The Journal of Clinical Pharmacology

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J. Clin. Pharmacol. 1997; 37; 767

The online version of this article can be found at:
http://www.jclinpharm.org

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
American College of Clinical Pharmacology

Defining the Maximum Tolerated Dose: Investigator, Academic, Industry and Regulatory Perspectives

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INTRODUCTION

The maximum tolerated dose (MTD) is an important concept in drug development, as it determines the optimal dose range for efficacy trials.[1–4] Determination of the MTD in Phase I helps to ensure both that the doses tested in Phase II are safe and that the potentially efficacious dose range is evaluated. At present, there is no consensus regarding what constitutes an MTD in humans. Considerable confusion arises from the use of different operational definitions of the MTD and from the failure of many investigators to state their definitions of the MTD in reporting their studies. The MTD has been variously defined as the maximum dose administered during a trial that elicits no toxicity,[5] the dose that produces mild to moderate sublethal toxic effects in a significant percent of individuals,[6] or some percentile of the tolerance distribution.[7] We believe that a discussion of the MTD will help clarify the important issues and promote standardization.

A variety of perspectives are presented in this article, which is based on a recent symposium given at the 25th Annual Meeting of the American College of Clinical Pharmacology in Philadelphia, Pennsylvania, on September 28, 1996. Each author has distinct concerns, ranging from the desire of investigators to have clearly defined definitions to the academic emphasis on the scientific merit of Phase I studies and from the pharmaceutical industry's need for safe and expeditious drug development to the responsibility of regulators to ensure that the overall approach to drug development is valid and that a focus is maintained on the critical information necessary to evaluate new compounds at transitions in the development process. Each of these perspectives sheds light on the issue of the MTD and will be helpful to all who are responsible for planning, conducting, and evaluating clinical drug studies.

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REGULATORY PERSPECTIVE ON THE MAXIMUM TOLERATED DOSE

Brian Davis, MD

I requested to speak first because I would like to cover some of the general principles associated with

drug development and the assumptions we make during the process. I will then introduce the concept of maximum tolerated dose (MTD) and consider whether studies designed to determine the MTD in patients can play a useful part in early drug development. Let me emphasize that there are no definitive experts in this field, and there may not be answers to all the questions, but we can foster serious discussion.

Suppose a company is trying to choose a drug to develop from among its battery of new drugs. If one does not quite work out, it is a disappointing commercial loss, but it is reasonable to discard it and select another. From the patient's point of view, however, particularly those with untreatable disease, if the discarded drug could have been effective but was dropped because of a suboptimal development process, it could be an irreplaceable loss. It would be another loss to patients if companies concentrated their resources on developing "me-too" drugs because of an unnecessarily high cost of discovery and early development of "breakthrough" drugs.

The scientific approach to developing a new drug for a disease begins with research in the basic sciences, advances toward the discovery of a specific agent, and ends with patient trials. Generally, a problem related to the disease is identified, a search of the literature and other resources helps the investigator to develop a hypothesis about why a particular drug should work, the hypothesis is then tested through experimentation, including animal screening tests to identify new candidate drugs, and the results are used to get new ideas and to design new experiments. This continues until a satisfactory solution to the problem is found.

In the case of a new chemical entity or biologic product intended for use as a medicine, we test the drug *in vitro* to examine its effects on receptors, such as affinity and selectivity. In animal studies, we can determine its pharmacologic and toxic effects on the target organs and gain some insight into its potential mechanism of action. Although these preclinical experiments may provide convincing evidence of potential efficacy, the full benefits of a drug depend on knowing how best to administer it to the target patient group. One major challenge in the development process is how to determine the optimum dose, that is, an effective dose or administration strategy that will provide benefit without substantial risk to as many patients in the target population as possible. This population generally includes patients with a wide variability in age and co-existing illnesses for which they may take other medication. If the initial dose selected for exploratory studies in patients is too low, time may be wasted during clinical trials

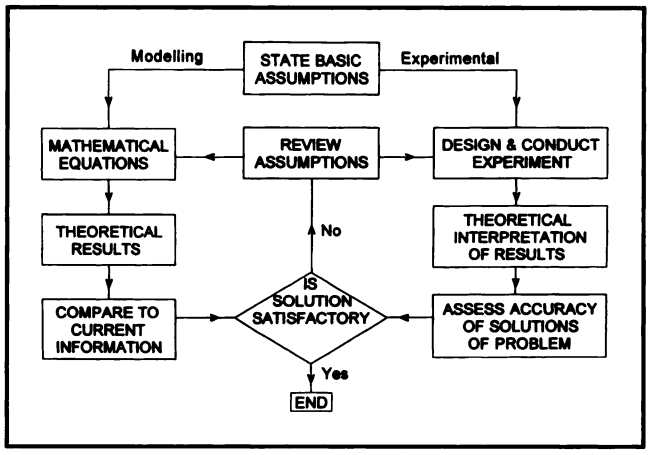

Figure 1. Two linked paths used in modeling a problem. Starting from basic assumptions, an approach to solving the problem is adopted. The right path shows steps in an experimental approach; the left path shows steps in a mathematical approach. The results from both approaches provide insights about the solution to the problem and the assumptions used. These insights form the basis of new assumptions and new approaches to the solution. This process continues until a satisfactory solution to the problem is discovered.

and development may be delayed, sometimes for years, or even abandoned. Also, in some cases, patients in trials may be receiving essentially placebo doses, which raises ethical concerns if it is avoidable.

Like many scientific questions, the "problem" of how to establish the optimum dose or administration regimen can be addressed through a recursive strategy or "model." To get started on solving the problem, researchers must make some assumptions (simple, if possible), conduct initial experiments, examine the results, and interpret them in terms of the theoretical solution to the problem. They must ask whether the conclusion of the experiments provides a satisfactory solution to the problem. If the solution is not satisfactory, they must review the assumptions and repeat the cycle (Figure 1).

A typical simplified assumption at the start of the problem of finding the optimum dose is that the dose–response in an animal adjusted, for example, for body weight reflects that in the target human population. However, when we examine the results of preclinical studies, we usually conclude that the assumption is not sufficiently accurate. The next assumption is that the effects of the drug in healthy humans indicate how the drug will act in the target population, but because the subjects lack the effects of the disease, the results from these studies may also provide an inadequate solution to the problem. The next assumption is that the effects of the drug

in a few patients may be representative of the effects in the target population. However, although these patients are selected to represent the target population, they may have to be chosen in a way that eliminates other criteria that may alter the response to the drug, such as advanced age, other medical conditions, and concomitant medication. Therefore, the results may still provide an inadequate solution to the problem. The estimate of the dose to be used in larger exploratory trials in patients that emerges from these approaches, even in combination, may be far lower or far higher than the optimum dose.

It may be helpful to examine why animal models fail to mimic effects of drugs in humans. When pharmacokinetics in animals are compared with those in humans, many drugs show major differences in absorption, distribution, metabolism, and excretion. When sufficient data are available, they can be used to make a rough approximation of the likely safe exposure level in humans using techniques such as allometric scaling. This does not take into account any differences that may exist at the receptor sites or in local conditions that may alter the target organ response to the drug. Physiologic effects in animals also often differ substantially from those in humans and may be of limited use in predicting human response, particularly in a target population in which organs are likely to be diseased. Moreover, some methods used to determine human physiology through clinical measurements are crude. For example, smooth muscle contraction in the airway of an animal can be determined by measuring it directly with a strain gauge, but in humans airway contraction is inferred from indirect measures of pulmonary function. There are also significant differences between animal models and humans in toxic responses to drugs. The results from animals serve as a guide to dangerous drug concentrations and types of toxic effects, but that is all.

The healthy human model does not usually predict effects of a drug in patients with the target disease because the disease may alter factors such as receptor activity and local concentration in the biophase at the receptor. Likewise, the physiologic responses of a healthy organ to a drug are frequently different to those of a diseased organ. These differences make the healthy subject a poor predictor for drug response in the target group. Obviously, healthy subjects cannot be used to measure potential therapeutic effects of a drug. Although healthy humans may provide some level of prediction of the toxic effects of a drug, the extent and severity of the reactions may be modulated by the diseased state.

The purpose of the symposium is to examine additional assumptions and approaches that might be used to estimate the optimum dose in the target population. The determination of MTD in a small group of patients from the target population as part of the approach to determine an effective dose for most of the target population in certain diseases is an interesting idea and possibly a concept that could be applied more widely. The assumption is that when a dose is reached that consistently causes an adverse reaction, it must be at the upper range of doses that can be tolerated by the target group, and if the candidate drug does not produce the desired effect on the disease, then it is not likely to be suitable for development.

The scientific approaches and ethical concerns in this type of study have recently been reviewed.[1] Briefly, in this approach to determining the optimum dose, an initial safe dose is selected based on preclinical work and a maximum tolerated dose is sought in healthy volunteers (MTD_{HV}) and used as a reference for subsequent administration regimens. The first cohort of patients from the target population, under very careful observation and monitoring, is exposed to an initial dose approximately 50% of the MTD_{HV}. The next cohort is exposed to a dose of drug increased by 25% of the MTD_{HV}, and so on, increasing in similar increments in further cohorts of very carefully monitored patients, until a dose is reached that causes adverse reactions that are not tolerated by most of the patients (50% or more). This dose could be defined as the minimum intolerated dose in patients (MID_P). The dose preceding this could be defined as the maximum tolerated dose in patients (MTD_P). However, definitions of these terms have not yet been agreed on. The MTD_P can be described as a safe dose beyond which unacceptably frequent adverse reactions begin to occur in patients. It has the potential to be close to the optimum dose for efficacy and therefore can be used as an early approach to the optimum dose. In addition, this kind of study can indicate a range of doses within which patients could be expected to have adverse reactions and the type of adverse reactions that can be expected. The relatively small size and cost of these types of studies may also encourage companies to determine MTD_P in special patient groups such as the elderly or patients with concomitant disease that might be part of the target population.

When starting larger exploratory trials in Phase II, an assumption could be made that a dose of 60% to 75% of the MTD_P would be a good estimate of a safe but potentially efficacious dose. In some diseases, such as cancer, it is often assumed that the greatest chance of being effective throughout a broad range of the target population lies in the upper portion of the tolerated dose range. In other diseases, a dose

used initially to be certain of widespread efficacy may be reduced during development or after marketing to improve the therapeutic index. The importance of knowing the MTD_P is that it reduces the chance that a company will abandon the development of a new drug because it was tested at a dose that was too low.

Certainly, the greatest area of concern in this approach to determining an effective dose is safety. As with any clinical trial, the potential for a serious adverse reaction exists. Whereas under most circumstances, patients agree to the *possibility* of an adverse event occurring, in the case of an MTD study, they must accept that they are more likely than not to have an adverse drug reaction as an end point to the study. Patients would have to be adequately informed of this and give consent. In addition, the proposed study would have to be reviewed and approved by an independent ethics committee with wide experience and high levels of expertise in the science and ethics of clinical trials. Typically, adverse events that are considered tolerable are those that are minor; for instance, headache, nausea, or vomiting would be acceptable in drug trials for cancer. Each patient would have to be monitored closely for unexpected serious adverse reactions by skilled professionals in a unit designed to provide intensive care for patients in drug trials. In this setting, a study would probably be more acceptable and safe than in a less well-supervised inpatient or outpatient setting, such as is often used in a Phase II study. Another important advantage of the inpatient MTD_P study is that the investigator can provide more information about the setting in which the adverse reaction will occur. Additional applications of MTD_P studies may include the ability to identify surrogate markers that mark the dose above which a more serious adverse reaction is likely to occur or the likelihood of a drug causing toxic effects in patients with concomitant diseases or special groups of patients.

Determining the best dose strategy is a key to success in developing a new medicine. One major problem is finding an effective dose for the widest range of the target population at an early enough stage of the development program. Industry, academia, and regulators have all devoted a lot of time and money trying to solve this problem. As is discussed in detail in this article, one very plausible additional approach to this problem for certain diseases is the determination of the MTD of a new drug using small groups of carefully monitored patients and use of this as a basis for selecting a dose strategy for further traditional exploratory studies in Phase II of development.

I am very grateful to Professor John Lewis and Dr. David Snodin for their helpful contributions to the revision of this manuscript.

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Question and Answer

Question: From our perspective (industry), we have struggles with the issue of MTD, especially with central nervous system drugs. Typically, we conduct Phase I studies in healthy individuals, and we are encouraged to find the safety windows, such that in subsequent trials when higher doses in patients were required, the safety data would support this. However, in this process, some of our colleagues called it "human toxicology." What balance should we be striking with drugs that perhaps have efficacy at much lower doses? Would it not be preferable to find those surrogate end points rather than pushing for MTD and show that the drug is getting into the central nervous system?

Answer: If you are fortunate enough to have a surrogate marker that accurately reflects the required clinical benefit, then that is another way to approach drug development. However, there are many conditions in which such a surrogate marker is lacking. The MTD study may be used in diseases for which there is no other way to estimate the optimum dosage range accurately in the target population. By defining the MTD, you can ascertain a dose range that is safe for the target population and hope that you will also observe efficacy of the drug in a wide range of patients. This could be thought of as "human safety."

Question: Most pharmaceutical companies expect extensive safety/tolerability testing in normal volunteers before administering the drug to patients. In those patients in which the disease state and the risk/benefit relationship that accompanies the disease state do not exist, what type of approach should we take?

Answer: This is one of the major questions that this symposium explores. Briefly, the approach should be a conservative one. One option would be to determine the MTD starting with a very low initial dose based on preclinical studies, using a small number of patients to be exposed to the drug under the safest possible conditions. Data from these patients are likely to suggest a safe range of doses for further exploratory studies.

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