ACCELERATOR MASS SPECTROMETRY AND POSITRON EMISSION TOMOGRAPHY IN HUMAN MICRODOSING

ZHENGDONG CHENG

Artie McFerrin Department of Chemical Engineering, Professional Program in Biotechnology and Materials Science and Engineering Program, Texas A&M University, College Station, Texas

1 INTRODUCTION

Human microdosing is a novel method that permits improved drug candidate selection by taking the investigational drugs into humans earlier to obtain human metabolism data. In 1991, there was a 40% failure rate associated with inappropriate drug metabolism and pharmacokinetics of candidate drug molecules in the traditional early clinical drug development (phase I) [1, 2]. Over the subsequent decade (1991–2000), attrition for poor pharmacokinetic properties decreased considerably and represented less than 10% of total attribution. More recently, lack of efficacy and/or inadequate safety (clinical or toxicological) have become the primary reasons for attrition [attrition was highest during phase II (62%) but still significant in phase III (45%) and at the time of registration (23%)] [3]. On average, it takes 10–12 years for a molecule from discovery to regulatory approval. The cost of drug development is now greater than $800 million per registered drug [4]. The costs of compounds abandoned during testing were linked to the costs of compounds that obtained marketing approval [5].

There are three main techniques that are used in microdosing studies: AMS (accelerator mass spectrometry), PET (positron emission tomography), and liquid chromatography–tandem mass spectrometry (LC-MS/MS). Both AMS and PET provide much greater sensitivity than LC-MS/MS, allowing the quantification of very low drug levels in plasma after microdosing. However, microdose/AMS or PET studies are labor and resource intensive compared to LC-MS/MS. PET can provide pharmacodynamic (PD) information, whereas AMS provides pharmacokinetic information (PK).

2 DEFINITIONS

ADME A drug's absorption, distribution, metabolism, and excretion characteristics. A drug's PK and PD define the ADME.

Human Microdosing A technique for studying the behavior of a drug candidate in humans through the administration of low dose at levels typically about 100 times lower than the therapeutic dosage predicted from animal in vitro models, and also not exceeding 100 μg, but high enough to evaluate PK properties of the candidate [6, 7]. This technique is also called trace-dose human ADME screening studies, or human phase 0 trials, in contrast to "phase 0 studies" or preclinical studies conducted in animals [8].

Microdose A subpharmacological active dose of drug: 1/100th of the projected pharmacologic dose in humans or a maximum of 100 μg [9].

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad
Copyright © 2010 John Wiley & Sons, Inc.