

DOSE ESTIMATION, CONVERSION AND TRANSLATION FROM ANIMAL TO HUMAN AND HUMAN TO ANIMAL FOR CLINICAL AND ANIMAL STUDIES

Noor Kamil¹ and Saba Kamil²

¹Department of Basic Medical Sciences, Faculty of Pharmacy, Barrett Hodgson University, Karachi, Pakistan.

²Department of Pathology, Institute of Basic Medical Sciences, Dow University of Health Sciences, Karachi, Pakistan

ABSTRACT

To describe scientific methods for dose estimation and conversion for herbal, experimental and traditional drugs from animal to human and vice versa.

Various databases were searched like FDA for guidelines and PubMed, SciFinder, and Google for different articles discussing potential problems of dose conversion.

Development and screening of drugs required appropriate dose and dosage form translation from animal species to human or human to animal. All the investigators have realized that the most common problem is the extrapolation of animal to human equivalent dose based on body weight especially for clinical uses and to determine efficacy toxicity and mechanism of action. Many studies proved the reliability of dose translation and conversion by normalization method using the body surface area.

It is thus imperative to use normalization method based on body surface area for dose translation. Generally, body normalization method correlates various parameters efficiently such as energy expenditure, oxygen consumption, basal metabolic rate, and level of plasma proteins and volume of blood. Similarly a factor of safety must be consider especially when calculating dose for toxicity screening in animals.

Hence, importance of dose translation by body surface area and initial dose calculation for clinical trials has been explained and proved with suitable examples.

Key Words: Dose translation, dose estimation, dose determination, body surface area.

INTRODUCTION

Development and screening of old or new drugs required animal testing with appropriate dose and dosage form translation from one animal species to another (animal to human or human to animal), because in vitro methods and computer simulation/modeling do not provide complete information. Medicinal herbs testing on animals often misunderstood by both clinicians and investigators due to lack of reliable information concerning their predictability, equivalent human dose and possible value.

Most commonly encountered problem in designing or starting new animal or clinical studies is extrapolation of animal to human corresponding doses by body weight which can lead to wrong dose estimation for toxicity screening and clinical use. Pharmacokinetic and pharmacodynamic variabilities in species inadvertently directed towards some errors irrespective of conversion method used to extrapolate the results. Allometric scaling or surface area (BSA) normalization method is a much more reliable method for dose translation because it covers a range of different parameter such as specie biology, including oxygen and caloric consumption, basal metabolic rate, volume of blood, plasma proteins, and hepatic and renal function, therefore it is highly recommended to use body surface area to translate dose from animal to human particularly for initial phases of clinical trials.

Scientists greatly depend on animal studies which provide a foundation for human drug testing. Animal studies are conducted for medicinal drugs to provide scientific data to prove their mechanism of action and efficacy for clinical use. Similarly preclinical studies are required to determine their toxicity and safety to use them as over the counter or legal drugs. Drugs which are effective in humans may not be proved well in animals due to various factors but misinterpreted allometric dose conversion especially in toxicity profiling can cause some serious problems for initial dose determination in clinical trials. Significance of an appropriate dose translation is not well realized either by scientists and nonscientists, especially in new animal or clinical studies. It is imperative to use normalization of body surface area method to calculate initial dose in humans from animals. It was introduced first time in oncology to determine nontoxic initial dose from animal toxicology studies in phase I clinical trials of antineoplastic agents. Safe starting dose determination derived from body weight alone for a translational study results in appropriate comparisons between studies. There are examples of misinformation disseminated from conversion of animal dose into human equivalent doses and give unrealistic dose calculations like in case of very popular studies conducted by Lagouge et al., (2006) and Baur *et al.*, (2006) suggested antioxidant resveratrol an

antioxidant derived from red wine can improve energy balance and prevent aging, interpreted by media that the average dose for mice will be tons of liters of wine per day to human corresponding doses. This raised questions on the reliability and authenticity of scientific research. This classic example of inappropriate dose calculations and translation urged the need of proper and valid method of dose translation from animal to human and vice versa.

MATERIALS AND METHODS

Various databases were searched like FDA for guidelines and PubMed, SciFinder, and Google for different articles discussing potential problems of dose conversion. Common problems in dose calculations, conversion, estimation and safety factor determination were searched and analyzed and addressed accordingly with the help of various equations, general steps and standard tables.

RESULTS AND DISCUSSION

Body surface area normalization method for dose translation

Oxygen demand and calorie requirements of various species found to be equivalent for different mammals and different members of different sizes of similar species when compared on body surface area basis. This concept has been confirmed and endorsed the expression of basal metabolic rate by body surface area instead of body weight. Later on relationship between plasma volume, proteins and renal function successfully correlated in various species by body surface area Reagan-Shaw et al (2008). Furthermore BSA also proved more effective method to relate other biological parameter of various species of mammals and make it a realistic choice for allometric scaling of dose translation. Studies conducted by Freireich *et al.*, (1966) and Schein *et al.*, (1970) described the correlation of maximum tolerated dose of anticancer drugs in other animals with lethal dose in rodents when doses normalize to same administration and calculated using body surface area mg/m^2 . They also mentioned that the safe use of new drugs can be derived from animal toxicology studies.

Fig 1. Formulas for dose conversion by BSA.

Formula 1.

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

Formula 2.

$$\text{Animal dose} (\text{mg}/\text{kg}) = HED(\text{mg}/\text{kg}) \times \text{Conversion factor}$$

Formula 3.

$$HED (\text{mg}/\text{kg}) = \text{Animal dose} (\text{mg}/\text{kg}) \div \text{Conversion Factor}$$

Formula 4.

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

Screening of new compounds usually begins with the selection of most suitable animal species which is followed by the toxicological screening. While there were no effective to calculate the doses for medicinal herbs, Food and Drug Administration (FDA) has provided equation to determine human equivalent dose (HED). Dose can be translated from mg/kg into mg/m^2 with the help of formulas 1-4 depending upon the requirements are given in Fig 1. The values of Km factor, conversion factor are given in Table 1 for various animal species along with human for rapid calculations (Center for Drug Evaluation and Research, 2002). Examples of errors are shown in Table 2 if doses were calculated on the body weight bases only. Initial clinical trials dose will be driven from normalization method by BSA of animal dose when no observed adverse effects were found. Safe initial dose for phase 1 human trials will be determined from Lethal dose 10 in any suitable animal species, and first human dose need to be translated through allometric conversion by BSA of $1/10^{\text{th}}$ of lethal dose (LD10) for particular animal species. BSA

normalization is extremely necessary to define the safest initial doses for any new chemical entity because elementary human testing lacks pharmacokinetics parameters comparison (Kaestner and Sewell, 2007). Since antineoplastic drugs are highly toxic in nature it is now customary to calculate pediatric dose bases on BSA using various methods in Fig 2. Mosteller (1987) and DuBois and DuBois (1989) formulas are commonly used with limitations of measuring only body weight and height; whereas, some drugs need to administer drugs on serum concentration bases using pharmacokinetic data. Although DuBois formula has been challenged many times but still its valid to calculate the accurate doses. Variants of this formula were also presented by Haycock *et al.* (1978), Gehan and George (1970) and Boyd (1935) and a number of other strategies were also introduced like, Lean and Ideal body weight and body mass index (BMI) given in Fig 3, although these were proved effective to calculate the doses in different situations but DuBois is still a most common method of dose calculation on the basis of BSA especially for anticancer drugs.

Fig 2. Formulas for dose calculation based on Body Surface Area.

$$\text{Mosteller: } BSA (m^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

$$\text{DuBois \& DuBois: } BSA (m^2) = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$$

$$\text{Haycock: } BSA (m^2) = 0.024265 \times \text{height (cm)}^{0.3964} \times \text{weight (kg)}^{0.5378}$$

$$\text{Gehan \& George: } BSA (m^2) = 0.0235 \times \text{height (cm)}^{0.42246} \times \text{weight (kg)}^{0.51456}$$

$$\text{Boyd: } BSA = 0.0003207 \times \text{height (cm)}^{0.3} \times \text{weight (gm)}^{0.7285 - (0.0188 \times \log(\text{weight}))}$$

Fig 3. Formulas for calculation of Lean and Ideal body weight and BMI.

$$\text{Lean Body Weight (men)} = (1.10 \times \text{weight})(\text{kg}) - \frac{128 (\text{weight}^2)}{(100 \times \text{Height})(\text{m}^2)}$$

$$\text{Lean Body Weight (women)} = (1.07 \times \text{weight})(\text{kg}) - \frac{148 (\text{weight}^2)}{(100 \times \text{Height})(\text{m}^2)}$$

$$\text{Ideal Body Weight (men)} = 50 + 2.3 (\text{Height})(\text{in}) - 60$$

$$\text{Ideal Body Weight (women)} = 45.5 + 2.3 (\text{Height})(\text{in}) - 60$$

$$\text{Body Mass Index} = \text{Weight (kg)} / (\text{Height})(\text{m})^2$$

DuBois and DuBois (1989) stated that the drug dose is directly related to the body surface area rather body weight and this can be interpreted that bigger animals commonly need lower doses on mg/kg basis. Pediatric Isometric scale is not applicable in children because pediatric dose cannot be based on mg/kg of adult dose, due to the fact that their pharmacokinetic parameters are all in developmental phase especially in infants and potentially hazardous to give unproven doses of herbal drugs in children of age less than 18 months (Sharma and McNeill, 2009). Alternatively Johnson described formulas (Fig 4, Formula 1) on Body surface area bases suitable in children older than 18 months of age (Cella *et al.*, 2010). Another important method is modified Clark's Body weight formula (Fig 4, Formula 2) (Johnson, 2008). Various researchers described that dose translation from animal studies

to the children must not be attempted on isometric scaling (Cella *et al.*, 2010; Lack and Stuart-Taylor, 1997; Sharma and McNeill, 2009).

Fig 4. Formulas for pediatric dose calculations.

Formula 1.

$$\text{Pediatric dose} = \text{adult dose} \times \frac{\text{BSA of Child}}{\text{BSA of Adult}}$$

Formula 2.

$$\text{Peditric dose} = \left[\text{adult dose} - \frac{\text{Child's Weight}}{\text{Adult's Weight}} \right] \times 0.75$$

Practical Applications

Recently several authors highlighted the correct use of dose translation and its significance in clinical use of herbal medicines. St. John's wort in an excellent example to describe the dose translation from animal to human, Khalili *et al.* (2012) described the use of dried extract of *Hypericum perforatum* in dose of 300 to 500 mg/kg every alternate day found to reduce forty percent in renal calculus in rodents. Equivalent human doses can be determined calculated by following steps.

$$\text{Average Animal Dose (mg/kg)} = 150 \text{ (mg/kg)}$$

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \div \text{Conversion Factor}$$

$$\text{HED (mg/kg)} = 150 \div 6.2 = 24.19$$

$$\text{Adult (60 kg) HED} = 24.19 \times 60 = 1451.61 \text{ mg/kg}$$

Dose determined by the HED calculation provided a very careful test dose estimation which is used in the clinical trial of *H. perforatum* for the treatment of depression in humans and found to be well tolerated towards its various side effects (Kasper *et al.*, 2010).

Optimal dose determination is a difficult from animal studies, because no effect will be observed if dose is too low, and there will be no point to continue further studies on that herbal or new drug entity. Similarly other scientists have also proved the significance of human equivalent dose calculations for human trials Dost *et al.*, 2009, Birincioglu 2009, Mercado-Feliciano *et al.*, 2012. General step to calculate HED are given in Fig 5, whereas general steps for high dose estimation in toxicity testing is depicted in Fig 6.

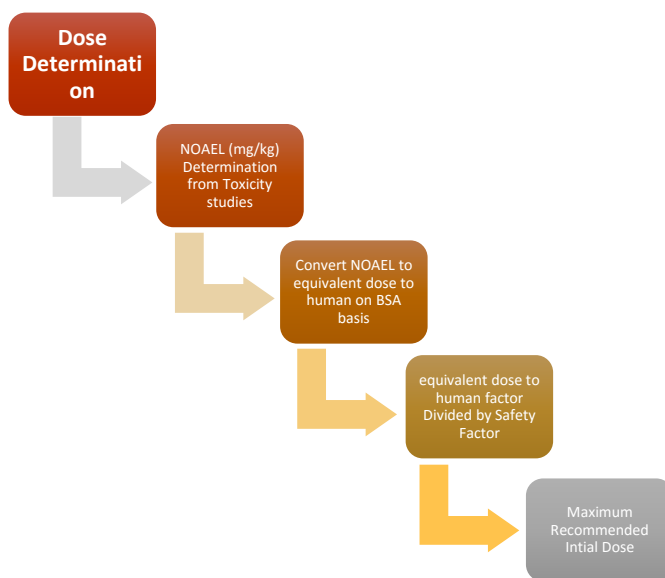


Fig 5. Schematic representation of maximum initial recommended dose.

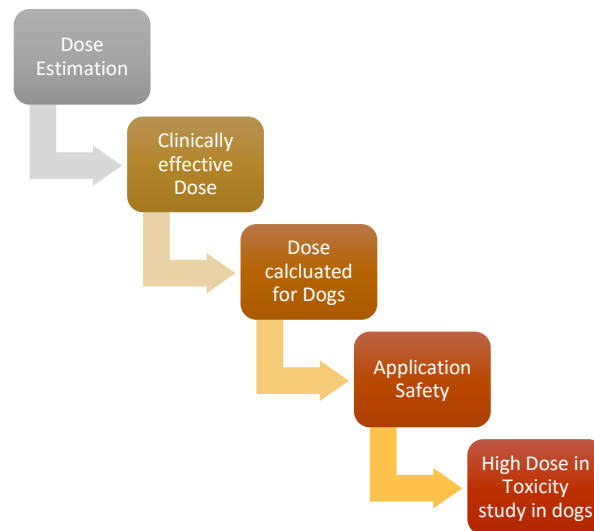


Fig 6. Schematic Representation of high dose estimation in toxicity testing.

It is not always the HED which gives clear insight of effectiveness of proper dose calculations rather in some cases it must be supplemented with the other important histological examinations (Greaves et al., 2004). Another important aspect is the significance of several pharmacokinetic parameters which act as marker, besides the rules recommended by FDA for toxicity studies to elaborate the human to animal comparison (Chauhan & Singh, 2012).

No observed adverse effect level (NOAEL)

NOAEL could be in milligram per kilogram basis or mg/kg daily is the maximum dose at which no significant increase occurred in terms of adverse effects when compared with the control group, other biologically significant effects must be consider even those are not statistically significant. It is used only as findings and usually not considered as a reference for safe initial dose in clinical trials.

Safety factor applications

Safety factor permits the variations in extrapolating from toxicities found in animal studies in humans due to problems in sensitivity to pharmacological effects in man to animal, pathological changes can only be described by human for example headache, myalgia etc., receptor population and responsiveness some sudden toxicological effects and interspecies variability in basic pharmacokinetic parameters. In clinical trials maximum recommended initial dose can be driven by dividing the human equivalent dose with safety factor. Over the years a most common safety factor of value 10 was acceptable, but it is not applicable in all the cases. Safety factor need to be raised wherever necessary due to some specific reasons and can be decreased accordingly in some cases.

CONCLUSION

Clear understanding of importance of dose conversing by body surface area is crucial for the accurate dose calculation, estimation and determination from animal to human or vice versa is not only useful to researchers but also for general public as well. A number of studies conducted on proper dose calculation and estimation have proved the practical significance of using the proper equation for dose conversion. Various important formulas were identified for accurate dose conversion, estimation and determination along with the safety factor involvement and Km factor for HED. NOAEL and maximum recommended initial dose calculations were also discussed. Common problems encountered with isometric method of dose calculations were addressed and significance of allometric dose calculation discussed, because herbal drug experiments on animals are not flawless and cannot apply on humans due to the interspecies differences on various pharmacokinetic and pharmacodynamic parameters.

Table 1. Conversion of human doses to animal and animal to Human equivalent dose based on BSA.

Species	Weight (kg)	Working Range (kg)	Weight	BSA (m ²)	K _m Factor	Conversion factor	Rapid Calculation ^a
Human							
Adult	60.01	-		1.6	37	1.00	-
Child	20.03	-		0.8	25	1.48	-
Baboon	12.1	7-23		0.6	20	1.85	-
Dog	10	5-17		0.5	20	1.85	1.8
Monkey	3.1	1.4-4.9		0.24	12	3.08	3.1
Rabbit	1.8	0.20-0.70		0.15	12	0.08	3.1
Guinea pig	0.4	0.9-3.0		0.05	8	4.63	4.6
Rat	0.15	0.080-0.270		0.25	6	6.17	6.2
Hamster	0.08	0.047-0.157		0.02	5	7.40	7.4
Mouse	0.02	0.011-0.034		0.007	3	12.33	12.3

Values based on data from FDA Draft Guidelines (Center for Drug Evaluation and Research, 2002). To convert dose in mg/kg to dose in mg/m², multiply by Km value.

Km factors are derived by dividing body weight in kg by BSA in m².

^a Calculation of HED for known animal dose, divide animal dose in mg/kg by the number given in column.

^a Calculation of the animal dose for known human dose, multiply the mg/kg human dose by the number in the rapid calculation column and then multiply by the weight of the animal.

Table 2. Examples of the variations found in dose conversion by isometric versus allometric scaling.

Species	Animal dose (mg/kg)	Isometric scaling dose for 60 kg human (mg)	Allometric scaling of corresponding dose to human (mg/kg)	Allometric scaling 60 kg human (mg)
Mouse	100	6000	8.130081	487.8049
Hamster	100	6000	13.51351	810.8108
Rat	100	6000	16.12903	967.7419
Ferret	100	6000	18.86792	1132.075
Guinea pig	100	6000	21.73913	1304.348
Cat	100	6000	27.02703	1621.622
Rabbit	100	6000	32.25806	1935.484
Monkey	100	6000	32.25806	1935.484
Dog	100	6000	55.5556	3333.333
Gelding	100	6000	222.2222	13333.33

Examples of the errors by isometric scaling (direct extrapolation based on mg/kg) of a 100mg/kg dose from animal to human. A dose of 100 mg/kg for any species is extrapolated to 6000 mg for 60 kg human for isometric scaling.

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