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The role of Pharmacokinetics in drug development

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Abstract

This review aims to summarize the present status of Pharmacokinetics in Drug Discovery. The review is structured into four sections. The first section is a general overview of what we understand by Pharmacokinetics and the different LADMET aspects: Liberation, Absorption, Distribution, Metabolism, Excretion, and Toxicity. The second section highlights the different computational or in silico approaches to estimate/predict one or several aspects of the pharmacokinetic profile of a discovery lead compound. The third section discusses the most commonly used in vitro methodologies. The fourth and last section examines the various approaches employed towards the pharmacokinetic assessment of discovery molecules, including all the LADME processes, discussing the different mathematical methodologies available to establish the PK profile of a test compound, what the main differences are, and what should be the criteria for using one or another mathematical approach. The primary conclusion of this review is that the use of the appropriate preclinical assays has a key role in the long-term viability of a pharmaceutical company since applying the right tools early in discovery will play a key role in determining the company's ability to discover novel safe and effective therapeutics to patients as quickly as possible.

Keywords: Structure-Activity Relationship (SAR); Population Pharmacokinetics; Pharmacokinetic/Pharmacodynamic Models; Biopharmaceutics Classification System (BCS); Bioequivalence; ADME.

1. Introduction

Pharmacokinetics is the kinetics of drug absorption, distribution, metabolism, and excretion (KADM)and their relationship with the pharmacological therapeutic or toxicological response in man and animal. Pharmacokinetics is the quantitative study of drug movement and out of the body.

This productivity paradox is made worse because patents associated with many drugs with sales above US$ 1 billion are now beginning to expire[1].

Each phase of the drug development process is designed to accrue the necessary information to assess the probability of technical success for a new chemical entity (NCE). Continually expanding the knowledge base supporting the efficacy and safety attributes of an NCE remains the fundamental pathway to successful drug development. The learn-and-confirm paradigm has been proposed as an efficient and rational approach to drug development. Effective learning and confirmation implementation requires the timely application of modeling and simulation (M&S) tools. Advancements in computational tools have greatly facilitated the wider application of M&S in clinical trials[2].

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The general objectives and the mode, learn or confirm, at each phase, as outlined, help define specific M&S tasks. The questions and functions listed are not intended to be a comprehensive list. Still, they stimulate thought and guide the appropriate use of M&S. The impact of M&S on NCE development depends on the type and amount of prior information available. Two extreme cases of previous details are outlined. Most of the time, development program teams will be in an intermediate scenario. In these cases, it is vital to leverage the existing data and simultaneously manage the risk and uncertainty because certain critical aspects remain unknown. In every case, robust trial design strategies are needed. Robustness can be achieved by understanding and using prior information and carefully acknowledging and assessing risk and uncertainty.

Pharmaceutical companies continually reinvent their tion, compound screening, chemical synthesis, molecular biology, organizational structure, investing in new technologies, pharmacology, and computer-aided drug design. Drug discovery is changing scientific cultures to maintain returns, and development organizations have embraced new technologies and research investments. The process of discovering, developing, and such analytical instrumentation, cheimstryand biology robotic marketing new drugs has changed considerably in the last decade systems, computerized data handling systems, and computational with advances in technologies and new strategies in target selection- and simulation software. Combinatorial chemistry techniques, high-throughput compound library screening, and genomic and proteomic information have dominated drug discovery strategies. Although several successes have arisen from these changes, the cost of discovering, developing, and marketing new drugs remains staggeringly high[3].

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Drug research encompasses several diverse disciplines united by a common goal: developing novel therapeutic agents while l The search for new drugs can be divided into discovery and development. The former consists of setting up a working hypothesis of the target enzyme or receptor for a particular disease, establishing suitable models (or surrogate markers) to test biological activities, and screening the new drug molecules for in vitro and/or in vivo biological activities. In the development stage, efforts are focused on evaluation of the toxicity and efficacy of new drug candidates. Recent surveys indicate that the average new chemical entity taken to market in the United States requires 10 to 15 years of research and costs more than $300 million. To aid in a discovery program, accurate pharmacokinetic and metabolic data must be available almost as early as the in vitro biological screening results. Early pharmacokinetic and metabolic evaluation with rapid information feedback is crucial for optimal pharmacokinetic and pharmacological properties. To be effective, the turnover rate needs at least three to five compounds per week to support each program. Due to time constraints and the availability of only small quantities of each compound in the discovery stage, studies are often limited to one or two animal species. Therefore, the selection of animal species and the experimental design of studies are essential in providing a reliable prediction of human drug absorption and elimination. A suitable compound could be excluded based on results from an inappropriate animal species or poor experimental design.

1.1. LADMET-R and Pharmacokinetics[6]

When the studies are focused solely on one specific pharmacokinetic aspect (Absorption, Distribution, Metabolism, or Excretion) by in vitro, in situ, in vivo, or silico techniques, it is usually referred to as ADME studies. In contrast, Pharmacokinetics is typically reserved for in vivo studies where an integrated approach of all the ADME processes is taken together. For either ADME or Pharmacokinetics, the truth is that under both methods, it is necessary to command a more or less sophisticated knowledge of algebra and calculus to interpret the dataset correctly. Although ADME assays

have been the gold standard in PK, additional tests should be incorporated since they play a key role in Drug Discovery and further development.

Liberation of the drug from the pharmaceutical form is a key parameter in bioequivalence studies for intravenous formulations, where the rate of release from the formulation determines the disposition of the drug.8–12 Response and toxic effects are the other two key aspects to consider since they are the main reasons for Drug Discovery failure summary when we refer to the different individual assays that should be performed to characterize the PK profile of a new drug in vitro, in situ, in vivo or silico we should also consider, besides the "gold standard" ADME, release from the pharmaceutical form, toxicity, and activity/response in the target site (LADMET-R).

1.2. Discovery and Development

New drug development can be divided into two stages: discovery and development. Recently, Kola and Landis13 reviewed the significant causes of attrition in development. In their review, they showed how the root causes of drug failure have evolved. In 1991, PK and bioavailability were the primary reasons for drug failure (40%), dropping dramatically to 10% in 2000. This significant change is mainly due to the time and effort that the Industry has invested in the last decade toward a more profound and better understanding of PK, partially in an attempt to overcome poor bioavailability but also trying to look into more predictive kinetic behavior of the drug candidates to allow for more efficient dose regimens. Lack of efficacy and safety were reported as the most relevant causes of why compounds underwent attrition in the clinic in 2000 (30%)[7].

The Tufts Center for the Study of Drug Development14 published in 2005 the three main reasons for terminating the unpromising of new drugs. Again, safety and efficacy were listed among the main three. In summary, the identified issues in that report have been the main focus of study in recent years and a driving force in determining which strategy to follow in Drug Discovery. The composite of activity, safety, and acceptable LADME properties, rather than a specific Attribute, will dictate the success of the drug program. To identify potential liabilities in discovery and eliminate those molecules from further consideration, high throughput screening (HTS) of reliable and appropriate in vitro and/or in situ assays seems to be the fastest and most efficient way to proceed,15–17 as shown in. Generally, when a drug is granted to progress into development, a project team is formed with members of different areas of expertise to establish an early development plan. Successful drug development results from getting to this stage with enough information about the previously mentioned processes and a worthwhile investment that provides value to the sponsor[8].

The project team needs to be aware of the target product profile to make educated decisions about the direction in which the project needs to evolve to reach the next milestone in development. Components of the target product profile are disease indication, minimum efficacy requirements, required safety profile, desirable dose regimen, dosage form, the maximum cost of goods, planned date of regulatory submission, and expected approval date planning exploratory studies in humans under an Investigational New Drug (IND) application. There is some preclinical data as well as chemistry, manufacturing, and control information that need to be generated. The approaches to developing this data can be optimized to expedite the progress into development and increase the chances of success of the IND filing by efficiently compiling a good-quality dataset. Depending on the goals of the proposed investigation, the amount of data that needs to be submitted can vary [9].

1.3. Role of Pharmacokinetics and Metabolism in Drug Design

The pharmaceutical Industry's history shows that a combination of fortuity and luck has discovered many essential drugs. The discovery of Isoniazid best exemplifies this serendipity. Meyer and Mall first synthesized Isoniazid and gave Isoniazid to 92 "hopeless" patients with progressive caseous-pneumonic pulmonary tuberculosis who had failed to show improvement after any therapy. Furthermore, both indomethacin and ibuprofen compounds were developed as antirheumatic agents even without knowing their mode of action, showing that these nonsteroidal anti-inflammatory drugs inhibit the synthesis of prostaglandins. Another example of serendipity is the discovery of anxiolytics. Diazepam and chlordiazepoxide, the most widely used benzodiazepines, were found to have anxiolytic activity in 1958 and were marketed in 1960. Efforts to determine the mechanism of benzodiazepine action were initiated only after their introduction into the clinic[10].

It was not until 1974 that convincing evidence from behavioral, electrophysiological, and biochemical experiments was accumulated to demonstrate that benzodiazepines act specifically at synapses in which g-aminobutyric acid (GABA)b functions as a neurotransmitter. Over the past decades, through a better understanding of disease processes, mechanism-based drug design has evolved and produced drugs that interrupt specific biochemical pathways by targeting certain NOT enzymes or receptors[11].

This approach does not require a knowledge of the three-dimensional environment in which drugs act. Recent advances in molecular biology and protein chemistry have provided pure protein in sufficient quantities to allow structural studies to be carried out. Visualization of these structures by sophisticated computer graphics has made structure-based drug design feasible. These rational drug design approaches have been successful historically in the fields of HIV protease inhibitors and angiotensin-converting enzyme inhibitors. Today, many medicinal chemists still receive the design of new drugs to maximize the desired drug activity within certain structural limits. However, compounds that show very high activity in vitro may prove later to have no in vivo activity, or to be highly toxic in in vivo models. Lack of in vivo activity may be attributed to undesirable pharmacokinetic properties, and the toxicity may result from the formation of reactive metabolites.

Therefore, rational drug design should also consider both pharmacokinetic and metabolic information, and the information should be incorporated with molecular biochemical and pharmacological data to provide well rounded drug design.

From toxicological and pharmacological points of view, it is desirable to design a "safer" drug that undergoes predictable metabolic inactivation or even underb Abbreviations:3-methylcholanthrene; 6-TGN, 6-thioguanine nucleotide; ACE, angiotensin-converting enzyme; AFB, alfatoxin B1; Ah, aromatic hydrocarbon; AUC, area under the curve; AZT, zidovudine; BBB, blood-brain barrier; CCKB cholecystokinin;clearance; cLH hepatic clearance; cLint, intrinsic clearance; CNS, central nervous system; CSF, cerebrospinal fluid; DMBA, 7,12-dimethylbenz[a]anthracene; dimethylbutyl)-5-ethyl barbituric acid; EM, extensive metabolizer; fp, fraction of unbound drug in plasma; ft, free fraction in tissue; GABA, g-aminobutyric acid; GSH, glutathione; Ki , dissociation constant of an inhibitor; Kinact, maximum inactivation rate constant; Km, Michaelis constant; Kp, ratio of drug concentration in tissue to that in plasma after drug administration; L-dopa, levodopa; MPH, methylphenidate; NAT, Nacetyltransferase; NSAID, nonsteroidal anti-inflammatorypolyethelene glycol; PFDA, perfluorodecanoic acid; PM, poor metabolizers; PPAR, peroxisome proliferator-activatedthiopurine methyltransferase; UDPGT, uridinediphosphoglucosetransferase; Vd, volume of distribution; Vi , velocity of an enzymic reaction in the presence of of inhibitor extensive metabolizers; Vmax, maximum velocity; Vo, velocity of an enzymic reaction in the absence of inhibitor[12].

1.4. Hard drugs

The concept of nonmetabolizable drugs, or so-called hard drugs, was proposed byand Arie¨ns and Simonis. The hard drug design is quite attractive. Not only does it solve the problem of toxicity due to reactive intermediates or active metabolites, but the Pharmacokinetics also are simplified because the drugs are excreted primarily through either the bile or kidney. If a drug is excreted mainly by the kidney, the differences in the elimination between animal species and humans will be dependent primarily on the renal function of the corresponding species giving highly predictable pharmacokinetic profiles using the allometric approach A few successful examples of such hard drugs include bisphosphonates and certain ACE inhibitors. Bisphosphonates are a unique class of drugs. As a class, they are characterized pharmacologically by their ability to inhibit bone resorption, whereas pharmacokinetically, they are classified by their similarity in absorption, distribution and elimination. In the clinic, these drugs are used in patients as antiosteolytic agents for the treatment of a broad range of bone disorders characterized by excessive bone resorption. These include hypercalcemia of malignancy, metastatic bone disease, Paget's disease, and osteoporosis. The discovery of bisphosphonates was based on earlier studies of inorganic pyrophosphate by Fleisch and his coworkers They found that pyrophosphate bound very strongly to calcium phosphate and inhibited not only the formation of calcium phosphate crystals, but also the crystal dissolution in vitro. However, pyrophosphate axhobotad no effect on bone resorption in vivo. This was later explained by the observation that pyrophosphate is hydrolyzed before it reaches the site of bone resorption. These findings led to a search for analogs that would display the activities similar to pyrophosphate, but would also resist enzymatic hydrolysis. It was found that the bisphosphonates, characterized by a P-C-P bond rather than the P-O-P bond of pyrophosphate, fulfilled these criteria. As hard drugs, bisphosphonates are not metabolized in animals or humans, and the only route of elimination is renal excretion[13].

1.5. Soft Drugs[14]

In contrast to the concept of hard drugs, Bodor (1984, 1982) and Bodor et (1980) have proposed the approach of soft drugs.

A soft drug is pharmacologically active as such, and it undergoes a predictable and controllable metabolism to nontoxic and inactive metabolites.

The main concept of soft drug design is to avoid oxidative metabolism as much as possible and to use hydrolytic enzymes to achieve predictable and controllable drug metabolism.Most oxidative reactions of drugs are mediated by hepatic

cytochrome P-450 enzyme systems that are often affected by age, sex, disease, and environmental factors, resulting in complex biotransformation and pharmacokinetic variability . In addition, P-450 oxidative reactions have the potential to form reactive intermediates and active metabolites that can mediate toxicity .

These undesirable effects attributed to oxidative metabolism may be circumvented to some extent by incorporating metabolic structural "softness."

1.6. Active Metabolites[15]

For many years, the process of biotransformation was considered synonymous with the inactivation of pharmacologically active compounds. There is increasing evidence, however, that the metabolites of some drugs are pharmacologically active. Numerous examples of pharmacologically active metabolites being used as a source of new drug candidates existbecause these metabolites often are subject to phase II reactions and have better safety profiles.

Perhaps the best-known example is acetaminophen, an O-deethylated phenacetin metabolite.

2. Pharmacokinetics and Drug Design

Many of the failures of drug candidates in development programs are attributed to their undesirable pharmacokinetic properties, such as too long or too shortpoor absorption, and extensive first-pass metabolism.

2.1. Absorption

drug absorption is influenced by many biological and physicochemical factors. The two most important physicochemical factors that affect both the extent and the rate of absorption are lipophilicity and solubility The membrane of the gastrointestinal epithelial cells is composed of tightly packed phospholipids interspersed with proteins. Thus, the transcellular passage of drugs depends on their permeability characteristics to penetrate the lipid bilayer of the epithelial cell membrane, which is in turn dependent on the lipophilicity of the drugs. As in the example of bisphosphonates, drugs with poor lipophilicity will be poorly absorbed after oral administration. The effect of lipophilicity on oral absorption is best exemplified by the classical study of barbiturates conducted by Schanker.In this study, the absorption of these compounds increased with increasing lipophilicity as a result of increased membrane permeability. Similarly, Taylorhave shown that the absorption rates of a series of b-blockers in rat small intestine correlated well with their lipophilicity. However, it should be noted that although there is a correlation between lipophilicity and increased permeability, lipophilicity, in some cases, is not predictive of permeability because of external factors.

2.2. Pro-Drugs[16]

The prodrug concept was first proposed by Albert (1958). Since then, this approach has been widely used in drug design. Although there are many reasons to use prodrugs, improvement of oral absorption is by far the most common. Antibiotic prodrugs comprise the largest group of prodrugs developed to improve oral absorption (Wermuth, 1984). Pivampicillin, talampicillin, and bacampicillin are prodrugs of ampicillin, all resulting from the esterification of the polar carboxylate group to form lipophilic, enzymatically labile esters. The absorption of these prodrugs is nearly complete (98– 99%), whereas that of ampicillin is , Enalapril, the most widely prescribed ACE inhibitor, is the ethyl ester prodrug of the active diacid, enalaprilat.

Enalaprilat is poorly absorbed from the gastrointestinal tract (,10%), but absorption of the prodrug enalapril is greatly improved (60%).

2.3. Distribution

The lipophilicity of a drug not only affects its absorption and metabolism but also its binding and distribution. Generally, the higher the lipophilicity of a drug, the stronger its binding to protein and the greater its distribution. In studies with structure related sulfonamides, Seydel.(1973) have shown that there was a strong positive correlation between plasma protein binding of the drugs and their lipophilicity. Watanabe and Kozaki (1978) found that the volume of distribution increased with increasing lipophilicity when administering 15 basic drugs to dogs. Recent studies by Bickel (1994) have shown that although the initial uptake of drugs into adipose tissue is related to their lipophilicity, the degree of adipose tissue storage does not correlate with their lipophilicity. Factors such as drug binding to plasma and tissue proteins also play a significant role in drug storage in adipose tissues.

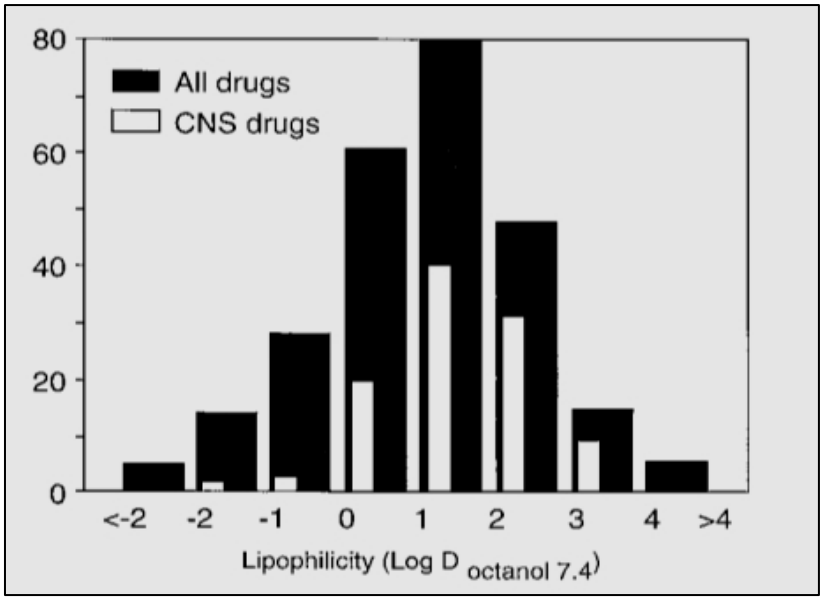

Figure 1 Lipophilicity of CNS and All Drugs

3. Conclusion

The goal of using 'screening' preclinical assays in drug discovery- procedures are provided. These assays have reasonable samples that eliminate drug candidates with inferior potency/selective- throughput and require minimal compounds. As ques- ty and/or pharmacokinetic/toxicity problems promptly, tions arise concerning physicochemical, absorption, clearance, and transfer of more promising drug candidates to preclinical metabolism, distribution, and inhibition properties, the structure of development with sufficient characterization to lower their attrithese drug candidates can be modified and new drug candidates tion rates in development.

Compliance with ethical standards

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Disclosure of conflict of interest

There are no conflicts of interest.

Authors Contributions

All the authors have contributed equally.

Data Availability Statement

The data presented in this study are available upon request from the corresponding author.

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