Editorial

Transforming Events: Hepatic Metabolism and Individual Variability

Variability in individual therapeutic response to medication has long been recognized. These patient-specific phenomena, characterized as “idiosyncrasy or constitutional peculiarity” >150 years ago,¹ have in many ways now been explained through the combined efforts and discovery of clinical medicine and science. Nevertheless, in some cases, individual differences in drug disposition in various patient groups are well recognized and anticipated, such as sex differences in pharmacokinetics (PK), yet their root causes are not completely understood. Individual differences in drug response are sometimes striking in their magnitude, often unpredictable, and may compromise therapeutic outcomes. Accordingly, ongoing efforts and assessments are made to assure that drug formulations and specific dosing regimens are both predictable and sufficient to provide safe and effective treatment to patients. The current issue of Clinical Therapeutics comprises a diverse collection of articles whose unifying theme is the overall goal of assuring adequate delivery of hepatically cleared medications into the systemic circulation and target organ(s) in a safe and effective manner, despite the presence of potentially complicating factors. These factors include compromised hepatic function, substantial presystemic metabolism that may limit bioavailability, and the potential for clinically significant drug–drug interactions (DDIs) as a result of concomitant drug therapies.

Variability in individual drug response may involve perturbations in PK and/or pharmacodynamic response. Interindividual variability in PK is often of major clinical significance and is now known to be influenced by a host of factors, including age, sex, body habitus, diet, genetic variation, and concurrent drug therapies. Furthermore, the presence of disease and altered pathophysiologic conditions can significantly influence drug metabolism and PK. Indeed, impaired organ function, particularly hepatic and/or renal dysfunction, represents 1 of the major sources of altered metabolism and disposition of therapeutic agents. Accordingly, as part of the drug evaluation and approval process, and at times in the postmarketing period, thorough evaluations must be conducted to assess the influence of a host of factors that might contribute to variability in an effort to provide recommendations on both general as well as individualized dosing regimens.

The liver plays a central role in the absorption, distribution, metabolism, and elimination of the majority of therapeutic agents and their respective active and inactive metabolites. Although this role is not exclusive (ie, the gastrointestinal tract, kidneys, and lungs also exhibit significant metabolic capabilities), beyond being the major drug biotransformation site, other variable factors including hepatic blood flow and biliary excretion can further influence drug PK and, ultimately, response. Liver dysfunction may not only reduce the blood/plasma clearance of drugs eliminated by hepatic metabolism via phase I processes (eg, oxidation, hydrolysis) and phase II processes (eg, glucuronidation, sulfation), it can also influence plasma protein binding, which in turn can alter the processes of distribution and elimination of highly protein-bound drugs. Drug transporters also play a crucial role in the absorption, distribution, metabolism, and elimination processes of xenobiotics in navigating the cellular barriers. Chronic liver disease is a well-recognized cause of variable and nonuniform reductions in drug-metabolizing activities as well as transporter protein expression.² Significant reductions in metabolic capacity have the potential to influence numerous drug substrates deactivated by 1 or more hepatic enzymes, as well as agents formulated as prodrugs that are dependent on specific catalytic enzymes for metabolic conversion or activation. Thus, chronic liver disease influences the PK of medications in 3 major ways: reduction of portal blood flow, which affects the presystemic elimination of high-extraction drugs; decreased synthesis of plasma proteins, such as albumin and α-glycoprotein altering the bioavailability of highly bound plasma proteins; and reduced drug-metabolizing capacity.²
The development of dosage adjustment recommendations for patients with liver dysfunction is essential for many drugs to avoid the potential accumulation of excessive amounts of drug, or active metabolite(s), which may have untoward consequences. The US Food and Drug Administration has issued guidance for sponsors of new drug applications and recommends that PK studies be conducted in patients with impaired hepatic function when hepatic metabolism and/or excretion is believed to account for ≥20% of the elimination of the parent drug or active metabolite(s).3 The guidance further recommends the conduction of hepatic impairment studies when the drug and/or active metabolite(s) are eliminated to a lesser extent (<20%) if available data suggest that it is an agent with a narrow therapeutic range. Typically, studies are conducted in patients classified according to the Child-Pugh score system, which is based on 5 variables: the presence of ascites, the presence of encephalopathy, plasma concentration of bilirubin, plasma concentration albumin, and measured prothrombin time. The Child-Pugh score is composed of 3 basic categories: mild impairment (Child-Pugh A; score 5–6), moderate impairment (Child-Pugh B; score 7–9), and severe impairment (Child-Pugh C; score 10–15) versus nonimpaired controls.2,3 Unlike renal insufficiency, in the presence of hepatic insufficiency there are no general guidelines, specific biomarkers, or algorithms of reference to facilitate dosage individualization. In this issue of Clinical Therapeutics, Peveling-Oberhag et al4 present the results of 1 such study specifically designed to assess the influence of hepatic impairment on the PK disposition of the immunosuppressant and antineoplastic agent everolimus.

Presystemic or first-pass metabolism, the biotransformation of orally administered drugs by hepatic (and gastrointestinal) enzymes, can result in significant reductions in the amount of active drug reaching the systemic circulation. For drugs undergoing significant first-pass metabolism, bioavailability may be substantially limited. These limitations can be circumvented in some cases by the use of prodrug formulations or by using alternative routes of oral administration that utilize dosage forms suitable for sublingual (SL) or transmucosal administration. Because the oral mucosa is highly vascularized, and SL venous drainage is systemic rather than portal, the absorbed drug bypasses the gastrointestinal tract and first-pass metabolism with SL dosage forms. Drugs absorbed through the oral mucosa enter the systemic circulation directly; for some drugs, this route also results in a more rapid onset of action. In this issue, Parikh et al5 present the results of a single-dose, randomized crossover study in which the PK of the opioid analgesic fentanyl delivered via SL spray is compared with oral transmucosal administration. In addition, Roh et al6 report the results of a healthy volunteer crossover study in which they compared the PK profile of the cyclic guanosine monophosphate–specific phosphodiesterase type 5 inhibitor sildenafil, formulated as an orally disintegrating film formulation versus that of a more standard film-coated tablet.

Concomitant medications, dietary supplements, and some foodstuffs such as grapefruit juice are well-documented, widely publicized causes of altered metabolism and/or drug transport via metabolic inhibition. Conversely, although not as rapid in onset as inhibition, metabolic induction may also occur when specific therapeutic regimens are combined or when drugs are combined with certain dietary supplements. In some ways, DDIs of an inhibitory nature can be viewed as nonuniform, albeit reversible, causes of diminished hepatic function, at least in terms of the liver’s normal metabolic capacity to clear medications. The study of DDI potential for drugs in clinical development typically begins with high-throughput in vitro assays directed at determining if the drug is a substrate, inhibitor, or inducer of 1 or more major drug-metabolizing enzymes. The results of these initial in vitro studies then serve as a guide to the nature and extent of follow-up in vivo studies that may be required to definitively assess the potential for clinically significant DDIs.7 In addition, in vivo studies are frequently conducted to assess the potential interactions between a drug in clinical development and other medications already in current use that may be anticipated to be frequently used concomitantly and which may have narrow therapeutic indices. In this issue, the article by Macha et al8 presents a systematic assessment of the DDI potential between the sodium glucose cotransporter 2 inhibitor empagliflozin and the frequently used therapeutic agents verapamil, ramipril, and digoxin.

It is the intent of this issue to provide clinicians with a “sampling” of PK studies which evaluate the influence of a range of factors that can alter the disposition of hepatically cleared medications. Pharmacokinetic studies of this nature have high clinical value that is often overlooked, and they should be viewed as far more than exercises to satisfy particular regulatory requirements. Indeed, they are often underappreciated and underused in terms of their
scientific rationale, rigor of design, complexity in their performance, and usefulness in explaining and anticipating clinical response and outcomes in the premarketing and postmarketing periods.

John S. Markowitz, PharmD
University of Florida
College of Pharmacy
Department of Pharmacotherapy and Translational Medicine
Gainesville, Florida

REFERENCES