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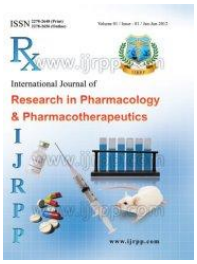

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Review Article ***Open Access***

Microdosing – An unprecedented move

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ABSTRACT

MICRODOSING OR PHASE 0

An early phase of a trial has a vital role in the unprecedented expansion of the clinical trial sector and the drug development process in the emerging era. Micro dosing as the name reflects its definition, in this phase, healthy volunteers are administered a drug at doses of 100 micrograms or $1/100^{th}$ of a normal dose, whichever is lesser. At such low doses volunteers are not exposed to drug toxicity but still drug effect can be determined because the drug is bound to a radiolig and which makes it easier for the detection of even minute amount of dosage .By possible powerful detection techniques like accelerator mass spectroscopy and positron emission tomography samples are drawn and pharmacokinetics as well as pharmacodynamics can be studied .Thus it is helpful for both the patients and the pharmaceutical organisations as this stands as an attractive approach that requires only few preclinical studies , phase 1 trial and a reduced amount of candidate drug on human beings . Microdosing has a promising role in the study of drug- drug interaction besides pharmacokinetic aspects.

KEYWORDS: Microdosing, Drug toxicity, Positron emission tomography

INTRODUCTION

Drug development is a long , complex and expensive activity ,it typically involves a total cost of US $500 million to $1 billion per marketed drug and is spread over 10-15 years[**1**] .A conventional phase 1 study may cost about US $0.3 to $0.5 million . In the drug development process one of the reasons for drug failures during the late developmental phase is suboptimal pharmacokinetics (clearance, volume of distribution etc.) or change in metabolic studies in humans. Hence the pharmacokinetic studies before going for larger trial have shown to be beneficial and a new experimental approach has been developed, known as micro dosing or phase 0 in human [**2**]. A micro dose is defined as a dose of 100 microgram or less and at least 100-fold lower than the anticipated pharmacologically active dose (determined using animal models and/or invitro systems) [**3**]. In the years to come , research methods and technology involved in phase 0 trials become more worldly wise and human micro dosing may be employed to a vast number of drugs that could potentially be administered .Thus phase 0 trials provide an immense opportunity to generate pharmacokinetic and pharmacodynamic data earlier in the drug development scenario . If any discrepancy is found we can abort the trial at this phase itself [**4**]. Hence not only the volunteers are exposed to less toxic drugs but also the pharmaceutical organisations save money and time by avoiding such drugs in early phase of a trial.

DESIGN OF THE PHASE 0 TRIALS

To understand the phase 0 trials explicitly one has to be familiar with the drug development process.

PRE CLINICAL TRIALS

Before the drug is given in humans it is administered in animals to confirm efficacy, toxicity, teratogenicity and other effects of drugs .once approved it can move to the next stage i.e. clinical trial in which One to three phases for approval of a drug, fourth phase being a mandatory phase follows drug approval .once it is approved the clinical trial can be started from phase 1 under Good clinical practice.

CLINICAL TRIALS

PHASE 1/HUMAN PHARMACOLOGY AND TOXICITY STUDY

Study period is from months to a year with healthy volunteers in 20-80 in number .the aim of the first phase is to determine the toxicity **and** maximum tolerated dose of drug, which helps to determine the dose range for patients in phase 2**.**

PHASE 2/THERAPEUTIC EXPLORATORY TRIAL

The aim of this phase is to determine efficacy of the drug. Usually 100-500 patients are taken at one centre (unicentric).study time is one to two years. This phase is known for maximum drug failure i.e. around 75%.

PHASE3 /THERAPEUTIC CONFIRMATORY TRIAL

This phase is a replica of phase 2 and the aim is to confirm the safety and efficacy in a larger group of patients (as in a study the subject increases, error decreases) usually 500-3000 patients are taken and studied continuously for 3-5 years in many centres (multicentre). Immediately after this phase NDA (New drug application) is filed with the FDA (Food and drug administration). Once FDA gives permission for marketing the drug is available for patients throughout the country .this process i.e. the conventional process may cost about billions of dollars and as mentioned above it is a time taking process.

MICRODOSING

Here comes microdosing into the picture where by developing this concept one can easily find the analysis and the performance of different candidate drugs and extrapolate better solutions in the preliminary stage itself. A candidate drug is defined as a compound with strong therapeutic potential whose activity and specificity have been optimised which enters the pre clinical trials. Thus we can reduce the cost and moreover the time duration is very less to know the performance of the candidate drug in human subjects with a microdose.

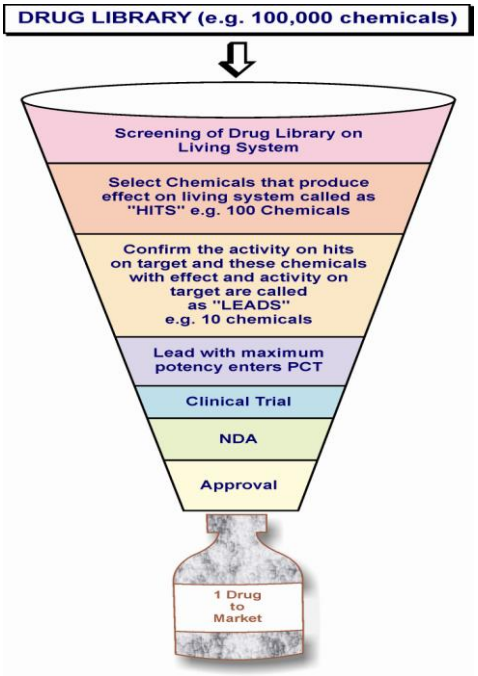

Figure 1: Drug Development Process

RECENT DEVELOPMENT

Besides being a PK and PD determiner microdosing has also been applied to the study of drug-drug interaction by giving human volunteers a microdose of a candidate drug before and after the administration of a drug known to inhibit or induce certain enzymes such as cytochrome P450's. Early data on the metabolism of a candidate drug can be obtained by administering a carbon-14 isotope to human volunteers and comparing the plasma concentration –time curves for total Carbon-14 and unchanged parent compound .the application of microdosing as a tool in drug development is therefore widening into new and previously unforeseen fields.[5]

PROS

The risk of adverse effects is less, a microdose is so small that when administered to human subjects a smaller toxicology package is required, thus further animal studies can be avoided with compounds having unsuitable pharmacokinetic profiles[6] .

CONS

The question of concern is whether microdosing predicts pharmacokinetic parameters accurately for drugs showing non linear kinetics .so caution should be exercised when microdosing is employed to drugs with complex pharmacokinetics, especially during early development of new chemical entities [6].

METHODOLOGY

Microdose is a very low dose compared to the pharmacological active dose, so its analysis and assessment depends on the availability of ultrasensitive analytical methods to measure drug and its metabolite (may measure at the level of pictogram to femtogram range) [7] .as only microdose levels of the drug are used, analytical methods are limited, extreme sensitivity is needed, accelerated mass spectroscopy is the most common method for microdose analysis. AMS like other mass spectrometry methods, measures ionic species according to mass to charge ratio [8]

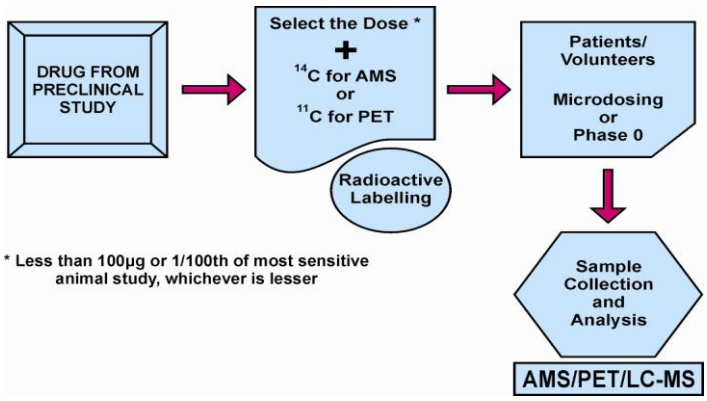

Figure 2: Procedure for Microdosing [9]

ACCELERATOR MASS SPECTROSCOPY (AMS)

Accelerometer mass spectroscopy is used for determining pk data by taking body samples overtime, processing the samples in the laboratory and then analysing their drug content.

Note: PK data can be obtained up to 100 days after administration by using AMS. AMS is a method used for dating, and has a characteristic high sensitivity. In microdosing candidate compounds are labelled with carbon-14. After administering a microdose of labelled compound to a human subject, samples such as blood, urine and faeces are analysed using AMS [10]. It typically displays excellent sensitivity with lower limit of quantification at femtogram. The basic step is to label an investigational drug using the radioisotope carbon-14. The half life for carbon -14 is 5740 years. It quantifies the total number of labelled atoms present in a sample rather than distinguishing between parent drug and metabolites.

POSITRON EMISSION TOMOGRAPHY (PET)

PET primarily provides PD data through real time imaging and some limited PK data.

Note: PK data can be obtained for only 2 hours after drug administration by PET while PK data can be obtained up to 100 days after administration by using AMS .positron emission tomography is a method used for cancer diagnosis. In medical institutions it measures the distribution and chronological changes of gamma waves emitted by a radioactive tracer labelled with a positron emitting nuclide with a short half life [11]. The half life of carbon -11 is 20 minutes. As said before both AMS and PET quantify the total number of labelled atoms present in a sample rather than distinguishing between parent drug and metabolites.

COMPARISON BETWEEN CONVENTIONAL AND MICRODOSING STRATEGIES

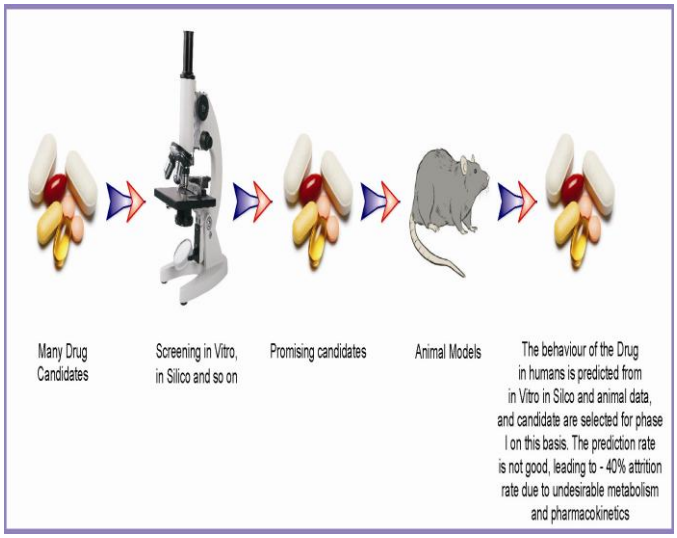

Figure 3: Conventional Strategy

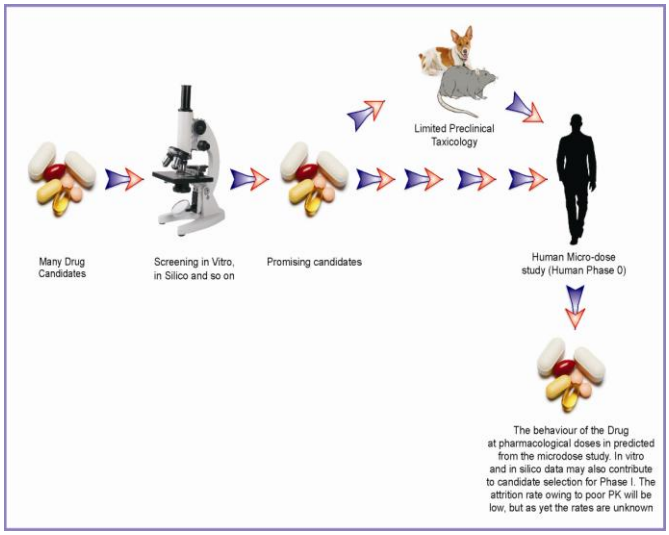

Figure 4: Microdosing Strategy

CONCLUSION

A Microdose is so small that when administered to human subjects, it is not intended to produce any toxicity , hence lesser toxicology package is required , thus further animal studies can be avoided with compounds having unsuitable pharmacokinetic profiles. If any discrepancy is found we can abort at this phase itself, so not only the volunteers are exposed to less toxic drugs but also the pharmaceutical organizations save money and time by avoiding such drugs in early phase of a trial. Micro dosing may later become an accepted

approach in drug development when in man, studies begin with a phase 0 study.

ACKNOWLEDGMENT

I have completed this study under the able guidance and supervision of my mentor and professor Dr. Purushotham reddy garu , I will be failed in my duty if I do not acknowledge the esteemed scholarly guidance , assistance and knowledge I have received from him toward fruitful and timely completion of this work. I have tried my best to present this information as clearly as possible using basic terms that I hope will be comprehended by the widest spectrum of researchers, analysts and students for further studies.

REFERENCES

[1]. Dimasi JA, Hansen RW, Grabowski HG.(2003). The price of innovation. *New estimates of drug development costs. Journal of health economics*; 2(22): 151-85.
[2]. Bikas medhi, Ajay prakash.(2010). *Practical manual of experimental and clinical pharmacology*. : Jaypee; 351.
[3]. Berend oosterhuis. (2010). *Trends in microdosing and other exploratory human pharmacokinetic studies for early drug development. Bioanalysis*. : 377-379.
[4]. Ranjan Kumar Patel. *Latest development in clinical trials*, First edition: Cbs publishers; 2015.
[5]. Graham Lappin. (2010).Microdosing: Current and the future; Bio analysis. ; .
[6]. *Microdosing in translational medicine: pros and cons Advances reports. Cambridge health associates.* :5-5.
[7]. Aboagye EO, Price PM et al. (2001).*In vivo pharmacokinetics and pharmacodynamics in drug development using PET. Drug discovery today.* : ; . 293-302.
[8]. G.Lappin, R.C.Garner. (2005). *the use of accelerator mass spectroscopy to obtain early human ADME/PK Data*, Expert opinion in Drug metabolism and toxicology ed.:23-31.
[9]. Bikas medhi, Ajay prakash. (2010). *Practical manual of experimental and clinical pharmacology.* :351.
[10]. G. Lappin, W. Kuhnz, R. Jochemsen, J. Kneer, A. Chaudhary, B. Oosterhuis et al. (2006). *Use of microdosing to predict pharmacokinetics at the therapeutic dose*, 80 ed.: 203-215.
[11]. Bhavesh N.Chauhan, Chirag M Modi et al. Pharmacoeconomics of microdosing clinical trials in Drug Develeopment Process. 2012; 1(2278-0246).