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Review Article

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Pharmacokinetics and Pharmacodynamics: New Insights and Implication in Drug Development

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Abstract: Characterizing the relationship between the pharmacokinetics and pharmacodynamics is an important tool in the discovery and development of new drugs in the pharmaceutical industry. The drug discovery and development enterprise, traditionally an industrial juggernaut, has spanned into the academic arena that is partially motivated by the National Institutes of Health Roadmap highlighting translational science and medicine. Since drug discovery and development represents a pipeline of basic to clinical investigations it meshes well with the prime "bench to the bedside" directive of translational medicine. The renewed interest in drug discovery and develpoment in academia provides an opportunity to rethink the hiearchary of studies with the hope to improve the staid approaches that have been critizied for lacking innovation. This review focuses on three important elements of successful PK/PD studies, namely partnership among key scientists involved in the study execution; parameters that influence study designs; and data analysis and interpretation. Specific examples and case studies are highlighted to help demonstrate key points for consideration. The intent is to provide a broad PK/PD foundation for colleagues in the pharmaceutical industry and serve as a tool to promote appropriate discussions on early research project teams with key scientists involved in PK/PD studies.

Keywords: Pharmacokinetics, Pharmacodynamics, Translational medicine, Health roadmap

1. Introduction

Pharmacokinetics is the term that describes the four stages of absorption, distribution, metabolism, and excretion of drugs. Drugs are medications or other substances that have a physiological effect when introduced to the body. There are four basic stages a medication goes through within the human body: absorption, distribution, metabolism, and excretion. This entire process is sometimes abbreviated ADME.

Absorption is the first stage of pharmacokinetics and occurs after medications enter the body and travel from the site of administration into the body's circulation. Distribution is the second stage of pharmacokinetics. It is the process by which medication is spread throughout the body. Metabolism is the third stage of pharmacokinetics and involves the breakdown of a drug molecule. Excretion is the final stage of pharmacokinetics and refers to the process in which the body eliminates waste. Each of these stages is described separately in the following sections of this chapter.

Research scientists who specialize in pharmacokinetics must also pay attention to another dimension of drug action within the body: time. Scientists do not have the ability to visualize where a drug is going or how long it is active.

To compensate, they use mathematical models and precise measurements of blood and urine to determine where a drug goes and how much of the drug (or breakdown product) remains after the body processes it. Other indicators, such as blood levels of liver enzymes, can help predict how much of a drug is going to be absorbed.

Pharmacodynamics refers to the effects of drugs in the body and the mechanism of their action. As a drug travels through the bloodstream, it exhibits a unique affinity for a drug-receptor site, meaning how strongly it binds to the site. Drugs and receptor sites create a lock and key system (Figure 1) that affect how drugs work and the presence of a drug in the bloodstream after it is administered. This concept is broadly termed as drug bioavailability.

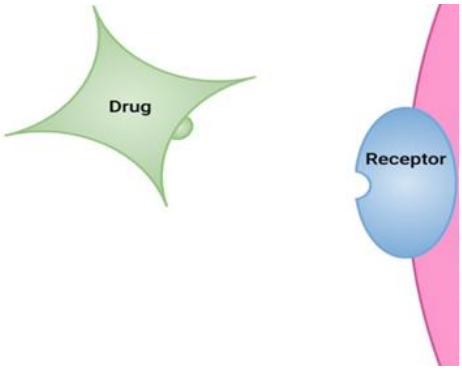


Figure 1: Drug and Receptor Binding

Pharmacokinetics (PK) is defined as the quantitative study of drug absorption, distribution, metabolism, and excretion (ADME)—i.e., the ways the body processes a drug1 while the drug exerts its actions in the body. Effective and successful pharmacokinetics/pharmacodynamics (PK/PD) studies during drug discovery and development phases require input from scientific experts in complementary disciplines in the pharmaceutical industry. In the majority of cases, the pharmacodynamic portion of PK/PD studies (e.g., animal dosing and measurement of response) are conducted by pharmacology laboratories within a given disease area whereas the measurement of concentrations and evaluation of pharmacokinetics are conducted by DMPK laboratories.

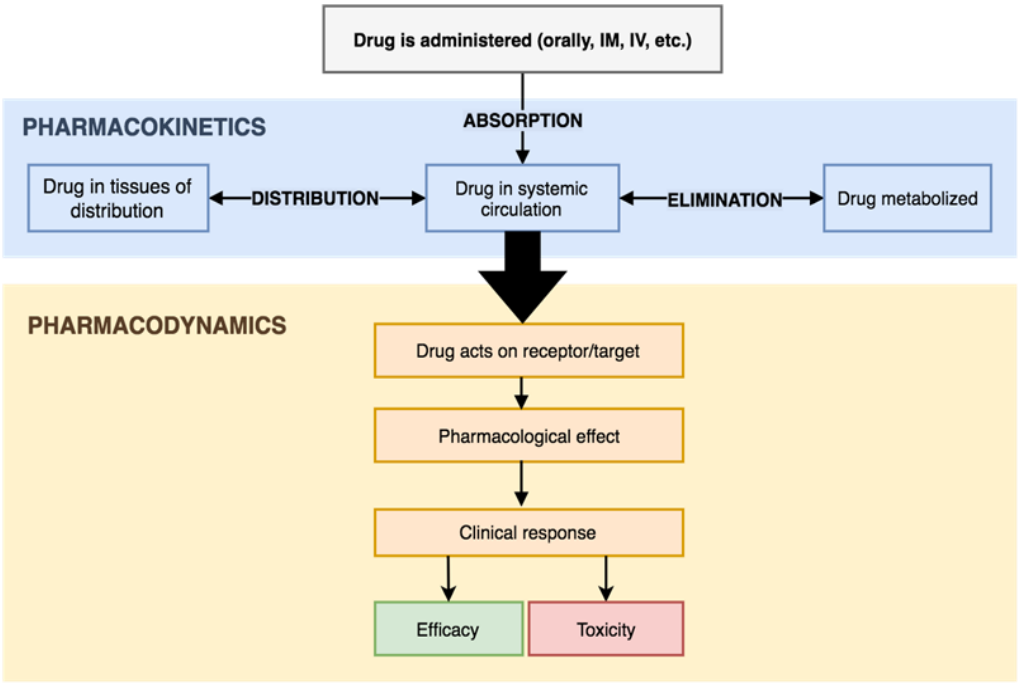
In some cases pharmacokinetics are not determined in the same animals used in the PD study. Rather, the PK and PD datasets might be generated completely independent of each other, not only in different laboratories but also different timeframes. In the latter scenario, generation and reporting of data can happen in isolation, and project teams are then faced with downstream integration and evaluation of results that lack an integrated analysis defining a concentration and effect relationship. Optimally, when PK/PD studies are designed and conducted, the PK/PD analysis, conclusions and interpretations are performed by both DMPK and pharmacology experts, with input from other relevant partners (e.g., formulation and mathematical modeling experts).

The resulting report thus reflects integration of all relevant data and addresses the hypothesis or question asked at the outset of the study. The report will capture any assumptions made in the analysis and suggest what subsequent studies the results enable, and reflects shared ownership and responsibility of both the DMPK and pharmacology experts. The major objective of early drug development is to select promising compounds and to identify potentially safe and effective doses and dosing regimens. Integration of PK/PD in early development helps with compound selection and guides creation of an efficient clinical development strategy.

Initiate And Refine a PK/PD Model:

PK/PD modeling is a valuable approach to integrate quantitative information about the information about the pharmacologic properties of a compound with its pharmacokinetics. Rational study design is based on the assumption of a causal relationship between exposure to a medication and its therapeutic activity. Such relationships are generally complex. Therefore, it is important to design robust preclinical studies that will provide information to build mechanistically relevant PK/PD mathematical models. As data becomes available, initial models can be refined through an iterative process. The ultimate output is a powerful predictive tool based on an in-depth

understanding of the requirements for efficacy. A well designed PK/PD study offers a rational approach to efficient and informative drug development and can help the project team to understand the mechanism of action of a drug and select the optimal compound. Applying PK/PD modeling in early discovery and development programs can minimize animal usage, shorten the development time, estimate the therapeutic index, and predict the dose ranges in early clinical testing. PK/PD models allow integration of data from different studies in a logical manner based on the understanding of drug and disease. Drug discovery and development can be viewed as a model building exercise during in which the knowledge of new compounds is continuously updated and used to inform decision-making and drug development strategy.



Drug Development: A time for change

The drug development process is intertwined with government regulations and the FDA. The FDA has a primary directive to ensure that drugs are safe and effective, and maintain essential standards in clinical trials, yet there is an expectation and growing demand to accelerate the drug development process.

If one considers the drug development pipeline and the pharmaceutical industry's mandate to gain regulatory approvals rapidly one can understand why drug development science needs to be rethought.

The pipeline starting with early drug discovery has been supported by basic science and its fundamental discoveries in biology, and “omic” technologies that have afforded a rich milieu for disease targets and new chemical entities.

This basic science enterprise has traditionally been supported by academic institutions in conjunction with NIH research grants. The data indicate that this paradigm is deficient with R&D expenditures rising and the number of new drug approvals stagnant, and in fact is at a low since 2004. The FDA in 2004 initiated the Critical Path Initiative to improve the drug development process and incorporate the latest scientific advances in the process, and in mostly focused on biomarkers, bioinformatics and clinical design.

In somewhat parallel fashion, the NIH Roadmap was launched as a means to transform biomedical research to ensure basic scientific discovery impacted the treatment of diseases. Thus, both government agencies were trying to grapple with significant advances in scientific discovery and the public demand for tangible benefits that led to cross-fertilization of research disciplines and an emphasis on translational science.

The fall-out from these large initiatives did lead to a renewed appreciation of quantitative pharmacology in translational medicine, and terms such as “pharmacometrics”, and “model-based drug development” were ever

present, yet these procedures found traction in the clinical domain, and much of the standard way of doing "business" in preclinical animal testing was unchanged.

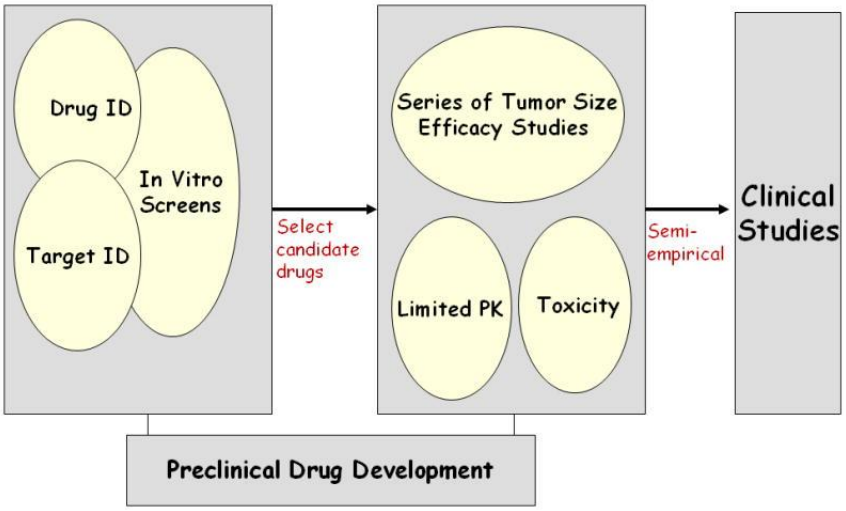
Historical role of pharmacokinetics and pharmacodynamics in drug development:

Most often PKs and PDs operated independently in the drug development arena with PK studies the dominant focus for the purposes of meeting regulatory requirements.

The FDA mandated studies to provide PK characteristics, referred to as ADME (Absorption, Distribution, Metabolism and Excretion) of new single agents, issued in the forms of "guidances" emphasized systemic PK characteristics, toxicokinetics and safety rather than establishing PK/PD relationships that define efficacy. Given these guidelines there was little motivation for companies to examine drug distribution in a systematic manner or in particular to understand drug disposition in target tissues.

For anticancer drugs, in which the tumor serves as the target tissue it is alarming that well-defined protocols were not established to characterize tumor-specific PK properties.

The lack of preclinical PK/PD data is not simply an issue in choosing starting doses for patients, but curtails the usefulness of available PK/PD data obtained from patients. It is understandable that measurements of tumor drug concentrations and PD responses in patients will be sparse, singular timed samples that present a challenge as to how to integrate across subjects into meaningful assessments of drug delivery to the tumor and target inhibition. Preclinical PK/PD models that have been derived from tumor measurements provides a means to scale-up the models to patients.



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