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Review Article

Interpretation of Dose Translation from Animal to Human Equivalent Dose

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ABSTRACT

It is required to appropriately translate the drug dosage from one animal species to another when a new drug is developed. The animal dose should not be extrapolated to a human equivalent dose (HED) by a simple conversion based on body weight as was reported. For the more appropriate conversion of drug doses from animal studies to human studies body surface area (BSA) normalization method is more accurate. BSA correlates well across several mammalian species with several parameters of biology including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function.

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INTRODUCTION

In the development of new drugs to manage diseases, the scientific community depends heavily on animal studies that provide a framework for human clinical trials. Often, a drug that works well in animals is ostensibly not effective in humans. Several explanations exist for the lack of effectiveness. One often-ignored explanation for drug ineffectiveness is the inappropriate translation of a drug dose from one animal species to another [1]. The scientific as well as nonscientific communities do not understand the need for an appropriate method of allometric dose translation, especially when starting new animal or clinical studies. The calculations for determining starting dose in humans as extrapolated from animals should use the more appropriate normalization of body surface area (BSA) [2]. This method was first introduced into medical oncology in order to derive a safe starting dose for phase I studies of anticancer [3, 4] drugs from preclinical animal toxicology data. Unfortunately, for a translational study many convert the safe starting dose based on body weight alone which can result in inappropriate comparisons between studies.

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Correct Dose Calculation

In recent times the mode of drug administration has included tablets, pills, capsules, viscose extracts and granules. Each of these forms of drug administration has volume limitations. In cross-species extrapolation, various factors including pharmacological, physiological, and anatomical factors, metabolic function, receptor, life span, size, and so on should be considered. In general, the life span of humans is from 4.4 to 66.0 times that of test species). Body size is important in the rate of distribution of compounds. For example, the mouse turns its blood volume every minute whereas in humans the cardiac output per minute is only 1/20 of blood volume. Therefore the mouse turns over its blood volume 20 times faster than the human. Small animals excrete compounds more rapidly than larger animals in a rather systematic manner. Among various factors, body weight and body surface area are considered as two major approaches to scaling for general toxicity. In body weight approach the ratio of blood volume in rabbits, guinea pigs and mice decreases with increasing body weight, while the relationship between blood volume to BSA is constant. Smaller animals have relatively larger surface area than larger animals. Oxygen utilization and caloric expenditure are similar for various mammalian species. Moreover, plasma volume and total circulating plasma protein in normal

adults are better correlated with BSA than with either height or weight. Therefore, BSA is useful to estimate normal blood volume. Analyses of the impact of the allometric exponent on the conversion of an animal dose to human equivalent dose (HED) [5] have emphasized that the use of BSA for dose calculation increases clinical trial safety. Accordingly, the approach of converting animal doses to an HED based on BSA is standard for estimating starting doses for initial study in health volunteers. The Food and Drug Administration has also suggested that the extrapolation of animal dose to human dose is correctly performed only through normalization to BSA.

The Use of BSA for Dose Translation

In research BSA method is used for conversion of drug doses between species for many years. The origin for understanding the relationship between the BSA of different species began in 1883 when observations that oxygen utilization and caloric expenditure were similar for various mammalian species and differently sized members of the same species when computed on the basis of body surface [6]. These observations were then confirmed and applied to humans, which gave rise to expressing human basal metabolism in terms of BSA rather than body weight [7]. Correlations between blood volume, circulating plasma proteins, and renal function with BSA in several species also have been illustrated. Thus, BSA correlates well with parameters of mammalian biology, which makes BSA normalization logical for allometric scaling of drug doses between species, given that the activity of most drugs corresponds to the relationship between the drug and some physiological process or function.

Accurate conversion of a mg/kg dose to a mg/m^2 dose depends on the actual body weight of the species. Surface area has generally been calculated in formulae for converting doses as mg/m^2= km ×mg/kg. The km factor is not constant for any species, but increases as body weight increases. The km factor was calculated for a range of body weight Using:

$$Km=100/K \times W^{0.33}$$

Where, K is a value unique to each species. From the results of an analysis, the HED calculated using the standard km value as shown in table 1 will not vary more than ± 20 percent fromthe HED calculated using a km value, based on the exact animal weight within working weight range (Table 1). Human weight will vary broadly, it is not usually necessary to be concerned about the effects of the variation of animal weights within a species on the HED calculation. HED can be calculated from the following formula:

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \frac{\text{Animal Km}}{\text{Human Km}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

This can be calculated simply using the conversion factor in Table 1.

$$\text{Animal dose}\left(\frac{\text{mg}}{\text{kg}}\right) = \text{HED}\left(\frac{\text{mg}}{\text{kg}}\right) \times \text{Conversion factor} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Table 1: Conversion of animal doses to HED based on BSA [8]

Species	Weight (kg)	BSA (m^2)	*Km* factor	Conversion Factor
Human				
Adult	60	1.6	37	1
Child	20	0.8	25	1.48
Baboon	12	0.6	20	1.85
Dog	10	0.5	20	1.85
Monkey	3	0.24	12	3.08
Rabbit	1.8	0.15	12	3.08
Guinea pig	0.4	0.05	8	4.63
Rat	0.15	0.025	6	6.17
Hamster	0.08	0.02	5	7.40
Mouse	0.02	0.007	3	12.33

For animal weights outside the working weight range in Table 1 or for species not included in the table, HED can be calculated from the formula as follows:

$$\text{HED}\left(\frac{\text{mg}}{\text{kg}}\right) = \text{Animal dose}\left(\frac{\text{mg}}{\text{kg}}\right) \times \left[\frac{\text{Animal weight (kg)}}{\text{Human weight (kg)}}\right]0.33 \quad \ldots\ldots\ldots\ldots (3)$$

No Observed Adverse Effect Level Determination (NOAEL)

NOAEL (mg/kg or mg/kg/day) is the highest dose level that does not produce any significant increase in adverse effects in comparison to the control group. Even if not statistically significant, adverse effects that are biologically significant should be considered in the determination of NOAEL. NOAEL should not be confused with lowest observed adverse effect level (LOAEL) or maximum tolerated dose (MTD). These concepts are based on findings of adverse effects and are

not generally used as benchmarks for establishing safe starting doses in adult healthy volunteers. The use of NOAEL should be acceptable to all responsible investigators. However, the dose-setting produced by initial therapeutic dose in a phase 1 clinical trial would be unacceptable.

In phase I studies, data derived from animal models where the drug doses are tested until the LD10 is reached are used to derive the safe starting dose for human studies. The first human dose employed is the allometric conversion, based on BSA, of 1/10 of the LD10 for the relevant animal species [9]. In practice, the maximum recommended starting dose (MRSD) for clinical trial should be determined by dividing the HED derived from the animal NOAEL by the safety factor. The historically accepted default safety factor value is 10. However, a safety factor of 10 may not be appropriated for all cases. The safety factor should be increased with a steep dose response curve, severe toxicities, non-monitorable toxicity, toxicities without premonitory signs, variable bioavailability, irreversible toxicity, unexplained mortality, large variability in doses or plasma drug level eliciting effects, nonlinear pharmacokinetics, inadequate dose-response data, novel therapeutic targets and animal models with limited utility. In general, the safety factor should be raised when there are specific reasons for increased concern, and lowered when concern is reduced because of available data that provide added assurance of safety. In some conditions a safety factor less than 10 may be appropriate. However, toxicological testing in these cases should be of the highest caliber in both conduct and design. Within a well-characterized class the route, schedule, and duration of administration of therapeutics should be the same. Further, it should have a similar bioavailability, metabolic and a similar toxicity profile across all the species tested, including humans. A smaller safety factor might also be used when toxicities produced by the therapeutics are easily monitored, reversible, predictable, and exhibit a moderate-to-shallow dose-response relationship with toxicities that are consistent across the tested species (both qualitatively and with respect to appropriately scaled dose and exposure). A safety factor smaller than 10 could be justified when the NOAEL was determined based on toxicity studies of longer duration compared to the proposed clinical schedule in healthy volunteers.BSA normalization of doses must be used to determine safe starting doses of new drugs because initial studies conducted in humans, by definition, lack formal allometric comparison of the pharmacokinetics of absorption, distribution, and elimination parameters [10].

Expanded Use of BSA in Clinical Medicine

Some drugs are administered to patients based on estimations for desired plasma concentrations using available pharmacokinetics and pharmacodynamics data. Studies have suggested that the role of BSA could be expanded for drug dose calculation in an attempt to more accurately administer cytotoxic drugs to children. The major problem with using BSA as a factor for dose individualization is that BSA can only be estimated with a formula generally incorporating measures [11, 12] of body weight and height. The customary approach for calculation of BSA uses the Du Bois height-weight formula:

$$\text{BSA (m2)} = \text{body weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184 \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where, the constants were derived from only 9 patients.

Subsequently, this formula has been challenged and re-evaluated in similar forms with updated constants. Alternative body-size measurements have been proposed, including lean body mass, ideal body weight, adjusted ideal body weight, and body mass index. However, scientific evidence does not favor one alternative formula over another.

CONCLUSION

Understanding the more appropriate method based on BSA conversion for dose translation across species is an important issue for both the scientific community as well as the general public. Currently, BSA-based dose calculation is the most appropriate method and is far superior to the simple conversion based on body weight. However, a concerted effort toward designing more appropriate conversions that eliminate the problems associated with the BSA method is needed in order to improve therapeutic outcomes in trials.

REFERENCES

[1] Verbraecken, J., Van de Heyning, P., De Backer, W., and Van Gaal, L. (2006). Body surface area in normal-weight, overweight,

and obese adults A comparison study. Metabolism 55: 515–524

[2] Shaw SR, Nihal M, and Ahmad N. (2007). Dose translation from animal to human studies revisited. The FASEB Journal 22:659-661

[3] Pinkel, D. (1958). The use of body surface area as a criterion of drug dosage in cancer chemotherapy. Cancer Res.18: 853–856

[4] Freireich, EJ, Gehan, EA, Rall, DP., Schmidt, LH., and Skipper HE. (1966). Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother. Rep. 50: 219–244

[5] Dreyer G, Ray W. (1912). Further experiments upon the blood volume of mammals and its relation to the surface area of the body. Ibid. 202:191- 212.

[6] Sawyer M., and Ratain, M. J. (2001). Body surface area as a determinant of pharmacokinetics and drug dosing. Invest. New Drugs 19: 171–177

[7] Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. (2002). Estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers, U.S. Food and Drug Administration, Rockville, Maryland, USA.

[8] Jang-Woo S, In-Chan S, Chang-Gue S. (2010). Interpretation of Animal Dose and Human Equivalent Dose for Drug Development. The Journal of Korean Oriental Medicine 2010; 31(3):1-7

[9] Wang, J., and Hihara, E. (2004). A unified formula for calculating body surface area of humans and animals. Eur. J. Appl. Physiol.92: 13–17

[10] Kaestner S A., and Sewell G J. (2007). Chemotherapy dosing part I: scientific basis for current practice and use of body surface area. Clin. Oncol. (R. Coll. Radiol.). 19:23–37

[11] Du Bois, D., Du Bois, EF. (1915). The measurement of the surface area of man. Arch. Intern. Med. 15:868–881

[12] Du Bois, D., Du Bois, EF. (1916). A formula to estimate the approximate surface area if height and weight be known. Arch. Intern. Med. 17: 863–871.