Review Article

Microdosing: An Emerging Tool for Drug Development

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ABSTRACT

Microdose studies are gaining increasing importance in clinical drug development as they have the potential to shorten time-lines and cut costs. A microdose study is one of a suit of exploratory studies intended to be conducted in early phase-I that involve limited human exposure, have no therapeutic intent and are not intended to examine clinical tolerability. Microdosing may help both patients and the pharma industry with earlier availability of new test drugs, reduced failure of compounds at later stages and reduce the cost of drug development. A new product development tool kit is urgently needed to improve predictability and efficiency. These studies are based on the availability of ultra sensitive analytical methods like accelerator mass spectrometry (AMS) and positron emission tomography (PET) to measure the drug and its metabolite concentrations in the range of picograms or even lower. Both these techniques rely on the assessment and analysis of the radio isotopes incorporated into the drug under study. With evolution of technology (more sensitive mass specs, advances in LC equipment) LC-MS/MS is becoming a viable alternative.

Keywords: AMS, LC-MS/MS, micro dosing, PET

Received 12 May 2015 Received in revised form 8 June 2015 Accepted 10 June 2015

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INTRODUCTION

Micro dose is a study to obtain the pharmacokinetic data of drug candidate at early stage of development. As per FDA and European medicine agency the dose decided for study is 1/100th of the predicted pharmacologic dose [1]. The Regulatory authorities had accepted this study on human volunteers due to its low dose concept. Microdosing, thus, appears as a new viable concept in the 'toolbox' of the drug development activity [2]. It appears that micro dosing strategy could complement standard animal-to-human scaling, redefining the existing concept of phase I clinical research. It is assumed that microdosing will help to reduce or replace the extensive animal testing of compounds for kinetics, which may later be rejected in human studies [3]. Data collected from a phase 0 trial are beneficial not only in prioritizing promising compounds but also in allowing the modification of phase I study design before initiation [4]. The dose administered is in picograms to fentograms, it may not cause any adverse events also, but may produce useful pharmacokinetic information and help in further development of the compound [5]. Ultra-sensitive AMS (accelerator mass spectrometry), PET and LC/MS/MS has made it possible to undertake clinical studies in man using extremely low drug doses to obtain early PK and ADME data. The pharmacokinetic data provided by microdosing is better predictor of pharmacokinetics at therapeutic dose than the allometeric scaling [6]. The rationale behind the current literature on micro dosing is how well micro dose data have predicted the pharmacokinetics obtained at a therapeutic dose.

MERITS

Microdosing utilizes the smallest possible dose with which no adverse reactions are expected. Phase zero trials can enable the

sponsors and manufacturing pharmaceutical companies to identify the most promising of similar agents in their pipeline [7] and to explore clinical characteristics of a candidate agent with very less number of patients in a short duration of time [8]. The study reduces expense and overall cost of the trial and provides better approximation of active and safe starting dose for phase I trials. Require lesser preclinical testing data than what is mandated for traditional phase I studies. It helps in detection of endogenous bio-markers and even beneficial in oncology by reducing the number of subjects exposed to toxic effect of chemotherapeutic agent [9].

DEMERITS

In phase zero study it is difficult to predict body's reaction to a particular compound, when used as microdose and in its pharmacological dose. These leads to false negatives (compound being rejected) or false positives (compound acceptable based on microdose data but rejected subsequently when used in pharmacological doses) [10]. Expertise required while applying this methodology to the drugs showing complex/non-linear kinetics since certain drugs dissolves readily at low doses but exhibit limited solubility at higher doses, it may be difficult to predict the absorption characteristics at the microdose levels [11]. Dose doesn't offer any therapeutic benefit to the volunteers as subtherapeutic dose is administered. The analytical tools are expensive. It cannot replace dose escalation, safety, tolerance study and impact of drug on the targeted disease. The database for microdosing studies is very small [12].

ANALYTICAL METHODS

Microdosing is dependent on the availability of ultrasensitive analytical methods able to measure drug and metabolite concentrations in the low picogram to femotgram range [13]. Two big nuclear physics have been applied to conduct analyses at these concentrations, *viz.* accelerator mass spectrometry (AMS) and positron emission tomography (PET) [2]. Both techniques rely on the analysis of radioisotopes incorporated into the drugs under study. In the case of AMS, [^{14}C] is the most useful isotope for drug metabolism studies whereas for PET [^{11}C] is proving to be the most useful. It is worth noting the huge contrast in radioactive half-life of the two isotopes[2].

Accelerator mass spectrometry (AMS), a technology new to the pharmaceutical industry, is an ultrasensitive technique for measuring tracers such as ^{14}C. AMS measures an isotope ratio that is converted to equivalent amounts of drug per milliliter or milligram of sample using the known isotopic content of the labeled compound and the average or individual carbon content of each sample [14]. AMS has extremely high sensitivity for tracing isotopically labeled compounds, uses small sample sizes (5–10ul), and can provide detailed kinetic profiles at low drug concentrations. It uses a particle accelerator in conjunction with ion sources, large magnets, and detectors to separate out interferences and count single radionucleotide atoms in the presence of $1x10^{15}$ stable atoms [15]. Because of the powerful magnet employed, AMS typically displays excellent sensitivity with the lower limit of quantitation at femtogram or attogram per mL levels.

It requires the synthesis of 14C-radiolabeled drug, which can be costly and time-consuming and necessitates extra precautions during sample handling and preparation to prevent contamination by extraneous sources of 14C [16]. In addition, AMS measures total 14C radioactivity, that is, drug plus metabolites. In order to accurately measure parent drug concentrations, the parent drug in plasma or blood extracts must first be separated by high performance liquid chromatography (HPLC) with fraction collection followed by subsequent analysis using AMS [17].

AMS methodology requires biological samples to be graphitized prior to analysis, which involves a time-consuming process of sample oxidation followed by reduction. These procedures result in low throughput, large instrument space and high operating cost [15].

PET is a relatively new imaging technique that, due to its high sensitivity, has the potential to support microdosing studies. In pharmacokinetic studies using PET imaging technology, a drug labeled with a positron-emitting radiotracer, such as 11C, is administered [18]. Typically, the radiotracers employed have very high

specific activity, which allows for doses of 10 µg or less, consistent with the micro dosing concept [19]. However, the short half-life of positron emitting radionucleotides typically limits the duration of these studies and prevents accurate assessment of pharmacokinetics beyond the initial distribution phase. The main advantage of PET compared with other analytical techniques is the ability to quantitatively image drug distribution in the clinic under a microdosing paradigm, gaining insight into concentrations of drug in specific tissues of interest [20]. Another advantage of PET is that it is non-invasive. Other disadvantages of PET are that the instrument is expensive and only available at certain locations that have the specialized hot chemistry facilities, an on-site cyclotron and a positron emission tomography camera [21].

LC-MS/MS is also available as a powerful analytical tool to measure drug concentrations. It is easy to use and highly automated [22]. It has the functionality to characterize drug metabolites and is relatively inexpensive compared to AMS or PET, and occupies much smaller footprint in the laboratory setting [23]. At present, however, LC-MS/MS can only achieve lower limits of quantitation at picogram or femtogram per mL level, an order of magnitude less sensitive compared to AMS technique [24].

CONCLUSION

Microdosing is a new tool to accelerate the drug development process and to reduce attrition rate on drug candidates. In recent years, human micro-dosing clearly holds significant promise as an analytical tool .It will also help in the drug repurposing and pharmacogenomics activity by expediting the initial work. This review focuses on the purpose as well as need of microdosing in drug development.

REFERENCES

1. Martin B., Claudia W. et al; Microdosing studies in Humans, Drugs in R & D, 2008, 9(2), 73-81.
2. Colin R., Lappin G.; The phase 0 microdosing concept, Br J Clin Pharmacol. 2006, 61(4): 367–370.
3. Seth et al, Human microdosing , Indian J Med Res, 2009, 202-204.
4. Ingle PV, Patel RA, Patil PH, Surana SJ. Phase-0: A General Overview. Indian Journal of Pharmacy Practice. 2013 July-Sept, 6(3):16-20.
5. Bertino J., Greenberg H., Reed M.; The use of microdosing in the drug development process. J Clin Pharmacol 2007; 47:418-422.
6. Yamane N. et al; Clinical relevance of liquid chromatography tandem mass spectrometry as an analytical method in microdose clinical studies, Pharm Res. 2011; 28(8):1963-72.
7. Phase 0 - Microdosing strategy in clinical trials Indian J Pharmacology, Dec 2008, 40(6), 240-242.
8. Vijayaraghavan R, Ramesh Kumar R; Impact of phase zero trials (microdosing) in clinical trial research, International Journal of Applied Biology and Pharmaceutical Technology, 2010, I(2), 486-490.
9. Chris H. Takimoto; Phase 0 clinical trials in oncology: a paradigm shift for early drug development? Cancer Chemotherapy and Pharmacology 2009, 63(4), 703-709.
10. Tushar T, Shoibal M; Microdosing: Concept, Application and Relevance,Indian.J. Pharmacol. 2008, 40(6), 240–242.
11. Wilding I., Bell A.; Improved early clinical development through human microdosing studies, Drug Discoveries and Therapeutics, 2005, 10(13), 890-894.
12. Usha.P , Naidu.M ; Phase 0 - Microdosing strategy in clinical trials, Indian J. Pharmacol, 2008 ,40(6),240–242.
13. Sugiyama.Y, Yamashita. S.; Impact of microdosing clinical study-why necessary and how useful? Advanced drug delivery reviews, 2011, 63(7), 494-502.
14. Garner RC. Et al; Practical experience of using human microdosing with AMS analysis to Obtain early human drug metabolism and PK data, Bioanalysis. 2010, 2(3), 429-40.
15. Lappin, G; Use of Microdosing to Predict Pharmacokinetics at the Therapeutic Dose: Experience with Five Drugs. Clinical Pharmacology & Therapeutics, (2006), 80(3), 203-215.
16. Lappin, G., Garner, R. C; The Use of Accelerator Mass Spectrometry to Obtain Early Human ADME/PK Data. Expert Opinion on Drug Metabolism & Toxicology, (2005), 1(1), 23-31.
17. Sandhu, P.et al; Evaluation of Microdosing Strategies for Studies in Preclinical Drug Development: Demonstration of Linear Pharmacokinetics in Dogs of a Nucleoside Analog Over a 50-Fold Dose Range, Drug Metabolism and Disposition, (2004), 32(11), 1254-1259.
18. Lappin, G., Wagner, C. C. & Merbel, N.; New Ultrasensitive Detection Technologies for Use in Micro dosing Studies. Bioanalysis. (2009), 1(2), 357-366.
19. Claudia C. Wagner, Oliver Langer; Approaches using molecular imaging technology — use of

PET in clinical microdose studies, Advanced Drug Delivery Reviews, 2011, 63(7),539–546
20. Graham Lappin, Colin.R; Innovation: Big physics, small doses: the use of AMS and PET in human microdosing of development drugs, Nature Reviews Drug Discovery,2003, 2, 233-240.
21. Tushar T, Shoibal M; Microdosing: concept, application & dosing, Research Methdology, 2010, 1(2) , 61-63.
22. Balani SK.et al; Evaluation of microdosing to assess pharmacokinetic linearity in rats using liquid chromatography-tandem mass spectrometry, Drug Metab Dispos. 2006, 34(3), 384-388.
23. Chirag et al, Pharmaco-economics of microdosing clinical trials in drug development process, International Journal of Analytical, Pharmaceutical and Biomedical Sciences, 2012, 1(3).
24. Di Masi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003; 22, 151–85.