The Effects of CKD on Cytochrome P450–Mediated Drug Metabolism

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CKD affects a significant proportion of the world's population, and the prevalence of CKD is increasing. Standard practice currently is to adjust the dose of renally eliminated medications as kidney function declines in effort to prevent adverse drug reactions. It is increasingly becoming recognized that CKD also impacts nonrenal clearance mechanisms such as hepatic and intestinal cytochrome P450 (CYP) enzymes and drug transport proteins, the latter of which is beyond the scope of this review. CYPs are responsible for the metabolism of many clinically used drugs. Genetics, patient factors (eg, age and disease) and drug interactions are well known to affect CYP metabolism resulting in variable pharmacokinetics and responses to medications. There now exists an abundance of evidence demonstrating that CKD can impact the activity of many CYP isoforms either through direct inhibition by circulating uremic toxins and/or by reducing CYP gene expression. Evidence suggests that reductions in CYP metabolism in ESRD are reversed by kidney transplantation and temporarily restored via hemodialysis. This review summarizes the current understanding of the effects that CKD can have on CYP metabolism and also discusses the impact that CYP metabolism phenotypes can have on the development of kidney injury.

Key Words: Renal insufficiency chronic, Cytochrome P-450 enzyme system, Pharmacogenetics, Pharmacokinetics, Drug metabolism

INTRODUCTION

CKD is defined as a progressive decline in kidney function for a period of at least 3 months and is classified by cause, glomerular filtration rate (GFR) category, and albuminuria category.[1] With an estimated worldwide prevalence of 8% to 16%, CKD is a major cause of morbidity and mortality and a significant contributor to the burden of chronic disease.[2] In many parts of the world, the burden of CKD has increased over the past 20 years.[3] Furthermore, the number of people with CKD is projected to remain on an upward trajectory as the prevalence of diabetes, hypertension, and obesity increases, all of which are leading risk factors for CKD.

The management of patients with CKD can be complex due to the prevalence of comorbid conditions such as hypertension and diabetes, as well as the drug-dosing modifications that must be done corresponding to the patient's severity of disease. As an example of this complexity, dialysis patients have been found to have a median daily pill burden of 19, among the highest for any chronic disease state.[4] Estimated GFR is typically used to classify the severity of a CKD case, and using the estimated GFR to adjust the dosage of drugs that are primarily renally eliminated is currently standard practice in the management of patients with CKD to prevent the accumulation of drug in the body and subsequent adverse effects.[5] Despite the existence of numerous guidelines regarding the dose adjustment of renally eliminated medications in patients with CKD, impaired kidney function remains to be associated with an increased risk of adverse drug events.[6] However, 1 factor that is often not taken into consideration is that kidney disease impacts nonrenal clearances in addition to kidney clearances. Dose adjustments to accommodate for these decreases in nonrenal clearances are not common practice. It is possible that this lack of consideration given to the impact of declining kidney function on nonrenal clearances may account for some of the increased occurrence of adverse effects seen in CKD patients.

The impact of nonrenal clearances such as reduced cytochrome P450 (CYP) enzyme and drug transporter function on the pharmacokinetics of drugs administered to CKD patients is increasingly being demonstrated in the literature.[7] The United States Food and Drug Administration has recently published a draft guidance document for industry regarding pharmacokinetic studies in patients with impaired kidney function.[8] Contained within this document is the recommendation that pharmacokinetic studies in kidney impairment models be conducted for medications intended for chronic use, including those of which are not eliminated renally, acknowledging the fact that nonrenal clearance mechanisms can be altered in CKD. Furthermore, with an increasing awareness of the influence of genetics on pharmacotherapy, more studies are now considering how genetic polymorphisms affecting CYP function contribute to altered drug pharmacokinetics in CKD or the development of kidney disease itself. The aim of this article was to provide an update on the impact of CKD on the function of the major drug-metabolizing CYPs and insight into the impact of CYP pharmacogenetics on drug disposition in CKD.

Overview of Cytochrome P450 Enzymes in Drug Metabolism and Pharmacokinetics

The pharmacokinetic processes of drug absorption, distribution, metabolism, and excretion are highly influenced

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by the coordinated action of many different drug metabolism enzymes including CYPs and drug transporters in the intestines, liver, and kidney (Fig 1). With regard to the involvement of CYPs in these pharmacokinetic processes, the 6 isozymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 collectively are responsible for the metabolism of 90% of drugs.[9] Individual drugs can be metabolized by either a single CYP enzyme or multiple CYP enzymes and are typically converted to more polar inactive metabolites that are more readily eliminated in the bile or urine than the parent compound. In some cases, active metabolites of prodrugs can also be produced as in the case of the CYP2D6-mediated conversion of codeine to morphine. The CYP enzymes are most abundant in the liver, and the liver is generally appreciated to be the most important organ for systemic drug metabolism. In addition, certain CYP isoforms are found in other organs where they mediate local metabolism and may contribute to tissue-specific effects of drugs.[10] For example, in the human intestine, CYP3A4 predominates and plays an important role in first pass metabolism and the oral bioavailability of drugs, whereas in the kidney, the expression of CYP2B6 and CYP3A5 has been confirmed.[10]

Acute and chronic diseases, drug–drug and drug–food interactions, and other patient-specific factors including genetics, age, gender, and obesity can lead to variability of CYP metabolism within a population or within the same individual at different times, which may sometimes necessitate drug dosing or drug therapy alterations. With this known fact, it is not surprising that CKD can also significantly impact CYP metabolism.

CLINICAL SUMMARY

- There are numerous examples of predominantly cytochrome P450 (CYP)–metabolized medications that display altered pharmacokinetics in CKD.
- Pharmacokinetic alterations occur in CKD because of a reduction in hepatic and/or intestinal CYP metabolism and most often manifest as an increased oral bioavailability, greater systemic exposure, and prolonged half-life of the affected drug.
- In end-stage CKD, the pharmacokinetic alterations can be reversed by kidney transplantation and temporarily restored via hemodialysis.
- Health-care providers should recognize that altered CYP metabolism is a potential factor leading to variability of drug responses and adverse drug events in patients with CKD and that dosing adjustments may be required in some situations.

Observations of Pharmacokinetic Alterations of CYP-Metabolized Drugs in Humans with CKD

Over the past 30+ years, there have been many reports of altered pharmacokinetics of drugs that are moderately or extensively metabolized by CYPs in patients with CKD. Table 1 summarizes a selection of affected orally or intravenously administered drugs. Many affected drugs are metabolized by CYP3A4, which is understandable given that the CYP3A family metabolizes approximately 50% of clinically used drugs. Alterations in the pharmacokinetics of CYP1A2, CYP2B6, CYP2C9, and CYP2D6-metabolized drugs have also been reported in CKD and could lead to excessive exposure of many different medications that are metabolized by these enzymes (Table 2). Most frequently reported are an increase in area under the curve, that is, a measure of systemic drug exposure, the maximal plasma concentration (C_{max}), a prolongation of the systemic half-life ($t_{1/2}$), and reduction in oral clearance (CL/F). These changes are consistent with a reduction in CYP metabolism leading to increased oral bioavailability and/or reduced systemic elimination and are not necessarily trivial. For example, the intravenously administered CYP3A4 substrate and nonrenally cleared drug midazolam had a 6-fold higher systemic exposure when given to hemodialysis patients immediately before a dialysis session compared to healthy controls.[11] Thus, for drugs that have a small range of therapeutic concentrations, the impact CKD can have on CYP metabolism is likely clinically significant. Reflecting this, for a number of the CYP-metabolized drugs listed in Table 1 (highlighted with asterisks), dose adjustments, cautions, or avoidance of use are recommended with advanced stages of CKD.

Experimental Evidence Supporting Reduced CYP Function in CKD

With mounting evidence supporting enhanced oral bioavailability and/or decreased systemic elimination of many different CYP-metabolized drugs in CKD, research efforts have attempted to experimentally model this phenomenon to uncover the mechanisms underlying these changes. Several animal studies carried out by Pichette and colleagues over the past 2 decades have been instrumental in this regard. This work most often used the 2-stage 5/6-nephrectomy rat model of CKD. In these studies, CKD rats showed significant reductions in CYP2C11 and CYP3A1/2 enzyme activity and protein levels that were later linked to a reduction in messenger RNA (mRNA) of the respective genes.[12,13] CYP1A2, CYP2D1/2, and CYP2E1 were not affected indicating that CKD affects some but not all hepatic CYPs in rats. Recent research has validated the effect of CKD on hepatic CYP3A2 and CYP2C11 enzyme expression and activity in rats while showing that degree of enzyme expression had an inverse exponential correlation to kidney function.[14] These results are interesting in that they suggest that significant changes in CYP metabolism could occur even in those with mild kidney impairment.

The Molecular Mediators and Mechanisms Leading to Reductions in Hepatic CYP Metabolism in CKD

In CKD patients there is retention of a variety of solutes known as uremic retention solutes that are otherwise excreted in healthy patients.[15] Uremic retention solutes can be classified as free water-soluble low molecular weight molecules (eg, reactive carbonyl compounds),