Drug Metabolism Considerations in Patients With Chronic Kidney Disease

Thomas C. Dowling, PhD, PharmD

Chronic kidney disease (CKD) is a progressive process leading to end stage renal disease and either dialysis or transplantation. Patients with CKD often have numerous comorbid conditions such as diabetes, hypertension, and acid-base and electrolyte disorders that can lead to alterations in homeostasis. Changes in drug disposition including hepatic metabolism via phase 1 (ie, cytochrome P-450 enzymes) and phase 2 (ie, conjugation) pathways have been reported. Biotransformation of drugs and endogenous substances within the kidney itself may also be compromised in the presence of CKD. Reduced hepatic and renal clearance leads to systemic accumulation of the parent drug as well as active and toxic metabolites. Characterization of specific hepatic cytochrome (CYP) enzyme pathways in patients with CKD is an area of current research and will lead to an understanding of phenotypic and genotypic expression patterns of several key drug-metabolizing enzymes. The evolving knowledge of CYP enzymes and the alterations that can occur in CKD should allow clinicians to predict adverse consequences of drug therapy and thus prevent these events from occurring. The pharmacy practitioner can also provide important pharmacotherapy interventions in this special patient population, including dose individualization, therapeutic drug monitoring, and evaluation of therapeutic outcomes.

KEY WORDS: kidney disease, drug metabolism, pharmacokinetics, cytochrome P-450

The prevalence of kidney disease has increased steadily over the past decade, with approximately 12 million chronic kidney disease (CKD) patients and 300,000 patients with end-stage renal disease (ESRD) currently receiving kidney dialysis or awaiting transplantation each year in the United States. Hypertension and diabetes are leading causes of ESRD, and are associated with a variety of comorbid conditions requiring multiple medications. Chronic hemodialysis patients are particularly vulnerable to adverse drug reactions (ADR) as they consume, on average, 8 to 12 medications daily. CKD and ESRD patients commonly require pharmacotherapy to treat symptoms of uremia such as fatigue, nausea, and pruritis that result from accumulation of endogenous toxins normally filtered by the kidneys. In addition, drug therapy is often required for management of calcium and phosphate imbalance, metabolic acidosis, acute and chronic anemia, fluid retention, hypertension, and electrolyte disorders.

The progressive loss of kidney function associated with CKD leads to impaired renal excretion of numerous drugs and their metabolites. Recent studies suggest that the presence of renal failure can have detrimental effects on drug metabolism in both the liver and kidney, as well as impaired excretion of active and toxic drug metabolites. Thus, the focus of this article is drug metabolism as it relates to the patient with CKD and ESRD, including specific pharmacotherapeutic considerations for the pharmacy practitioner.

REVIEW OF DRUG METABOLISM

The process of drug metabolism is normally divided into 2 primary phases. The initial phase (phase 1) involves reactions such as oxidation, reduction, hydrolysis, and hydration (Table 1). A primary purpose of phase 1 reactions is to prepare the drug for phase 2, or conjugative, metabolic reactions such as glucuronidation, sulfation, and acetylation. Products of phase 2
reactions are often detoxified, inactive compounds that are water soluble and readily excreted into the urine. Further oxidation of phase 2 products may also occur, resulting in formation of numerous metabolites (active and inactive) from a single parent drug entity.

Phase 1 oxidation of drugs occurs primarily by the cytochrome P-450 (CYP) enzyme system.6,7 These enzymes are located in microsomes of many cells such as liver, intestine, kidney, and lung cells. In the liver, CYP3A4/5 (CYP3A) is the major drug-metabolizing enzyme, accounting for over 30% of total CYP content. This enzyme system metabolizes a wide variety of orally administered medications, including approximately 60% of the top 100 prescription drugs of 2000, many of which are used to treat acute and chronic diseases in CKD and ESRD patients (Table 2).8-10 Other important CYP enzymes involved in drug metabolism include CYP2D6, 2C9, 2C19, and to a lesser extent, 1A2, and 2E1.7 A unique aspect of CYP2D6 is its genetic polymorphism, where enzyme activity may be absent, decreased, or increased in patients. Through the use of phenotypic probes, such as the debrisoquine metabolic ratio, it has been reported that approximately 5% to 10% of Caucasians are classified as poor metabolizers (PMs). Inhibition of CYP2D6 activity by drugs can also induce the PM phenotype, as recently observed with thioridazine.11 In PM patients, use of CYP2D6 substrates such as desipramine, fluoxetine, and paroxetine may result in an increased risk of cardiotoxicity such as ventricular tachycardia.12 CYP2D6 is also the enzyme responsible for converting codeine to its pharmacologically active metabolite morphine (Figure 1). Here, patients classified as PMs may not receive adequate pain relief following oral codeine administration, resulting in therapeutic failure. Other phase 1 processes that are less commonly involved in drug metabolism include reduction (via nicotinamide adenine dinucleotide phosphate [NADPH]), hydrolysis in plasma, and hydration.

The second stage in the biotransformation of drugs is classified as conjugation, or phase 2 metabolism. Here, the parent drug (or oxidized metabolite) is generally converted to a water-soluble derivative that can be excreted in urine or bile. Renal elimination of these phase 2 metabolites occurs by a combination of glomerular filtration and active tubular secretion. The process of tubular secretion is a highly effective means of eliminating many drug metabolites. For example, paraaminohippurate (PAH), a commonly used marker of renal blood flow, undergoes phase 2 metabolism to acetyl-PAH in the liver and possibly kidney. Recent studies have confirmed that acetyl-PAH also undergoes extensive tubular secretion, with renal clearance values exceeding that of the parent compound.13,14

METABOLISM IN THE KIDNEY

The kidney itself plays an important role in the metabolism of many endogenous proteins and small peptides in addition to some drugs.15 For example, insulin is filtered at the glomerulus, reabsorbed, and then metabolized in the proximal tubule by protein peptidases.16,17 In patients with kidney disease, this impaired renal elimination of insulin typically leads to insulin resistance and glucose intolerance.18 Furthermore, diabetic patients with renal insufficiency receiving hypoglycemic drug therapy should be monitored closely for signs and symptoms of hypoglycemia. Angiotensin II (AII), the potent endogenous vasoconstrictor, is also metabolized in the kidney by aminopeptidase A.19 Thus, increased levels of circulating AII due to decreased metabolism may contribute to hypertension in ESRD patients, often requiring aggressive therapy with angiotensin converting enzyme (ACE) inhibitors and AII receptor blockers (ARBs). Recent research indicates that the gene encoding for ACE is also subject to an insertion/deletion polymorphism.20 In this study, patients possessing the ACE DD
(deletion) genotype were reported to have higher plasma and tissue levels of ACE with higher degrees of vasoconstriction compared to the I/D and II genotypes, suggesting that they may be at increased risk for renal vascular disease.

Another route of metabolism within the kidney involves renal peptidases. The carbapenem antibiotic imipenem is inactivated by renal dehydrodipeptidase I, located in high concentrations along the brush border of the nephron.21 Thus, in an effort to reduce its renal metabolism to enhance therapeutic efficacy, imipenem is typically given in combination with cilastatin, a dipeptidase inhibitor, to achieve adequate antibacterial serum and urine concentrations. Cilastatin is then primarily excreted in urine as either parent compound (75%) or undergoes intrarenal acetylation to N-acetyl cilastatin (12%).22

Although relatively small amounts of CYP are present in the kidney with little effect on overall drug metabolism, oxidation to toxic metabolites may be an important contributor to nephrotoxicity. For example, renal oxidative metabolism is responsible for the nephrocarcinogenicity caused by diethylstilbestrol. Nephrotoxicity induced by cephaloridine, acetaminophen, and ifosfamide has also been associated with generation of toxic metabolites within the renal tubule.23-26

In terms of metabolism that occurs within the kidney, phase 2 reactions occur more frequently than phase 1 reactions. The 3 major routes of phase 2 metabolism of drugs in the kidney include acetylation, glycination, and glucuronidation. Glucuronidation has been reported for drugs such as sulfaphenizole, indomethacin, propofol, probenecid, naproxen, and ibuprofen.27 Although the liver is the primary site of acetylation, metabolism of compounds such as the renal blood flow marker PAH and sulfisoxazole occurs by renal N-acetyltransferase.13,14,28 Examples of glycination include the conversion of salicylic acid to salicyluric acid, and benzoic acid to hippuric acid.29

<table>
<thead>
<tr>
<th>CYP1A2</th>
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Table 2
Examples of Drugs/Compounds Metabolized by Cytochrome (CYP) Enzymes7,36,52
The effect of renal disease on the function of phase 2 enzymes in the kidney is less well understood and further complicated by the need for accurate determination of urinary metabolites, which is often difficult in this patient population.

HEPATIC METABOLISM IN EXPERIMENTAL RENAL FAILURE

Recent research has focused on the effects of CKD on liver function and drug metabolism using experimental approaches. In rodents with CKD, Uchida and colleagues reported that total hepatic CYP content (including CYP3A), as well as general markers of hepatic function such as aminopyrine N-demethylase (APD) activity and mitochondrial aminolevulonic acid synthetase (ALAS) activity were reduced by 30%-53%. Significant correlations were also observed between blood urea nitrogen concentration and liver function (ALAS activity, APD activity and CYP content) ($r^2 > .72$, $P < .001$), suggesting that inhibitory substances of hepatic metabolism may be present in animals with renal disease. Similar observations were reported by Patterson and colleagues, where hepatic microsomal oxidative enzyme activities were reduced in CKD rats by 24% to 31%, and total CYP content was reduced by

**Figure 1. Example of codeine metabolism involving phase 1 and phase 2 reactions.**

*Metabolites that are renally excreted.*
26%. More recently, Leblond and co-workers reported that total CYP hepatic activity was reduced more significantly than previously reported (40%). Analysis of 2 CYP subfamilies showed a 35% reduction in both hepatic CYP2C (by aminopyrine) and CYP3A (by erythromycin) activity in rats with CKD. These results are consistent with the hypothesis that accumulation of uremic toxins, such as organic anions and phenol conjugates, may inhibit hepatic drug metabolism by either directly reducing CYP content or inhibiting uptake of drugs into hepatocytes.  

HEPATIC METABOLISM IN CLINICAL RENAL IMPAIRMENT

Numerous studies evaluating the pharmacokinetics of drugs in patients with ESRD have been conducted. With few exceptions, there is increasing indirect evidence that nonrenal (metabolic) clearance of some drugs is reduced in ESRD patients (Table 3). In theory, the systemic clearance of drugs that are extensively metabolized with low hepatic extraction are most susceptible to changes in intrinsic clearance and protein binding in patients with renal failure. For example, a recent study evaluated the effect of varying degrees of renal insufficiency on the pharmacokinetics of reboxetine, which is extensively metabolized by CYP3A and minimally excreted unchanged by the kidneys. Interestingly, the nonrenal (metabolic) clearance in ESRD patients was 30% lower than in patients with mild renal impairment, and 67% lower than in participants with normal renal function. The pharmacokinetics of repaglinide, which is minimally excreted unchanged in urine and extensively metabolized by CYP3A, was investigated in ESRD patients and healthy controls. Here, plasma area under the curve and half-life values were 50% higher in ESRD patients compared with controls. Taken together, this reduction in apparent metabolic clearance is even more profound than that demonstrated in animal studies. These data suggest that patients with renal disease may have a marked decline in the expression or activity of liver CYP enzymes.

Recent research in drug metabolism has focused on pharmacogenetics, including genotyping and phenotyping of CYP to further understand the interindividual variability in drug response within various patient populations. Genotyping involves analysis of an individual’s genetic makeup (DNA or gene mapping), whereas phenotype analysis uses probe compounds to identify the functional expression or activity of a specific enzyme or receptor. Few examples of phenotypic analysis are available in patients with kidney disease, primarily due to urinary recovery methods that require timed urine collections. CYP2D6 enzyme activity was recently evaluated in patients with moderate renal insufficiency. In patients with a creatinine clearance of 20-70 mL/min, the CYP2D6 mediated O-demethylation of dextromethorphan was reduced by 49% (P = .02) compared to healthy controls. However, a strong correlation between the urinary excretion rate of the metabolite dextromethorphan and creatinine clearance was also observed, suggesting that reduced urinary recovery may have resulted not only from reduced CYP2D6 activity but also from impaired renal excretion of dextromethorphan. Thus, accurate characterization of CYP using urine-based probes is not optimal due to the influence of renal function on urinary metab-
olite recovery. The use of phenotypic probes without the need for urine collection, such as the erythromycin breath test (EBT) for CYP3A (Figure 2) would be optimal for studying CYP in patients with renal disease. The EBT involves intravenous (IV) administration of a tracer quantity of 14C-erythromycin (0.04 mg), followed by quantification of the metabolic product (14CO2) in exhaled breath air (20 minutes after injection) and calculation of the percent EBT dose metabolized per hour. This EBT procedure was used recently to evaluate hepatic metabolism in dialysis-dependent ESRD patients compared to healthy controls.40 In ESRD patients, CYP3A activity was reduced by 28% at baseline (P < .05) compared to controls; however, induction response was similar (106% vs 80%, P = .7) between groups. These results are consistent with experimental data in rodents, where EBT values were reduced by 35% in rats with renal failure compared to control animals.32 However, additional evaluations are required in humans to fully elucidate the effects of renal failure on CYP enzyme activity, as well as phase 2 metabolic processes.

The use of metabolic probes of specific CYP enzymes, such as the EBT for hepatic CYP3A activity, may also be useful for drug dose optimization in patients with renal disease. In kidney transplant patients, EBT values were found to be highly correlated with steady-state blood concentrations of cyclosporin A, a CYP3A substrate.41 In cancer patients, EBT values were also highly correlated with the clearance of docetaxel, which is extensively metabolized by CYP3A.42 It was also reported that cancer patients with the highest degrees of docetaxel toxicity were those with the lowest EBT results. Taken together, these results suggest that the EBT may be used to predict hepatic clearance, blood concentrations and toxicity profiles for some CYP3A-metabolized drugs.43 Thus, metabolic probes such as the EBT may provide clinically useful information in terms of drug dosing and for predicting patient populations at risk for ADRs.

Numerous drugs given orally undergo “first-pass” metabolism, or metabolism that occurs prior to entry into the systemic circulation. The 2 primary sites of presystemic drug metabolism are the intestinal wall and liver, which both contain high concentrations of CYP enzymes.43 Recent studies indicate that many drugs with extensive first-pass metabolism are also CYP3A substrates, such as nifedipine, saquinavir, and midazolam. Although the effect of renal disease on first-pass metabolism has not been rigorously evaluated, it can be anticipated that reduced intestinal or hepatic metabolism would lead to reduced first-pass metabolism and therefore increased drug bioavailability in these patients.

**CLINICAL CONSEQUENCES OF ALTERED METABOLITE PROFILES IN RENAL FAILURE**

The kidney is primarily responsible for elimination of drug metabolites from the body. Consequently, renal impairment can lead to reduced renal elimination of such metabolites that may be pharmacologically active or toxic (Table 4). For example, both morphine-3- and morphine-6-glucuronide are renally eliminated, with morphine-6-gluconide having nearly 40-fold more potent analgesic effects than morphine (Figure 1).44 Thus, patients with CKD receiving morphine or codeine must be monitored closely for excessive sedation and respiratory distress. The primary metabolite of meperidine, normeperidine, has half the analgesic potency but 2- to 3-times greater seizure potential than meperidine. In patients with renal failure, accumulation of this metabolite during chronic dosing results in seizure, which can be reversed only by hemodialysis.45 Thus, meperidine should be used cautiously in CKD patients and avoided in ESRD patients, due to the potential for serious neurotoxicity.

Procainamide is a class 1A antiarrythmic agent that undergoes extensive phase 2 metabolism (acetylation) to N-acetyl procainamide (NAPA), which has pro-dysrhythmic properties at high plasma concentrations. Both procainamide and NAPA are extensively renal eliminated, with renal clearance values approximately 2-fold greater than glomerular filtration rate.46 However, in patients with impaired renal function, accumulation of procainamide and NAPA may result in cardiac
action potential changes such as QT interval prolongation and torsades de pointes. Thus, appropriate dosage reductions based on creatinine clearance along with close monitoring of electrocardiogram and serum drug concentrations (procainamide and NAPA) are recommended in CKD and ESRD patients.

PHARMACOLOGIC APPROACHES TO MINIMIZING ADVERSE EVENTS IN PATIENTS WITH ALTERED RENAL AND HEPATIC FUNCTION

The goal of drug therapy in patients with CKD and ESRD is to maximize therapeutic benefit and avoid toxicity. The general approach involves avoidance of drugs that lead to systemic accumulation and drug toxicity in this patient population. More specific approaches include identification of drugs that undergo extensive hepatic metabolism, as such drugs may also have altered pharmacokinetic profiles in patients with renal insufficiency. It is important to also be aware of patients receiving drugs that may inhibit or induce CYP enzymes, leading to interactions with other drugs that undergo hepatic or intestinal metabolism. Here, patients with renal insufficiency may also be at increased risk of drug interactions due to polypharmacy (increased number of medications), a potential for reduced hepatic metabolism of some drugs, and reduced renal excretion of drugs that rely on the kidney for removal from the body. Further research using phenotypic probes, such as dextromethorphan for CYP2D6, will help define the clinical implications of various types of renal disease on hepatic metabolism in patients with reduced renal function.

In terms of dose individualization for CKD and ESRD patients, this can be achieved using a pharmacokinetic approach that takes into account disease-related changes in renal and nonrenal drug clearance, volume of distribution, and total elimination rate (total kel, renal + hepatic). The most common approach is based on the concept of dose or interval adjustment, with a goal of achieving and maintaining a target steady-state average plasma concentration (Cpss,ave). Here, a dose adjustment factor (Q) is calculated from total elimination rate values obtained from the literature in patients with ESRD (KRF) and those with normal renal function (Kn), as proposed by Dettli:

\[ Q = \frac{K_{RF}}{K_{N}}. \]

The next step in this approach involves calculation of a new dose (Drf):

\[ D_{RF} = D_{N} \times Q, \]

where DN is the typical dose used in patients with normal renal function. A new dose interval (TRF) can also be calculated as:

\[ T_{RF} = T_{N}/Q, \]

where TN is the typical dose interval for patients with normal renal function. Alternatively, a new dose can be calculated using a predetermined fixed dosage interval (TRf) as:

\[ D_{RF} = \frac{[D_{N} \times Q \times T_{RF}]}{T_{N}}. \]

Following initiation of a specific dosage regimen, further dose adjustments can be made based on steady-state plasma concentrations, assuming linear pharmacokinetics, as:

\[ MD = C_{PSS,ave} \times CL, \]

where MD is the maintenance dose rate, and CL is the patient-specific drug clearance.

An example of this pharmacokinetic approach is shown in the following case:

J.Z. is a 59-year-old man with HIV, ESRD, and a creatinine clearance of 10 mL/min (not receiving hemodialysis). He is to receive IV aztreonam for Klebsiella pneumonia. Previous pharmacokinetic studies with aztreonam reported that both renal and nonrenal clearance values are reduced on patients with ESRD. Furthermore, half-life is increased from 2.0 hrs (total kel = 0.35 hr⁻¹) in healthy participants to 6.0

<table>
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<th>Drug</th>
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<th>Active (A)</th>
<th>Toxic (T)</th>
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Table 4: Selected Drugs With Pharmacologically Active and/or Toxic Metabolites
hours (total kel = 0.12 hr⁻¹) in patients with ESRD. Thus, the dose adjustment factor, Q, for aztreonam in this patient is:

\[ Q = 0.12/0.35 = 0.34. \]

Since the normal dose of aztreonam for this indication is 2 grams every 8 hours, a new dose of 1000 mg every 12 hours is recommended to avoid drug accumulation and toxicity. This approach can be used for any drug where total clearance and volume of distribution values (or total elimination rate constant) are available for ESRD patients and those with normal renal function.

**CONCLUSION**

Patients with CKD and ESRD present many pharmaco-logic challenges and are at increased risk for adverse events due to accumulation of drugs and their active or toxic metabolites. Important pharmacotherapeutic decisions can be made based on an awareness of each patient’s functional renal capacity and an understanding of the effects of renal disease on drug metabolism, metabolite formation, and renal excretion. The pharmacist can play a critical role in providing these patients rational drug therapy, including dose adjustments based on renal function, avoidance of drugs with toxic metabolites, and close therapeutic monitoring. This approach can be used to ensure maximum therapeutic outcomes in this special patient population.

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