Drug Disposition Issues in CKD: Implications for Drug Discovery and Regulatory Approval

Alvin Tieu, Andrew A. House, and Bradley L. Urquhart

Patients with chronic kidney disease (CKD) have several comorbidities that require pharmacologic intervention including hypertension, diabetes, anemia, and cardiovascular disease. Advanced CKD patients (eg, treated with hemodialysis) take an average of 12 medications concurrently and are known to suffer from an increased number of medication-related adverse drug events. Recent basic and clinical research has identified altered renal and nonrenal drug clearance in CKD as one mediator of the increased adverse drug events observed in this patient population. This review will briefly describe pharmacokinetic considerations in CKD, review the Food and Drug Administration guidelines for performing pharmacokinetic studies in CKD patients, and outline the roles of academia, industry, and regulatory agencies in improving drug safety in CKD patients.

Key Words: Drug disposition, CKD, Pharmacokinetics, Adverse events, Drug safety

INTRODUCTION

Similar to other economically developed nations, the United States is an aging society. Such a characterization has profound implications on the health care system, requiring greater emphasis on optimizing treatment for chronic diseases.[1] Current estimates suggest that nearly 30 million American citizens are living with some form of chronic kidney disease (CKD).[2] Specifically, the prevalence of end-stage renal disease (ESRD) in the United States has increased over 10-fold from 57,420 in 1980 to 594,189 in 2010.[2] Comprehensive care of CKD and its comorbidities—including metabolic, endocrine, and cardiovascular complications—has culminated in an average of 12 medications prescribed to these patients.[3,4] Despite dosing guidelines that compensate for reduced renal clearance, 1 medication-related complication still arises for every 2.7 drug exposures in hemodialysis patients.[5] In this issue of *Advances in Chronic Kidney Disease*, experts in this area review several important implications of drug therapy for patients with renal impairment. We will provide a brief synopsis of clinically relevant pharmacokinetic changes as possible contributing factors to the frequent adverse drug reactions associated with CKD. As a consequence of these findings, the 2010 US Food and Drug Administration (FDA) draft guidance has suggested inclusion of patients with renal impairment in the drug discovery process.[6,7] Roles of the clinical, research, and regulatory sectors and allocations of government and industry funding will be discussed in hopes of improving therapeutic efficacy and medication management for CKD patients.

PHARMACOKINETIC CONSIDERATIONS IN CKD

Emerging evidence demonstrates alterations of drug absorption, distribution, and nonrenal elimination in renal insufficiency, providing insight as to why CKD patient responses to pharmacotherapy are still widely variable with frequent adverse drug events.[5,8,9] Urea retention and its subsequent hydrolysis into ammonia by bacterial urease can increase intestinal pH, leading to changes in absorption of weakly basic drugs.[10,11] On reaching systemic circulation, attenuated production of albumin coinciding with competitive binding by uremic toxins results in elevated free fraction of medications—the outset for drug toxicity.[12] Recent preclinical and human studies display reductions in nonrenal clearance for CKD, which can ultimately potentiate drug toxicity by prolonging elevated drug concentrations in plasma.[13-21] One possible explanation for this change in drug pharmacokinetics is due to accumulation and circulation of uremic toxins as a result of kidney dysfunction. It has been proposed that indoxyl sulfate and other uremic toxins can inhibit the function and expression of hepatic drug metabolizing enzymes and drug transporters—both being essential contributors to drug disposition.[22-24] Subsequent articles appearing in this issue will elaborate in greater detail the specific mechanisms contributing to altered nonrenal drug elimination.

Although the prevalence of ESRD patients is consistently increasing every year, there is a paucity of available data to discern the effect of renal replacement therapy on drug disposition. The Dialysis of Drugs publication suggests that only 10% of currently marketed drugs have definitive reports for dialytic clearance.[11,25] The significance in this lack of information can be observed in a recent study, which demonstrates that hemodialysis patients prescribed beta-blockers that are extensively cleared by dialysis have substantially heightened risks for mortality

From the Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada; Division of Nephrology, Department of Medicine, Schulich School of Medicine and Dentistry, The University of Western Ontario; Lawson Health Research Institute, London, Ontario, Canada; and Department of Physiology and Pharmacology, Schulich School of Medicine and Dentistry, The University of Western Ontario; Division of Nephrology, Department of Medicine, Schulich School of Medicine and Dentistry, The University of Western Ontario; Lawson Health Research Institute, London, Ontario, Canada.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Bradley L. Urquhart, PhD, 1151 Richmond Street, Medical Sciences Building Room 216, London, Ontario, Canada, N6A5C1. E-mail: Brad.Urquhart@schulich.uwo.ca

1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2016.01.013

and cardiovascular complications.[26] These findings indicate that research into dialytic clearance of drugs is critically important to allow for adequate product labeling, determination of post-dialysis supplemental doses, and recognition of alternative drug therapies.

RENAL IMPAIRMENT STUDIES

Realizing that renal impairment can substantially impact all aspects of drug pharmacokinetics, the FDA Clinical Pharmacology Advisory Committee proposed several important changes to their 1998 FDA Renal Guidance document.[6] The result of this proposal is an updated draft guidance entitled: *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling*.[7] This draft has developed a detailed algorithm for deciding whether to incorporate patients with renal insufficiency in pharmacokinetic studies of new chemical entities (NCEs).[6,7] In short, if NCEs undergo substantial renal elimination (ie, if at least 30% of the dose is excreted unchanged in urine), subjects from each stage of CKD must be included in a "full" pharmacokinetic study. For drugs that are primarily nonrenally excreted, the new draft guidance recommends implementing a "reduced" study design—an important departure from the 1998 Renal Guidance. This design involves the comparison of drug disposition in healthy vs ESRD patients who have not yet been prescribed renal replacement therapy. If drug exposure is substantially elevated in ESRD patients (eg, an increase of at least 50% in area under the concentration time curve (AUC), or a smaller increase for drugs with a narrow therapeutic window), a full renal study must be conducted.

CLINICAL SUMMARY

- Renal and nonrenal drug clearance is decreased in CKD.
- Updated guidance from the Food and Drug Administration highlights the need to perform pharmacokinetic studies in patients with CKD.
- Improving the safety and efficacy of drug therapy in CKD is the collective responsibility of government, industry, clinicians, and academic researchers.

The importance of implementing a reduced design for drugs that may not exhibit renal elimination is evident for the analgesic compound, celecoxib—a selective cyclooxygenase-2 inhibitor.[27] It is well-recognized that prescription of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) is accompanied by heightened risks for nephrotoxicity, especially for patients with severe renal insufficiency. However, celecoxib did not undergo any form of renal impairment study during its drug approval process as its development occurred before publication of the 1998 Renal Guidance, and its primary route of elimination is through hepatic metabolism. Since then, post-marketing population studies combined with data from FDA's Adverse Event Reporting System have demonstrated associations of celecoxib with acute renal failure.[28-30] If overlooked by physicians, lack of appropriate dosage adjustments for CKD patients can lead to an accelerated progression into kidney failure.[31]

Fortunately, a recent survey conducted by Matzke and colleagues (2015) illustrates the positive impact on drug discovery created by the 1998 Renal Guidance. From 1999 to 2010, 71.6% of new investigational drugs conducted appropriate renal studies—a significant improvement from 51.6% in the 2-year span of 1996 to 1997.[32] As the 1998 Renal Guidance did not emphasize renal studies for nonrenally cleared drugs, the involvement of CKD patients was more likely observed in drugs characterized by renal excretion (89.6%) as compared with drugs that primarily display nonrenal elimination (65.8%).[32] Nearly 50% of NCEs with low renal clearance exhibited substantial pharmacokinetic changes. However, only one-third of those NCEs resulted in dosage recommendations and proper labeling. With greater emphasis in the 2010 draft guidance to complete renal studies in drugs with nonrenal clearance, these results provide an encouraging outlook for future NCEs to standardize the incorporation of CKD patients in pharmacokinetic studies.

ROLE OF ACADEMIA, INDUSTRY, AND REGULATORY AGENCIES

Although people living with CKD have reason to be optimistic in terms of improved pharmacokinetic profiling of new investigational drugs, many currently marketed medications still lack suitable dosage guidelines—especially drugs developed before the 1998 Renal Guidance.[32] The responsibility to optimize pharmacotherapy with these older xenobiotics should be distributed between the sectors of academia, regulation, and clinicians, although industry and government can contribute through cooperative funding. For academia, research to reduce the extensive void in pharmacokinetic knowledge of current medications administered in CKD comes with considerable challenges of attaining appropriate resources. These post-market renal studies are not hypothesis-driven and thus are not generally enticing for either industry or government grants.[33] However, pharmaceutical sponsors may be inclined to fund projects that optimize their own products for chronic prescription in renal insufficient patients. The potential for preventative pharmacotherapy to benefit health care economics by reducing adverse drug events, hospitalizations, and expensive procedures should also attract government interest.[34] Furthermore, researchers who wish to improve awareness of therapeutic issues require collaboration from government and industry to allow access to post-marketing databases. Medicare, Medicaid, the Department of Veterans Affair, and pharmaceutical benefit management companies have information that will be instrumental in identifying patterns for optimal disease management with drug therapy.[34]

Contemporary examples of academic programs that have developed collaborative partnerships in public-private and public-government settings include the Centers for Education and Research on Therapeutics and the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network.[35] The DEcIDE Network and Centers for Education and Research on Therapeutics