Importance of ADME and Bioanalysis in the Drug Discovery

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Editorial

The hunt for new drugs can be divided into two stages: discovery and development. Drug discovery includes generating a hypothesis of the target receptor for a particular disorder and screening the in vitro and/or in vivo biological activities of the new drug candidates. Drug development involves the assessment of efficacy and toxicity of the new drug candidates.

To aid in a discovery program, accurate data on pharmacokinetics and metabolism must be available as early as possible as it eventually contributes to the final success or failure of the compound. The initiation of early absorption, distribution, metabolism and excretion (ADME) screening has dramatically decreased the proportion of compounds failing in clinical trials. The main aim of preclinical ADME is to eliminate weak drug candidates in the early stages of drug development which allow resources to be focused on potential drug candidates [1]. Undesirable pharmacokinetic properties, such as poor absorption, too long or too short half-life ($t_{1/2}$), and extensive first-pass metabolism majorly contribute to the failure of many drug candidates in early stages of drug development programs. To be successful, a drug candidate needs to possess good bioavailability and a desirable half-life ($t_{1/2}$). Early ADME provides the necessary data for selecting preclinical candidates, appropriate dosage forms, formulation and accelerates the timeline for investigational new drug applications and subsequently new drug application submission to the FDA [2,3].

Pharmacokinetic (PK) parameters are extrapolated from measurement of drug concentration in the plasma, blood, or other biological matrix over a selected time period. Pharmacokinetic data provides information that can guide future animal and clinical studies for the selection of the dose levels and frequency of administration. Many of the approved drugs generate metabolites which possess biological activity. These active metabolites may have different pharmacology and PK properties than the parent drug. A thorough understanding of the properties of active metabolite is important for estimating toxicity and therapeutic outcome. It is ideal to assess the metabolism of new drugs in vitro before proceeding to clinical studies. Early information about the enzymes involved in the drug metabolism is very useful in the design of drug-drug interactions studies [4,5].

The prime determinant of efficacy and unexpected toxicity of a drug is how it penetrates biological barriers such as intestinal wall, or blood-brain barrier (BBB). This is true in central nervous system (CNS) drugs, because drug candidates possessing in vitro efficacy do not penetrate the BBB will not show in vivo efficacy. The entry of drugs in to the CNS is limited by the presence of the BBB. BBB effectively isolates the brain from the blood because of the presence of tight junctions connecting the endothelial cells of the brain vessels. In addition to this, drug metabolizing enzymes and efflux pumps, such as P-glycoprotein (P-gp) and the multi-drug-resistance protein located within the endothelial cells, push out the exogenous molecules from the brain. As a result, CNS drugs have high failure rate in the developmental stages [6].

Bioanalytical support plays a vital role during the lead optimization stages. The major goal of the bioanalysis is to assess the overall ADME characteristics of the new chemical entities (NCE’s). Arrays of bioanalytical methods are required to completely describe the pharmacokinetic behavior in laboratory animals as well as in humans [7]. Bioanalytical tools can play a significant role for the progress in drug discovery and development. Physiologic fluids such as blood, serum, plasma, urine and tissues are analyzed to determine the absorption and disposition of a drug candidate administered to a test animal [8]. Often the concentration of the NCE’s in the biological matrix changes with time, and perhaps fall below nanogram level, therefore, quantification limits for the bioanalytical methods should be much lower than those required for analytical methods [9]. Effects from the endogenous materials (such as plasma proteins) of the biological matrix and stability issues make the accurate analysis difficult. Methods developed to analyze the pharmacokinetic study samples need complete separation of the analytes from matrix components. The performance of the bioanalytical assay can be improved by removing interferences from the matrix trough complex sample preparation steps, and concentrating the analyte of interest. Common methods of sample preparation include protein precipitation, liquid-liquid extraction and solid phase extraction [10]. Appropriate bioanalytical methods are required to detect drug candidate at low nanogram levels, at the same time linearly over three orders of magnitude [8].

References


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