Microdosing

A robust tool for studying the pharmacokinetics, metabolism, and skin penetration of test compounds

Microdosing is one of the many cutting-edge tools currently used by researchers at CHDR. Because it can track extremely small doses of a test compound and its metabolites, microdosing has a wide range of practical applications in early-stage clinical drug development. For example, microdosing can be used to select the candidate compound that has the best pharmacokinetics profile. It can also be used to analyse the compound's metabolites. Importantly, microdosing can also demonstrate whether or not the active ingredient in a topical preparation is absorbed through the skin and enters the circulation.

What is microdosing?

With microdosing, the subject receives an extremely small dose of a compound labelled with a radioisotope such as ^{14}C, ^{26}Al, or ^{129}I (rather than the corresponding stable isotopes ^{12}C, ^{27}Al, and ^{127}I). The concentration of the labelled compound and/or its metabolites is then measured in various tissue samples using accelerator mass spectrometry (AMS). In this highly sensitive technique, particles are accelerated to an extremely high speed before mass analysis, thereby separating the tiny amounts of the rare isotope from the more abundant stable isotope. AMS was initially developed in the 1970s for carbon dating in archaeology. Since then, several applications for AMS, including microdosing, have been developed for use in biomedical science.

Microdosing: a closer look

Using microdosing to select the compound with the best pharmacokinetics profile

In some cases, preclinical research yields several promising leads, and the sponsor must decide which compound has the ideal profile in terms of its biological half-life (i.e. its pharmacokinetics). In these cases, performing a microdosing experiment in healthy volunteers can be used to measure the compound's elimination, providing an estimate of its half-life. Because the subjects receive only a fraction of the compound's lowest effective dose, this approach can be used even before toxicology studies are completed. Data obtained from the microdosing study can then be used to optimise the compound's clinical development based on its clinical applications. For example, a short half-life (e.g. a few hours) is useful for a sleep aid but would be impractical in an oral contraceptive.

It's important to keep in mind that pharmacokinetics data obtained using microdosing may not necessarily reflect the pharmacokinetics profile of a full, clinical dose. For example, if the drug has low solubility, the relationship between the dose and the elimination rate may not be linear, potentially reducing the reliability of the microdosing data.

Another useful application of microdosing is to establish the bioavailability, volume of distribution, and clearance of an oral compound. By combining data from a single ascending oral dose study with a labelled intravenous microdose given a few weeks later, we can measure the differences between oral and intravenous doses with extremely high accuracy, providing a highly precise pharmacokinetics profile.

Studying a compound's metabolism

Using a labelled compound can provide unique insights into the compound's metabolism, as each metabolite can be traced – provided of course that the isotope is located at a key structural position within the molecule. Using AMS, the major modes of excretion (e.g. in the stool, urine, etc.) can be monitored. Tracking all of the test compound's metabolites – including minor metabolites – can provide a complete picture of the compound's metabolic and pharmacokinetics profiles.

Why choose CHDR?

The Centre for Human Drug Research specialises in early-phase clinical drug research. CHDR's overall mission is to improve the drug development process by collecting as much information as possible regarding the candidate drug in the early phases of development. This information helps sponsors make informed decisions regarding the course of clinical development for their product.

Why choose CHDR?

Research at CHDR covers a wide range of fields, including the central nervous system (CNS) and pain, the cardiovascular system, haemostasis, immunology, and dermatology. In addition, CHDR is at the forefront in developing novel biomarkers and methods for measuring drug-related effects in all of these research areas.

Pharmacology matters

Whether studying a new cognitive-enhancing drug, a next-generation painkiller, or a new monoclonal antibody designed to treat rheumatoid arthritis, the goal is to determine how the compound's effects correlate with both the dose and blood concentration at any given moment. In addition, understanding which biological systems are activated is an essential first step towards quantifying this relationship. At CHDR, our focus on pharmacology is reflected clearly in what we call question-based drug development.

Question-based drug development

CHDR actively uses question-based drug development - or QBD - as a more rational approach to drug development compared to conventional approaches. QBD can be best described as a series of questions that are addressed throughout the process. These questions often seem simple enough, but failing to answer even one question - or even addressing the questions in the wrong order - can have dire consequences. Thus, using this approach can potentially save companies millions of dollars by helping predict a catastrophic issue early in the development process, before the more expensive latter stages (for example, large-scale clinical trials or the marketing phase).

From a general perspective, the most important questions are:

1. Does the biologically active compound and/or active metabolite(s) reach the intended site of action?
2. Does the compound cause its intended pharmacological and/or functional effect(s)?
3. Does the compound cause any unintended pharmacological and/or functional effect(s)?
4. Does the compound have a beneficial effect on the disease and/or clinical pathophysiology?
5. What is the compound's therapeutic window?
6. How does any variability with respect to the drug response in the target population affect the product's development?

Contact

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