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Original Article

Interpretation of Animal Dose and Human Equivalent Dose for Drug Development

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Objectives: To introduce to TKM scientific dose conversion methods of human to animal or animal to human for new drug investigations.
Methods: We searched guidelines of the FDA and KFDA, and compared them with references for drug-dose conversion from various databases such as PubMed and Google. Then, we analyzed the potential issues and problems related to dose conversion in safety documentation of new herbal drugs based on our experiences during Investigational New Drug (IND) applications of TKM.
Results: Dose conversion from human to animal or animal to human must be appropriately translated during new drug development. From time to time, investigators have some difficulty in determining the appropriate dose, because of misunderstandings of dose conversion, especially when they estimate starting dose in clinical or animal studies to investigate efficacy, toxicology and mechanisms. Therefore, education of appropriate dose calculation is crucial for investigators. The animal dose should not be extrapolated to humans by a simple conversion method based only on body weight, because many studies suggest the normalization method is based mainly on body surface area (BSA). In general, the body surface area seems to have good correlation among species with several parameters including oxygen utilization, caloric expenditure, basal metabolism, blood volume and circulating plasma protein. Likewise, a safety factor should be taken into consideration when deciding high dose in animal toxicology study.
Conclusion: Herein, we explain the significance of dose conversion based on body surface area and starting dose estimation for clinical trials with safety factor.

Key Words : clinical trial, dose conversion, safety factor, body surface area

Introduction

We usually perform animal studies to provide scientific data or to explain the mechanisms of traditional Korean medicines (TKM) based on their demonstrated efficacy in clinical application or as mentioned in old TKM literature. Similarly, we focus on toxic and safety aspects of TKM using pre-clinical models so as to promote them as effective over the counter (OTC) or ethical drugs. Often a prescribed drug that works well in humans is not as effective in animals as we expected and in many occasions the misinterpretation of allometric translation of dose in toxicological evaluation also creates some critical trouble for starting dose calculation in clinical studies. In addition, doctors or investigators in the TKM field are not always greatly familiar with new drug development; because of resulting misunderstanding of allometric dose conversion and safety factor application, lots of time and money are

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wasted. Recently, the Korean government has not only been promoting traditional Korean drug development, but also vigorously encourages research for drug development from TKM. Based on these prevailing concerns over dose calculation, our literature on scientific dose conversion could help many investigators to successful progress in drug development.

Materials and Methods

We searched the guidelines of the Food and Drug Administration (FDA) and Korea Food and Drug Administration (KFDA), and compared them with references to drug-dose conversion from various databases such as PubMed and Google. Then, we analyzed the potential issues and problems related to dose conversion in safety documentation of new herbal drugs based on our experiences during IND application of TKM.

Results and Discussion

1. Correct dose calculation

TKM drugs are usually administered in the form of decoctions obtained from crude extracts of a single-or multi-herbal formula. However, this type of drug administration seems to involve some inconvenience. Therefore, in recent times the mode of drug administration has included tablets, pills, capsules, viscose extracts and granules. Each of these forms of drug administration have volume limitations, but viscose extracts are relatively better. Decoctions are commonly taken three times a day, each dose of 80 ml~100 ml, which represents about 6~30 g of extracts/day (100-500 mg/kg in humans). Recommendations of higher doses of TKM may have resulted from literatures of old clinical practice. For example, a clinical dose of *Bojungikgitang* (as dry extracts) cited in old references is about 12 g/day/60kg person calculated by its yield and formula based on two packs/day[1,2]. To investigate its effects in animal models such as rat and mouse, we usually treat 200 mg/kg to rats or mice. In another case, 1000 mg/kg of *Bojungikgitang* prevented experimental lung fibrosis in a mouse disease model[3], so we usually determine the dose as 60 g/60kg person in clinical application. This amount is very difficult to take as a new drug form such as tablets or pills for humans. In view of this, some may suspect the role of drugs in humans because we cannot consume such large volumes of drugs. Hence both cases are good examples of misunderstandings of dose conversion.

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[4]. 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. The body weight approach is calculated simply as per above examples. However, 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[5,6]. Smaller animals have relatively larger surface area than larger animals. Oxygen utilization and caloric expenditure are similar for various mammalian species[7]. Moreover, plasma volume and total circulating plasma protein in normal adults are better correlated with BSA than with either height or weight[8]. Therefore, BSA is useful to estimate normal blood volume. Analyses of the impact of the allom-

etric exponent on the conversion of an animal dose to human equivalent dose (HED) 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[9].

2. Human equivalent dose calculation based on body surface area

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 × W$^{0.33}$ where K is a value unique to each species[10]. For example, the *km* value in rats varies from 5.2 for a 100 g rat to 7.0 for a 250 g rat. 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 from the 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:

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

For example, suppose effective dose in mice is 1000 mg/kg. HED (mg/kg) = 1000 mg/kg × (3/37) = 81.1 mg/kg (4.866 g/day) in humans. Controversy, suppose clinical effective dose is 200 mg/kg. Animal dose (mg/kg) = 200 mg/kg × (37/6) = 1233 mg/kg in rats. This can be calculated simply using the conversion factor in Table 1.

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

$$\mathrm{HED(mg/kg)} = \mathrm{Aimal\ dose(mg/kg)} \div \mathrm{Conversion\ factor}$$

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.

Table 1. Conversion of Human Doses to Animal Doses Based on BSA.

Species	Body Weight (kg)	Working Weight Range (kg)	Body Surface Area (m^2)	*km* Factor	Conversion Factor
Human					
Adult	60	-	1.6	37	1.00
Child	20	-	0.8	25	1.48
Baboon	12	7-23	0.6	20	1.85
Dog	10	5-17	0.5	20	1.85
Monkey	3	1.4-4.9	0.24	12	3.08
Rabbit	1.8	0.9-3.0	0.15	12	3.08
Guinea pig	0.4	0.208-0.700	0.05	8	4.63
Rat	0.15	0.080-0.270	0.025	6	6.17
Hamster	0.08	0.047-0.157	0.02	5	7.40
Mouse	0.02	0.011-0.034	0.007	3	12.33

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

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.

4. Application of safety factor

Safety factor allows variability in extrapolating from animal toxicity studies in humans resulting from: (1) uncertainties due to enhanced sensitivity to pharmacologic activity in humans versus animals; (2) difficulties in detecting certain pathologies in animals (e.g., headache, myalgia, and mental disturbances); (3) differences in receptor densities or affinities; (4) unexpected toxicities; and interspecies differences in absorption distribution metabolism excretion (ADME) of the therapeutic. 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 (Figure 1). 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

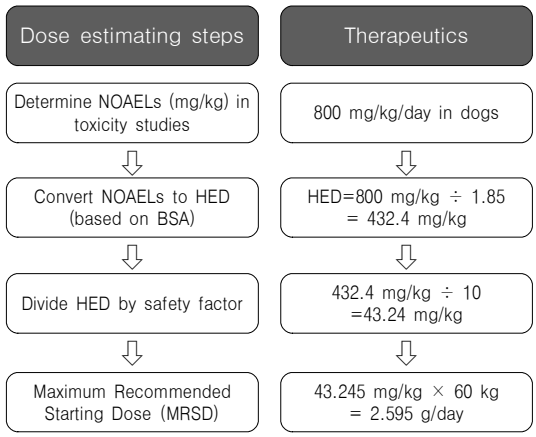

Fig. 1. General steps of MRSD calculation.

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[9].

5. Estimation of starting dose in initial clinical trials

If the pharmacologically active dose (PAD) is from an *in vivo* study, an HED can be derived from a PAD estimate by using a BSA-conversion factor. The MRSD has been determined from animal NOAEL and this HED value should be compared directly to the MRSD. If this pharmacologic HED is lower than the MRSD, then it may be appropriate to decrease the clinical starting dose for pragmatic or scientific reasons.

In the case of TKM literature clinical application is a starting point, whereas common new drug development procedures start from *in vitro* or *in vivo*. If the pharmacologically active dose (PAD) is from a clinical application, a high dose in animal toxicity study should be related to a higher level than animal doses converted from PAD. For example, in Figure 2, suppose 200 mg/kg of modified *Bojungikgitang* in humans is the effective dose, PAD is 200 mg/kg in humans. Dose in rats = 200 × (37/6) =1,233 mg/kg, multiply by safety factor (10), 12,233 mg/kg. This dose is over the maximum dose in toxicity study. In this case, 200 mg/kg as a starting dose in clinical trial seems to be badly chosen and not acceptable by KFDA. This problem could be solved by using dogs. High dose in dogs =200 × (37/20) × 10 = 3,700 mg/kg. However in dogs, capsule administration is generally preferable for

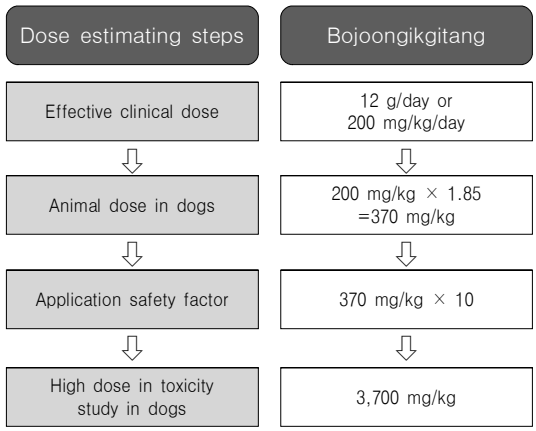

Fig. 2. General steps of estimating high dose in toxicity test for TKM.

repeated dose toxicity study because oral gavage is labor intensive and there is always the chance of gavage error or aspiration. Capsule fill weight depends on density of powder being filled. If a gelatin capsule (10 ml) containing 10 g powdered herbal medicine is administrated to 10 kg dog, then the dose is just 1 g/kg. Although administration of two more capsules to a dog may be hard work because dogs do not like to swallow a second capsule, we have to give sufficient dose in a toxicity test. In such cases, TKM with over 9 g/day clinical dose might be developed as a viscose syrup because the large volume of tablets or granules does lead to some inconvenience in their mode of treatment or administration.

The starting dose estimation in humans is the most crucial step in investigational new drug application (IND) for new herbal medicines. Even though most oriental doctors promote modified TKM

Table 2. Capsule and Dosing Guide.

Size	#10	#11	#12	#13
Volume (ml)	18	10	5	3
Typical fill weight (g)	10-18	6-10	3-5	2-3
Dog can be dosed	32+ kg	20+ kg	6+ kg	

for long-term clinical application, most of time this evidence is not accepted by the KFDA. According to *the Regulations on Registration and Licensing of Drug Products*[11], repeated dose toxicity studies for modified TKM is not desired, as shown in Table 2. However there is no mention of TKM in *the guidelines to clinical study for authorization for drugs*[12] and these statutes lead to confusion among public officials, reviewers and investigators. So the public officials request data of repeated dose toxicity and NOAEL in animals not only for the herbal medicines that contain new herbs or a new composition (extracted with organic solvent excluding water and ethanol) but also for modified TKM on IND approval. If clinical dose is higher than 270 mg/kg (16.2 g/day), it is impossible to confirm enough NOAEL in animal study and hence two strategies are considered: exemption for administration of repeated dose toxicity data or decreasing safety factor. It is very difficult to persuade public officials of KFDA about the safety of TKM without NOAEL. Investigators with ample scientific evidence must urge them to consider and agree with the use of decreasing safety factors, exclude NOAEL for TKM drugs based on their properties, and include the same in KFDA guidelines. Another option of investigators is to decrease the clinical dose through animal efficacy study or researcher's clinical trial, but in many cases of TKM, this is also not easy because no appropriate animal model has been developed. So we think researcher's clinical trials are good strategies to prove safety or estimating minimal efficacy dose in humans. Finally, to stimulate new drug development from TKM, we suggest that KFDA should prepare new guidelines for TKM with decreasing safety factors based on their clinical and toxic data of herbs. In addition, TKM investigators must make efforts to determine appropriate clinical dose through animal study. For example, the effects of *Bojungikgitang* at the concentration of 500 mg/kg and 100 mg/kg have been demonstrated in a murine model of chronic fatigue syndrome and lung injury respectively [3,13] and it indicated that lower doses of TKM also might be effective in humans. Actually, 6.4 g/day of *Bojungikgitang* is effective for weakness in elderly patients[1].

Around the world, use of herbal medicine is steadily increasing. However, domestic TKM industries are under recession. New drug development based on TKM is relatively easy, economical, and time saving. Based on the accumulation of scientific evidence and new drug developments, we can let people know about the excellence of TKMs so as to raise their competitive strength in the world market.

Conclusion

Understanding of dose conversion based on BSA between species is a very important issue for researchers studying TKM. Despite the beneficial properties of TKM, its recommendation of high dose in clinical practice appears to be the major obstacle towards drug development. Hence, understanding the correct dose conversion and applying safety factor would save time and money. On the other hand, KFDA should revise its guidelines in association with IND and NDA to stimulate TKM drug development and support TKM industries. Meanwhile, all investigators should understand the dose conversion methods and KFDA guidelines for a successful drug development.

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