TRIALS AND TRANSLATIONAL MEDICINE COMMENTARIES

Microdosing: A Critical Assessment of Human Data

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ABSTRACT: Ultrasensitive analytical methodologies have now made possible the ability to characterize the pharmacokinetics (PK) of compounds following administration to humans of a minute, subpharmacologic dose, a microdose. This has the potential to provide pre-IND information to help in early candidate selection, but only if such information is reasonably predictive of PK at pharmacologic doses. The published clinical data in this area are critically assessed and perspectives drawn. The place of microdosing, alone and coupled with other innovative methodologies, both pre-IND and during clinical development, is considered as a way forward to improve the efficiency and informativeness of drug development. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION

The dawn of the current millennium brought hope and high expectations, which unfortunately in many cases has been followed by disappointment in the light of natural and human calamities. But, one idea, microdosing, first espoused then,[1] is showing promise. This commentary considers the concept, its progress, limitations, and future potential, primarily within the context of drug development. Since 2000, there has been more than 160 publications dealing with microdosing, including several timely reviews[2,3] as well as an issue of a journal devoted to this topic (*Bioanalysis*, March 2010), with an upward trend in the annual publication rate over the period (Fig. 1). Primary emphasis in this commentary is on the setting and experience gained from published studies in humans with approximately 30 compounds, particularly within the context of predicting pharmacokinetics (PK) at pharmacologically active doses.

Examination of the literature indicates that the terms "microdose" and "microdosing" have been used more widely than originally intended, and discussed in this commentary. In the context of drug development, a microdose is a dose of compound that is intended to be subpharmacologic when administered; it is 1/100th of the known or expected active dose or 100 μg/adult, whichever is the smaller. It should be distinguished from a tracer dose, which is a dose aimed at tracing, and not disturbing, the behavior of an existing pool of compound in the body. In the biomedical arena, the latter requires the use of an isotopically labeled compound, to distinguish it from the unlabeled pool, whereas a microdose can be unlabeled or labeled, although as discussed later, there are advantages to the use of a radiolabeled compound. Tracers enjoy wide application in drug development, a topic beyond this commentary.

The two concepts behind microdosing are: the best model of human is human, and the PK seen following microdose administration is an acceptably accurate predictor of that at pharmacologic doses. It is widely accepted that many processes within the body are saturable, so that the PK of most drugs will exhibit dose dependency if the dose is large enough, which has caused many to question the value of microdosing. So the question to be answered is: in most cases are therapeutic doses operating effectively within the linear PK range. The consensus of acceptability is that the prediction lies within ±2-fold of the actual human pharmacologic dose PK, although the adequacy of these limits has been questioned by

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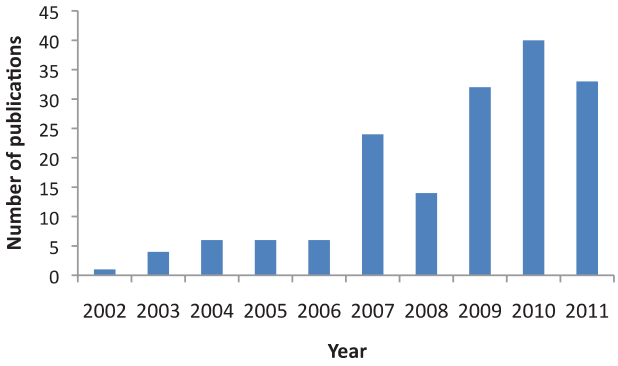

Figure 1. Annual number of pharmacokinetic microdosing publications between 2002 and 2011.

some when attempting to select from within a chemically related series.[4] The driving force behind human microdosing is the still often lack of the success of alternative approaches, such as allometry and physiologically based PK (PBPK) alone, to accurately predict human PK at pharmacologic doses from preclinical and *in vitro* data, particularly following oral administration.[5] This is coupled with the desire not to waste resources evaluating compounds, and administering them at stressful levels to animals during the required safety testing, that are subsequently found not to meet the desired human attributes, one of which is appropriate PK. The very limited preclinical safety assessment needed before employing human microdosing is also appealing, and has been given positive regulatory support.[6–8] The approach has sometimes been referred to as human Phase 0 testing.

There is some debate as to the primary causes of failure during clinical drug development. In the early 1990s and before, PK was identified as a significant cause but within a decade or two later, some reports suggested that it is now the cause of only a few percent of the failures,[9] with lack of efficacy and unacceptable adverse effects being the primary causes. Although this may be so, at least during Phase 2, where the greatest frequency of failure occurs, analysis indicates that to ensure the greatest chance of success it is necessary to demonstrate three components: that the drug achieves adequate exposure for long enough at the target site, that it binds to the target, and that there is a demonstrable downstream signal.[10] Although inadequate target exposure would clearly lead to a lack of efficacy, the cause of failure is still in PK. A review of 44 compounds in Phase 2 indicated that in 18 (41%) of these compounds adequate target exposure was not demonstrated, and none of these succeeded to go beyond Phase 2 (Piet van der Graaf, personal communication). PK may also be the cause of toxicity if the compound is concentrated excessively at an off-target site because of it being a substrate for an active uptake transporter there. So having an adequate target PK profile is important.

EXPLORING THE CLINICAL FINDINGS

Table 1 lists the published clinical microdose studies at the time of writing this commentary that tested the validity of the approach. These involve mainly marketed drugs for which there is a substantial body of PK data associated with therapeutic doses. In the majority of cases, the amount administered as a microdose was 100 μg. Much of the data come from three consortium programs, two European, the Consortium for Resourcing and Evaluating AMS Microdosing (CREAM) and European Union Microdose AMS Partnership Programme (EUMAPP) trials, and one Japanese, the NEDO program, led by Dr Yuichi Sugiyama. These, together with the findings by others, a few of which are published as abstracts, indicate that of the 24 compounds evaluated, approximately 70% met the criteria of the scaled microdose PK being within twofold of the oral therapeutic dose PK, and in most cases, the shape of plasma concentration–time curve was correctly predicted. Concern for shape is particularly important when predicting whether the plasma concentration is likely to be above some minimum target value at the end of a desired dosing interval. Overall, the success rate with oral microdosing is substantially higher than that seen with allometry, where, in a recent Pharmaceutical Research and Manufacturers of America (PhRMA) study of 108 modern diverse compounds evaluated, Phase 1 area under curve (AUC) was accurately predicted in less than 50% of cases even with the best method, and only in 20% was shape predicted with high or medium high accuracy, as defined by the authors.[5] Moreover, in the PhRMA study, the Phase 1 dose chosen as the reference was the lowest Phase 1 dose in which the PK was well defined, whereas, as noted in Table 1, the reference dose for microdosing comparison was generally equal to or higher than the maximum dose strength marketed. It should also be noted that in a single dose-raising Phase 1 study, to assess acute tolerance, top doses are often considerably higher than the eventual therapeutic dose. So, failure of an oral microdose to predict top Phase 1 doses is not necessarily a valid criticism of the approach.

Although fewer compounds have been studied, PK prediction accuracy, including shape, following an intravenous(ly) (i.v.) microdose is virtually 100% (Table 1). In most cases, the comparison was with an i.v. tracer dose given with an oral therapeutic dose. The reason for high success is that for many drugs the volume of distribution is sufficiently large that even following a therapeutic dose, the resulting systemic concentrations are too low to materially saturate any of the processes controlling the PK of the compound.