1. Introduction

Drug discovery and development is an exciting and complex process that begins with target identification and ends with regulatory approval, launch and product life-cycle management. Along this 10+ year journey, drug metabolism and pharmacokinetics (DMPK) is vital in characterizing the absorption, disposition, metabolism and excretion (ADME) of the drug. Over the past 30 years, DMPK had grown from a relatively qualitative science providing a general description of a drug’s excretion pathways and metabolism, to a robust, integrative and quantitative discipline addressing drug interactions and ADME of complex molecules (1). This transformation has occurred through disruptive advances in bioanalytical and imaging technologies, and software to support extensive modeling and simulations exercises. The integration of these technologies with advances in our understanding of the fundamental biological process underpinning the ADME of new chemical entities has enabled the DMPK field to make significant contributions to drug development and discovery. This plenary presentation will highlight the evolution of the DMPK discipline through several case studies.

2. Results

Drug development and the pharmaceutical industry is extensively regulated. The current process of modern clinical trials Phase I through IV testing to evaluate drug efficacy and safety extends back to Dr. Frances Oldham Kelsey, the FDA reviewer assigned to W.S. Merrell Company’s application for thalidomide (Kevadon) as a sedative agent (2). Dr. Kelsey withheld approval and requested further research on the safety of the compound. Eventually, the association of birth defects with the drug led to its withdrawal from all global markets. This event led to congress passing laws giving the FDA authority to require that drug products are efficacious and safe. Dr. Kelsey helped write the first rules for clinical trials still used today. Although never approved in the US as a sedative agent, thalidomide (Thalomid) is approved as a cancer and leprosy treatment (3). Recent research has demonstrated that Thalidomide promotes degradation of SALL4, a transcription factor implicated in Duane Radial Ray Syndrome (4).

Prior to the mid-1990s, ADME was generally a ‘qualitative’ discipline providing general descriptions for routes of excretion and metabolites. There was little mechanistic drug interaction or clinical translation of DMPK data. Therefore, this science was not a fully integrated part of drug discovery and development. Several scientific advances and safety events occurred in the 1990s that triggered the transformation of DMPK to a quantitative science and integrated drug discovery and development partner. Molecular biology, high-throughput screening, combinatorial chemistry, and advances in bioanalysis are a few of the key technological changes. These, coupled with a further focus on drug safety, drove the transition and industrialization of DMPK. One key event was the finding that terfenadine (Seldane), a non-sedating antihistamine prodrug, could cause fatal arrhythmias in some patients who took certain antifungals. At the time of the adverse safety reports, the mechanism was unknown. Further research demonstrated that inhibition of terfenadine’s metabolism via CYP3A4 resulted in higher exposure of the prodrug (5). With this new knowledge, the active metabolite, fexofenadine, was eventually developed, approved and marketed as Allegra.

DMPK has been an essential part of drug discovery and development over the past 20 years. There are robust development studies to quantitatively understand a molecule’s ADME properties (Figure 1). These include a host of in vitro studies...
to characterize if a drug molecule is a substrate or inhibitor of metabolic enzymes (e.g., cytochrome P450s, UGTs, esterases etc) and drug transporters (e.g., P-glycoprotein, BCRP, OATP), to elucidate the full in vivo metabolic and disposition pathways in humans (e.g., human ADME study) (1).

To highlight the advances in quantitative ADME, a case study on the HIV drug, Fosdevirine (FDV; GSK2248761; IDX899) will be presented. Briefly, during a Phase IIb study, several HIV patients experienced seizures (5/20 subjects) while receiving FDV (100 or 200 mg QD) w/ raltegravir or ritonavir + darunavir for a minimum of 4 weeks. These events began 28 to 81 days after start of treatment and continued from 1 week to 5 months after drug discontinuation. No such events were observed in preceding clinical studies in healthy volunteers or naïve HIV patients (187 subjects total). There were no changes in FDV plasma exposure. Using matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI IMS), a cysteine conjugate metabolite of FDV was the predominant drug-related component in the samples from patients, rabbits, and minipigs (all of which displayed CNS events). This metabolite persisted in the CNS for an extended period after the last dose and was localized to white matter in rabbit and minipig brains. In contrast, in monkey, which did not show CNS events, the predominant component in CNS was parent drug associated with the gray matter.

3. Conclusions

DMPK has evolved to become a quantitative and integral scientific discipline critical to the drug discovery and development process. The ability to integrate and translate diverse information from in vitro, in vivo and in silico ADME studies is critical, and allows the DMPK scientist to influence the direction of the project. A number of opportunities and challenges confront our discipline, including: how to incorporate machine learning and analytical tools into DMPK studies; to measure and visualize drug (and metabolites) at target or within the cell; to apply microphysiologic systems to advance our understanding of ADME-related biological processes; to leverage advances in chemistry, biology and genetics to select drug candidates; to build global collaborations between industry, academia and regulatory agencies; to harmonize DMPK assays, reagents, and kinetic analysis; how pharmaceutical companies are divesting out of DMPK; and to address the academic training gap.

4. Acknowledgements

To all my colleagues at ViiV Healthcare and GSK who have contributed to the work presented here.
References


