal studies. Furthermore, the review also provides an update on within-species dose extrapolation to address the issues of adapting adult human doses to pediatric and geriatric settings.

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INTRODUCTION
Interspecies and intraspecies (for age-related adjustments) dose extrapolation is an essential aspect of study design in drug research and development. Rising costs of research and development, as well as ethical considerations of experimentation in animals and humans, do not condone injudicious design of experiments (Festing and Wilkinson, 2007; Collier, 2009). This call to caution forms the essential premise of the current review. Well-structured reviews on dose extrapolation have been published in the past by Ings (1990) and Sharma and McNeill (2009). Extending a collection of these publications, the current article presents a review of recent data from dose extrapolation studies. Dose extrapolation is useful in arriving at human doses from animal data and forms an important methodological step during the initial phases of clinical trials.

Furthermore, pharmacological experiments may necessitate the conversion of human doses of a drug to animal doses. Interspecies dose extrapolation is a useful bidirectional procedure for both these contexts (Sharma and McNeill, 2009). While principles of allometry that relate body size and metabolic rate are essential considerations in interspecies dose extrapolation, it is important to note that the probability of a drug–target interaction, which depends on the concentration of a drug at its target, is modulated by both size-dependent and size-independent pharmacokinetic and pharmacodynamic processes (Sharma and McNeill, 2009; Mahmood, 2007). Thus, the importance of reit-
erating adequate cognizance to the applicability and limitations of allometric scaling and considerations to size-independent physiological processes are never superfluous in the contexts of the dose-extrapolation and dose-finding literature. Along with an emphasis on these aspects for extrapolating doses between species, the current review also presents an update on adjusting dosage in special populations, such as children and elderly.

**Interspecies dose extrapolation**

The posological literature on dose extrapolation is replete with terminologies such as large and small animals. Intuitively, these terminologies connote the real significance of size in dose extrapolation. The counterintuitive aspect of animal size in dose extrapolation stems from the constraints imposed by evolutionary selection pressures that have forced larger animals to decrease their specific metabolic rate as compared to smaller animals. Duncan et al. and others (Sharma and McNeill, 2009; Duncan et al., 2007; Griebeler and Werner, 2016) have published excellent reviews that explain these evolutionary selection pressures, which are not discussed here. This adaptive mechanism forms the basis for the fact that large animals, as compared to small animals, require a smaller dose (on an mg/kg basis). A power law provides the mathematical expression for the relationship between body size and metabolic rate, \( \theta = aW^b \), where \( \theta \) is the physiological parameter, \( a \) is a proportionality constant, \( W \) is the body weight in kilograms, and \( b \) is the exponent, whose value is around 0.75 for the whole body metabolic rate (Kleiber, 1932; Brody and Lardy, 1946; Sidhu, 1992). This expression forms the essential basis of allometric scaling in dose-extrapolation methodologies. As noted in Figure 1, the power-law would predict that mouse tissue would have about seven times higher specific metabolic rate when compared to human tissue (Demetrius, 2005). This prediction of the power-law agrees with the experimental observation (Reigner and Blesch, 2002).

It is important to note that the exponent (b) value of 0.75 applies to clearance processes. Along with clearance processes, several other size-independent pharmacokinetic and pharmacodynamic factors control the concentration of a drug at its site of action. Understanding the size-dependence and size-independence of these pharmacodynamic and pharmacokinetic determinants are crucial for a judicious application of dose extrapolation methodologies.

**Dose estimation for early-phase clinical studies**

The dose-by-factor method, the pharmacokinetically-guided approach, and the similar-drug approach are used to identify the human doses for the initial phases of clinical trials; principles of allometry lend premise to the first two methods (Reigner and Blesch, 2002). Table 1 presents a summary of considerations that are important for guiding allometric scaling (Nair and Jacob, 2016). Detailed reviews of allometric scaling, as well as its importance and limitations, have been published by others (Sharma and McNeill, 2009; Mahmood, 2007; Huang and Riviere, 2014; Martinez et al., 2006) and are not detailed here.

**Dose-by-factor method**

The dose-by-factor method uses allometric scaling and is recommended by the United States Food and Drug Administration (USFDA) when aiming to derive the maximum recommended starting dose employed in clinical studies (USFDA, 2005). This method uses the no observed adverse effect levels (NOAELs) of the drug from preclinical toxicological studies to estimate the human-equivalent dose (HED). Table 2 and Table 3 present the methodological steps (Nair and Jacob, 2016; USFDA, 2005) and conversion factors to calculate HED from NOAEL (USFDA, 2005). While there seem to be plausible arguments to use an exponent value of 0.75 (West, 2005) for interspecies dose scaling, the USFDA value of 0.67 gains merits because a critical requirement of the first-time adoption in human studies is a safe (not necessarily effective) dose. The exponent value of 0.67 provides a conservative and safe dose. Example 1 presents a sample calculation to explain the dose-by-factor method (Mahmood, 2007). Table 4 presents a comparative overview of the various methods.

**Example 1. Illustration of the dose-by-factor approach**

Step 1: Assume that the NOAEL for a novel drug X is 25 mg/kg/day.

Step 2: Calculate the HED using the following relationship:

1. \( \text{HED} = \text{animal dose (mg/kg)} \times (\text{animal weight (kg)/ human weight (kg)})^{0.33} \)

2. This would yield a value of 4.5 mg/day/day.

Step 3: For a human weighing 60 kg, the HED would be 270 mg/day.

Step 4: The starting human dose would be 27 mg (with a safety factor of 10).

**Similar drug approach**

This approach is useful when the study drug belongs to the same class of an already established drug, and
Assume:

A body weight of 60 kg for a human, apply the power law \( aWb \);
A body weight of 0.02 kg for a mouse, apply the power law \( aWb \),
use 0.75 for the exponent.

As noted by Demetrius a mouse is not a scaled-down human

Figure 1: Illustration of the relationship between specific metabolic rate and animal size

Table 1: Key considerations for interspecies dose-extrapolation methods that employ allometric scaling

| Sl. No. | Description |
|---------|-------------|
| 1       | Larger animals need smaller doses when compared to small animals on an mg/kg basis. |
| 2       | Do not use allometric equations for intraspecies dosage adjustments. |
| 3       | Do not use allometric scaling for converting adult doses to child doses. |
| 4       | Ensure that the species chosen for interspecies dose extrapolation have body weights that differ by three orders of magnitude. |
| 5       | Pharmacokinetic/pharmacodynamic (PKPD) modelling may be a preferred choice if size-independent factors influence the exponent. |

Table 2: Steps involved in the Dose-by-factor method

| No. Steps | Description |
|-----------|-------------|
| Step 1    | Determine the NOAEL in animal species (most sensitive species) |
| Step 2    | Convert the NOAEL into HED |
| Step 3    | Select the appropriate animal species |
| Step 4    | Apply the safety factor (the default safety factor is 10) |
| Step 5    | Derive the human dose |

Example 2 presents an illustration of this approach (Sharma and McNeill, 2009; Reigner and Blesch, 2002; Nair and Jacob, 2016).

Example 2. Illustration of the similar drug approach

Assume that:

1. A novel drug A (test drug) and drug B (established drug) share the following:

2. The NOAEL of drug A is 2 mg/kg.

3. The NOAEL of drug B (established drug) is 15 mg/kg, and

4. The starting dose of Drug B (established drug) is 25 mg/kg.

Then, according to the similar drug approach:

1. the dose of drug A = (dose of drug B × NOAEL of drug A) / NOAEL of drug B,

2. This would then yield a value of 25 × 2/15 = 3.33 mg/kg,

3. For an adult weighing 60 kg, this would mean a dose of 199.8 mg, and applying a safety factor of 10, the starting dose would be 19.98 mg.

Pharmacokinetically-guided approach

Over the years, the pharmacokinetically-guided approach has been gaining prominence. Example 3
Table 3: Conversion of animal doses (NOAELs) to human-equivalent doses (HEDs)

| Species            | Division Factor | Multiplication factor |
|--------------------|-----------------|-----------------------|
| Mouse              | 12.3            | 0.08                  |
| Hamster            | 7.4             | 0.13                  |
| Rat                | 6.2             | 0.16                  |
| Ferret             | 5.3             | 0.19                  |
| Guinea pig         | 4.6             | 0.22                  |
| Rabbit             | 3.1             | 0.32                  |
| Dog                | 1.8             | 0.54                  |
| Monkey             | 3.1             | 0.32                  |
| Marmoset           | 6.2             | 0.16                  |
| Squirrel monkey    | 5.3             | 0.19                  |
| Baboon             | 1.8             | 0.54                  |
| Micro-pig          | 1.4             | 0.73                  |
| Mini-pig           | 1.1             | 0.95                  |

To convert an animal dose to HED, use the division or multiplication factor as below:

Table 4: Comparative overview of Interspecies dose extrapolation methodologies

| Description                  | Advantages                                                                 | Limitations                                                                 |
|------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Allometric scaling           | 1. Simple calculations. 2. Reasonably useful in contexts where size-independent factors can be ignored. | 1. Size-independent pharmacokinetic and pharmacodynamic factors can cause serious confounds. 2. Cannot be used for within-species extrapolation |
| Dose-by-factor approach      | 1. Relatively well-validated 2. Recommended by USFDA                       | 1. Uses allometric scaling and hence prone to associated errors (see above column) |
| Pharmacokinetically-guided approach | 1. Promising method when linear pharmacokinetics can be safely assumed | 1. Non-linearities in pharmacokinetic parameters can lead to errors 2. Not useful when metabolites of a drug are active |
| Similar-drug approach        | 1. A useful approach when the study drug and established drug have similar PK/ PD. 2. Relatively well-validated and simple | 1. Variations in intraclass pharmacokinetics and pharmacodynamic can cause serious confounds |

Accurately extrapolating doses from adult doses to pediatric and geriatric settings is a topic of ongoing research, and many promises to these settings are offered by PKPD modelling.
illustrates this approach with an example. In this method, the NOAEL and its area under the curve are determined in multiple species. Using data from the species with the lowest NOAEL, the starting dose can be obtained, as depicted in example 3 (Reigner and Blesch, 2002). It is vital to note that this method, along with assuming the linearity of pharmacokinetic parameters (Sharma and McNeill, 2009), also relies on the assumption that metabolites of the drug are essentially inactive.

Example 3. Illustration of the pharmacokinetically-guided approach
Assume that:

1. The lowest NOAEL for drug A was observed in rodent models and was 30 \( \mu g \)/h/mL, and
2. The predicted clearance in humans is 25.0 L/h.

The equation gives the starting dose:

\[
\text{AUC in index species} \times \text{estimated clearance in humans}
\]

This would yield a value of 750 mg.

Applying a safety factor of 10, the starting dose would be 75 mg.

Dosing in animal studies
As discussed in the preceding section, interspecies dose extrapolation is a bidirectional procedure. There are many instances in which an established drug needs to be used as experimental tools or pharmacological probes in animal models, and prior data on optimal animal doses have been previously unreported.

In a conceptual similarity to human contexts, the decision to use certain animal doses also depends on considerations of dose-response relationships and pharmacokinetics.

The USFDA conversion factors in Table 1 can be easily manipulated to convert human doses to animal doses; however, it is important to note that in these contexts, it is the therapeutic dose and not the NOAEL that is scaled (Sharma and McNeill, 2009).

While using the effective therapeutic dose of a drug as an index for scaling is more straightforward and has clear conceptual advantages, further research may be needed to refine accurate strategies that circumvent the cost and ethical challenges of dose-optimization studies.

Despite this gap, dose-extrapolation to find the animal doses of established drugs appears to be far more rational when compared to empirical dose adjustments.

Within-species dose extrapolation
The issue of pediatric dosing continues to pose several problems, as differences in size-dependent and size-independent pharmacokinetic and pharmacodynamic properties are complex and scarcely understood. While PBPK and PKPD modelling offer a putative promise (Bjorkman, 2005), the currently used methods primarily utilize the Salisbury rule (Example 4) and Clark’s rule (Example 5).

Example 4. Illustration of the Salisbury rule
The proportion (%) of the adult dose for a child weighing less than 30 kilograms can be obtained by doubling the weight of the child.

1. Assume a child weighs 25 kg, and the adult dose of a drug is 200 mg:
2. Then, the % of the adult dose to be used in the child would be 50 (25 \( \times \) 2);
3. Thus, the dose would be 100 mg (50% of 200 mg).

The proportion (%) of the adult dose for a child weighing greater than 30 kilograms can be obtained by adding 30 to the weight of the child.

1. Assume a child weighs 35 kg, and the adult dose of a drug is 200 mg:
2. Then, the % of the adult dose to be used in the child would be 65 (35 + 30);
3. Thus, the dose would be 135 mg (65% of 200 mg).

Example 5. Illustration of Clark’s rule
Clark’s rule: Child dosage = (child’s weight (kg) \( \times \) adult dosage)/70

1. Assume a child weighs 25 kg, and the adult dose of a drug is 200 mg;
2. Then, as per Clark’s rule, the dose would be 25 \( \times \) 200 /70 = 71.42 mg.

Similar to pediatric settings, issues of dose extrapolation in geriatric settings are also largely under development and warrant additional studies. Data on the age-related alterations in pharmacokinetics and pharmacodynamics are currently being sought, and PKPD modelling offers a positive and promising future.
CONCLUSION

In the contexts of dose extrapolation, it is important to note that dose-finding (scaling) is an estimation and prone to error. While allometric principles and considerations of pharmacokinetic and pharmacodynamic variability all contribute to varying degrees in minimizing that error, no one method fits all. As such, it is essential to contextualize the applicability of a method based on the situation on hand. Appropriate dose-finding is an iterative process, and a well-informed practice of dose extrapolation can reduce the resources and ethical challenges of experimentation in animals and humans.

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Conflict of interest

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