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REVIEW ARTICLE

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Estimating the starting dose for entry into humans: principles and practice

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Abstract *Background*: Selection of the starting dose for the entry into humans (EIH) study is an essential first step in clinical drug development.
Objectives: This paper is a review of different approaches that may be used to calculate the starting dose, presents the results of a current practice survey that reflect practice patterns at a large pharmaceutical company, and discusses selected topics related to the calculation of the starting dose.
Results: The methods used in the field of oncology for cytotoxic compounds are usually derived from a dose associated with some toxicity in animals multiplied by a safety factor. In therapeutic areas other than oncology, the methods may be classified as four different approaches: (1) dose by factor methods that utilize the no observable adverse effect level (NOAEL) from preclinical toxicology studies multiplied by a safety factor; (2) the similar drug approach that may be used when clinical data are available for another compound of the same chemical class as the investigational drug; (3) the pharmacokinetically guided approach that uses systemic exposure rather than dose for the extrapolation from animal to man; and (4) the comparative approach that consists of utilizing two or more methods to estimate a starting dose and then critically comparing the results to arrive at the optimal starting dose. A ''real-life'' example illustrates the use of each method. Advantages, limitations, and underlying assumptions of each of the methods are discussed. The results of the survey showed that the pharmacokinetically guided approach is the most commonly used method, followed by dose by factor methods.
Conclusion: The task of estimating the starting dose is moving beyond empirical methods to those that are increasingly more systematic and theory based.

Keywords Starting dose · Entry into human study · Pharmacokinetics

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Introduction

The entry into humans (EIH) study is the first step in the clinical development of any molecule that has shown therapeutic promise in preclinical evaluations. An essential element of the EIH (also known as ''entry into man, EIM'' or ''first time in man, FTIM'') study is the calculation of the starting dose. Estimating the starting dose is a very common and important task, yet there is little uniformity or standardization of approaches. Starting-dose calculations are performed in many different ways, very often using empirical methods. The approach used often depends on the training and experience of the scientists involved, and/or the industrial or academic setting. Individual scientists may have their own rules and methods. Occasionally there is some consistency within a pharmaceutical company or academic setting, but the methods used vary considerably across these institutions.

Estimating the optimal starting dose is complicated and presents new challenges each time it is done. Extrapolation of doses from animals to humans is based on multiple assumptions about the compound's behavior across species. Different methods may yield widely varying results, and an approach that has worked well for one compound may not be appropriate for another compound. It is important to find a starting dose that is low enough to be safe in humans, but not so conservative that excessive costly and time consum-

ing dose escalations are needed. These challenges make it difficult to establish standard rules for this undertaking. In 1981 it was noted that considerable uncertainty and controversy surround the choice of the initial human dose of a drug [1], a circumstance that was echoed in 1990 [2]. More recently, Boxenbaum and DiLea [3] argued that, while there were some basic rules that could be followed to ensure the safety of patients and healthy volunteers, the present state of knowledge did not allow development of realistic or reasonable standardized procedures for determining optimal starting doses for entry into humans.

These sentiments seem to be confirmed by the wide variability in approaches used for starting-dose estimation and the fact that there currently are no guidance documents available from regulatory health authorities on this topic. A literature search identified a few papers that broadly address the issue of starting dose, most from the 1970s and 1980s [1, 2, 4, 5, 6] in addition to the 1995 paper [3] cited above. The number of references is small considering that a starting-dose calculation is needed for each molecule early in drug development – a very large number. This is possibly a reflection of the complexity of the task and the complicated but incomplete knowledge base that underlies it. The objectives of this article are to review the different approaches used to calculate the starting dose, to illustrate the approaches with a "real-life" example, to present the results of a current practice survey that reflect actual practice patterns at a large pharmaceutical company, and to discuss selected topics related to the calculation of the starting dose.

General considerations

For non-cytotoxic compounds, the initial EIH study is usually a single ascending dose (SAD) study in healthy volunteers. The main purpose of the study is to assess the tolerability of the new compound after administration of a single dose and to gain some information about the pharmacokinetics and pharmacodynamics (if possible) of the compound in human subjects. Dose estimation is based on a dose found to be safe in preclinical studies and then adjusted for human use, using various correction factors to ensure human safety. The optimal EIH starting dose is one that is safe, and not pharmacodynamically active, but is close to a dose with some minimal pharmacodynamic effect in humans. A starting dose that is too low results in the expenditure of additional time and resources in reaching potential informative and therapeutic dose levels, while a starting dose that is too high compromises subject safety and may overlook important clinical considerations for lower doses.

The approach just described is generally applicable to compounds in all therapeutic areas with the exception of cytotoxic compounds intended to treat conducted in patients with treatment-refractory cancer instead of healthy volunteers. In EIH studies for antineoplastics, there is always hope for a therapeutic benefit and a desire to minimize patient exposure to sub-therapeutic doses [7, 8], therefore the EIH study for these compounds is usually a multiple ascending dose (MAD) rather than a SAD study. In general, cytotoxic compounds have a very low therapeutic index and a steep concentration–response curve for safety; however, in oncology there is considerably more acceptance of toxicity to achieve therapeutic benefit. The starting-dose calculation for antineoplastics is generally based on a dose and dose schedule that have elicited some toxicity in animals rather than on a dose that has been identified as safe in animals. Starting doses of anti-cancer agents have traditionally been established with the goal of escalating quickly to a maximum tolerated dose (MTD) on a given dosing schedule.

There are multiple preclinical doses that can serve as the basis for estimating the starting dose. They have nearly identical meanings and are occasionally used interchangeably, although some subtle differences exist. For example, the highest non-toxic dose (HNTD) originated in cancer research and is defined as the highest dose at which no hematological, chemical, clinical, or morphological drug-induced alterations occur, and doubling this dose produces the aforementioned alterations [9]. The no observable adverse effect level (NOAEL) is defined as the highest dose at which no statistically significant and/or biologically relevant adverse effect is observed [10]. For the purposes of this paper we will use the term NOAEL when discussing doses from preclinical toxicology studies.

Figure 1 describes a simple decision tree for estimating a starting dose and serves as an organizing framework for this paper. Methods for estimating the starting dose are different depending on whether or not the drug is a cytotoxic intended for antineoplastic purposes; we have used this basic principle to divide the paper into its two main sections. If a drug is not a cytotoxic intended for antineoplastic purposes then, after estimating a starting dose on the basis of the NOAEL, it is reasonable to consider whether or not this dose is expected to be pharmacodynamically active and needs to be adjusted downward for entry into man.

Methods used for cytotoxic compounds

The literature related to estimating a starting dose for antineoplastics suggests an organized, knowledge-building effort by scientists focused on the task, and a clear evolution in methods is seen [11, 12, 13, 14, 15, 16], although considerable uncertainty continues to exist in this therapeutic area. Historically, starting doses of

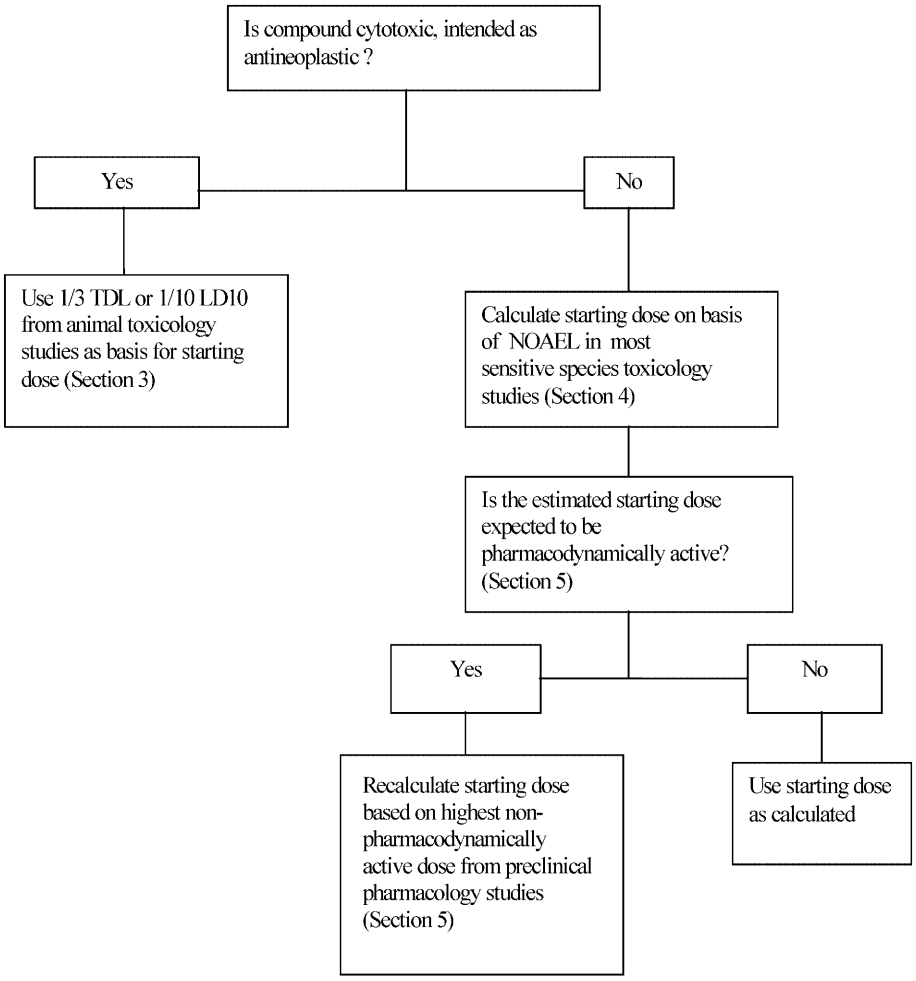

Fig. 1. Decision tree for starting-dose calculation

toxic doses determined in large animal species (e.g., dog and monkey). In 1979, based on a retrospective analysis of 12 anti-tumor agents, Penta and colleagues [14] demonstrated that mouse data could be effectively used in determining safe starting doses. In 1981, mouse data were further validated against traditional large-animal methods with 21 antineoplastic agents and were also found to produce safe starting doses [15]. Methods based on large animal species and on mice are both in use today.

One-third of the toxic dose low in a large animal species

Using this approach, the starting dose is calculated as one-third of the toxic dose low (TDL; expressed as mg/m^2) in a large animal species (either dog or monkey). This method was initially introduced by Freireich and colleagues [11] and remains widely in use. TDL is defined as the lowest dose that produces drug-induced pathological alterations in hematological, chemical, clinical, or morphological parameters and which, when doubled, produces no lethality [9]. The TDL is determined on two basic schedules, single dose and daily for

One-tenth of the lethal dose in mice

Here the starting dose for EIH is calculated as one-tenth of a dose (expressed in mg/m^2) that is lethal to 10% of non-tumor bearing mice (LD_{10}) during a specified period of observation [14]. The LD_{10} is determined on two basic schedules (single dose and daily for 5 days) with groups of ten mice at each dose level [14]. Collins et al. [17] investigated the use of 1/10 LD_{10} and noted that, for eight drugs, the area under the plasma concentration–time curve (AUC) of the compound observed in mice after administration of the LD_{10} was similar to that of the compound produced by the MTD in humans. The use of a new approach to dose escalation called pharmacologically guided dose escalation (PGDE) was advocated [18]. PGDE is now a well-accepted element of oncology phase-1 study design. Most papers that address issues related to PGDE utilize 1/10 LD_{10} in mice as the method of reference for estimating the starting dose [18, 19, 20]. If there is a significant discrepancy between 1/10 LD_{10} in mice and 1/3 TDL in large species, other authors have suggested that the lower of the two doses be used as the starting dose in

Example

For each method described in this paper, a "real-life" example of a starting-dose calculation is given. For the examples, we use the compound mofarotene. Mofarotene (Ro 40-8757) is a retinoid with cytostatic properties that was used in phase-I clinical trials for a potential antineoplastic indication. Mofarotene was chosen for the example because several methods for estimating the starting dose were used and compared before EIH, including methods that are usually restricted to cytotoxic drugs. Preclinical studies had indicated a NOAEL of 2 mg/kg/day in dogs and 50 mg/kg/day in rats. The TDL in dogs was 5 mg/kg/day (95 mg/m^2/day). The LD_{10} in mice was not available. Using the 1/3 TDL in large animal species, the estimated starting dose for mofarotene was:

$$1/3 \times 95\ \text{mg/m}^2 \times 1.8\ \text{m}^2 = 57\ \text{mg} \quad (1)$$

where 1.8 is the average body surface area of a human in m^2. The use of a fixed single dose in this example is an exception for an oncology phase-I trial. Generally, for cytotoxics, the starting dose for EIH studies in cancer patients is individualized based on patient body surface area rather than using a fixed dose for all patients [21]. Because mofarotene is cytostatic, with considerably less toxicity than a cytotoxic drug, it was initially administered as a single dose to healthy volunteers.

Critical assessment of the method

Multiple variations of the two basic approaches have been used by individual investigators and groups for various drugs (e.g., 1/50 safe dose in mouse for fazarabine, 1/3 dog TDL for elsamitrucin and docetaxel, 1/20 lethal dose in rat for gemcitabine, and less than 1/10 mouse lethal dose for trimetrexate, [22]). Despite the substantial work that has been done with starting doses for cytotoxics, there is still considerable variability, the basic methods haven't changed, and there is no "gold standard" for estimating the starting dose for oncology phase-I clinical trials. There has been wide concern that the basic methods provide doses that are too conservative and miss opportunities for therapeutic benefit in oncology phase-I and -II clinical trials [8, 16]. PGDE is considered to be an essential element of effective phase-I study design in this therapeutic area.

Methods used for non-cytotoxic compounds

There are four basic approaches to estimating the starting dose for EIH studies for non-cytotoxic compounds. For the purposes of this paper they are called: dose by factor, similar drug, pharmacokinetically guided, and comparative. The comparative approach uses cally evaluate and determine which starting dose is optimal. We describe each approach, including its strengths and weaknesses, and variations that have evolved from the original.

The dose by factor approach

This method consists of identifying a dose (usually expressed in mg/kg/day) associated with a specific effect in preclinical toxicology studies and then multiplying it by one or more factors to estimate a safe human starting dose. A commonly used approach is based on the highest dose of the compound found to have no toxic effect in the most sensitive species tested in 4-week to 13-week preclinical toxicology studies. This mg/kg/day dose is then reduced by a "sensitivity" factor that adjusts for anticipated differences in sensitivity to the drug between each animal species tested and man. The sensitivity factor is derived from estimated interspecies differences in sensitivity to drug toxicity published by the Association of Food and Drug Officials (AFDO) of the United States in 1959 [23]. According to this "modified AFDO" scheme, the maximum starting dose for the EIH study is the smallest of the following three doses: 1/10 of the highest no-effect dose in rodents, 1/6 of the highest no-effect dose in dogs, or 1/3 of the highest no-effect dose in monkeys [3, 24]. The smallest of the three doses is utilized because it reflects which animal species is most sensitive to the drug from the toxicology studies. The sensitivity factor (i.e., 1/10, 1/6, 1/3) reflects anticipated differences in drug sensitivity in the various animal species relative to humans [23]. If, for some reason, there is concern about the safety of the starting dose derived this way, the dose can be further reduced using an arbitrary safety factor.

Example

For mofarotene, the dog was the most sensitive species, with a NOAEL of 2 mg/kg/day. The starting dose was estimated using the "modified AFDO" approach as:

$$1/6 \times 2\text{mg/kg} \times 70\text{kg} = 23\text{mg} \quad (2)$$

where the NOAEL in the dog was multiplied by 1/6 and then 70 kg (average body weight of a human) to estimate a starting dose of 23 mg. Because the toxicologist was concerned about skin toxicity appearing several weeks after the start of administration, the 23-mg dose estimate was multiplied by a safety factor of 1/10 to give a final starting dose of 2.3 mg.

Critical assessment of the method

There are multiple variations of this approach that allow for more or less conservative results. Different

example, a sensitivity factor of 1/2 rather than 1/3 has been suggested when extrapolating from primates [25]. Kuhlman [26] noted that generally the starting dose is about 1/50 to 1/100 or lower of the no-effect dose from toxicology studies.

This is a classic approach that has been widely used and generally produces safe starting doses for EIH studies. Dose by factor methods have been criticized because they ignore preclinical pharmacokinetic data [3, 24]. The approach is somewhat simplistic and empirical, and easily lends itself to variations that may be considered to be rather arbitrary in nature. It has been noted that this type of extrapolation from animals to humans is truly appropriate only if both show similar absorption, bioavailability, biotransformation, and sensitivity to toxic effects by the drug or its biotransformation products [25]. While there is considerable flexibility and good safety with results, dose by factor methods may be criticized for estimating starting doses that are too conservative, requiring excessive dose escalations to reach a pharmacodynamically active or maximum tolerated dose.

Similar drug approach

The similar drug approach is used when human safety data are available for a drug similar to the one under investigation and can serve as a reference point for estimating the starting dose [1, 5]. The ''similar drug'' is usually of the same chemical class, with similar or related chemical structure. This situation is not uncommon in industry where one or more predecessor compounds in the same chemical class and with similar toxicological profiles may have been clinically investigated prior to the current drug under investigation. The ''similar drug'' is one that is already marketed or that has clinical safety data available when the compound under investigation is a follow-up compound.

This approach is based on the ratio of an optimal starting dose of the similar drug to its NOAEL. This optimal starting dose is one that has been identified as producing no drug-related adverse events or laboratory abnormalities after a single dose in humans and with no pharmacodynamic activity. The method assumes that this ratio is equal to the ratio of the starting dose for the compound under investigation to its NOAEL. The assumption can be expressed as:

$$SD_s/NOAEL_s = SD_i/NOAEL_i \quad (3)$$

where:

- SD_s is the optimal starting dose of the similar drug.
- NOAEL is the no-observable adverse effect level for drugs ''s'' and ''i'', where ''s'' is the similar drug and ''i'' is the investigational drug.
- SD_i is the estimated starting dose for the investiga-

The ratio $SD_s/NOAEL_s$ can then be applied to the $NOAEL_i$ to estimate a starting dose that is expected to be safe, but not too conservative as:

$$SD_i = (SD_s/NOAEL_s) \times NOAEL_i \quad (4)$$

The dose estimate obtained this way is usually multiplied by an arbitrary safety factor to accommodate uncertainty about safety in the estimate of the starting dose.

Example

For mofarotene, the similar drug was etretinate, a closely related retinoid with a similar toxicity profile in animals; the dose that would be an optimal starting dose of etretinate in humans was 10 mg. The NOAEL of etretinate in rats was 2 mg/kg/day and that of mofarotene in rats was 50 mg/kg/day. The NOAEL of etretinate in dogs was unknown. Applying Eq. 4:

$$SD_i = (10mg/2mg/kg \times 70kg) \times 50mg/kg \times 70kg = 250mg. \quad (5)$$

This dose was then multiplied by a safety factor of 1/4 to give a final human starting dose of 63 mg. In this case, as with the dose by factor method, an arbitrary safety factor was applied to ensure the safety of the healthy volunteers.

Critical assessment of the method

This ''similar drug'' method is not new, makes intuitive sense, and is known to provide safe starting doses. The main limitation is that applying a cross-species dosing ratio for one drug to another drug assumes that pharmacokinetic and pharmacodynamic differences between animal and man are the same for both compounds. The validity of this assumption should always be considered and may be tested by calculating the ratio $SD_s/NOAEL_s$ for another similar drug of the same chemical class to verify that the ratio remains reasonably constant. If this second ratio is not similar to the first, this approach should not be used.

Pharmacokinetically guided approach

The pharmacokinetically guided approach is increasingly being used in many pharmaceutical companies and institutions [24]. It uses systemic exposure instead of dose for the extrapolation from animal to man, a concept that was originally proposed more than three decades ago [26]. A desired systemic exposure (e.g., AUC) for humans is defined as the systemic exposure corresponding to the NOAEL. If a NOAEL and its corresponding AUC are available from more than one animal species, the animal species with the lowest AUC

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