# Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport

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**The pharmacokinetics of non-renally cleared drugs in patients with chronic kidney disease is often unpredictable. Some of this variability may be due to alterations in the expression and activity of extra renal drug-metabolizing enzymes and transporters, primarily localized in the liver and intestine. Studies conducted in rodent models of renal failure have shown decreased mRNA and protein expression of many members of the cytochrome P450 enzyme (CYP) gene family and the ATP-binding cassette (ABC) and solute carrier (SLC) gene families of drug transporters. Uremic toxins interfere with transcriptional activation, cause downregulation of gene expression mediated by proinflammatory cytokines, and directly inhibit the activity of the cytochrome P450s and drug transporters. While much has been learned about the effects of kidney disease on non-renal drug disposition, important questions remain regarding the mechanisms of these effects, as well as the interplay between drug-metabolizing enzymes and drug transporters in the uremic milieu. In this review, we have highlighted the existing gaps in our knowledge and understanding of the impact of chronic kidney disease on non-renal drug clearance, and identified areas of opportunity for future research.**

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Chronic kidney disease (CKD) is a public health problem that affects >20 million people in the United States.[1] Currently, almost 500,000 patients require chronic hemodialysis.[2] An average dialysis patient may require >12 medications.[3] A pooled analysis identified 1593 medication-related problems in 385 dialysis patients, with overdosing or underdosing errors accounting for 20.4% of these issues.[4] Despite the large number of patients affected and the devastating consequences of medication-related problems, our understanding of the impact of kidney disease on drug disposition is incomplete, particularly for those drugs eliminated primarily by non-renal pathways. Obviously, clearance of drugs that depend primarily on the kidneys for elimination is reduced, but significant changes also occur in drug exposure with medications that are eliminated by the liver, intestine, and possibly other organs.

In 2009, the Food and Drug Administration published a survey of New Drug Applications approved between January 2003 and July 2007 that assessed the impact of renal impairment on systemic exposure of new molecular entities.[5] In this analysis, New Drug Application sponsors for 37 orally administered drugs included renal impairment studies as part of their submission; 23 (62%) of these were eliminated by non-renal pathways (defined as the fraction eliminated via renal route <15). Despite being cleared non-renally, 13 of these 23 new drugs (57%) showed an average 1.5-fold increase in area under the plasma concentration–time curve (AUC) in renally impaired patients compared with healthy controls. In fact, the change in drug exposure for five drugs cleared mainly by hepatic metabolism and/or transport were of a magnitude (viz duloxetine $\Delta$AUC +2.0-fold, tadalafil $\Delta$AUC +2.7- to 4.1-fold, rosuvastatin $\Delta C_{plasma}$ +3-fold, telithromycin $\Delta$AUC +1.9-fold, solifenacin $\Delta$AUC +2.1-fold) that required labeling recommendations for dose adjustment in renally impaired patients. Seven other drugs showed an effect of renal impairment on drug exposure but did not require dosage adjustment (aliskiren, alfuzosin, aprepitant, ranolazine, vardenafil, darifenacin, and lanthanum). These data along with a large body of earlier literature suggest that CKD alters the pharmacokinetics of drugs that are cleared by non-renal mechanisms; however, the underlying molecular mechanisms accounting for these pharmacokinetic changes remain poorly defined (reviewed by Nolin,

LeBlond and others).[6–9] The purpose of the present mini review is to highlight the present gaps in our understanding of the impact of CKD on non-renal drug clearance involving metabolism and transport processes and to identify areas of opportunity for future research.

## DRUG METABOLISM AND TRANSPORT PROCESSES

The following is a brief introduction to the key drug-metabolizing enzymes and drug transporters whose function is known to be altered in CKD. Phase I drug metabolism, involving oxidation, reduction, and hydrolysis, generally converts drug molecules to more polar or water-soluble metabolites that are readily excreted by the kidneys or via the biliary system. Drug oxidation, which is particularly known to be altered in CKD, is catalyzed by two large families of enzymes, namely the cytochrome P450 (CYPs) and flavin-containing monoxygenases (FMOs).[10] Many of the CYPs exhibit genetic polymorphisms that range from gene duplication resulting in gene overexpression to null mutations producing a nonfunctional enzyme. The recent focus of CYP research is on enzymes expressed in the liver and the intestinal mucosa, which govern the oral bioavailability (i.e., first-pass metabolism) and systemic metabolic clearance of drug molecules. Human hepatic CYPs include CYP3A4 and 3A5 (40% of total liver P450 content), CYP2Cs (25%), CYP1A2 (18%), CYP2E1 (9%), CYP2A6 (2%), CYP2D6 (2%), and CYP2B6 ($<1\%$), as well as FMO3. Human intestinal CYPs that are functionally important include CYP1A1, CYP3A4, CYP3A5, and CYP2J2.[11] CYP1A1, CYP1A2, CYP3A5, CYP4A1, and FMO1 are also expressed in human kidneys, but at levels much lower than those in the liver and intestine.[11,12] Many drugs or their phase I metabolites also undergo conjugation reactions mediated by phase II enzymes.[10] In particular, *N*-acetylation and *O*-glucuronidation of drugs or drug metabolites are known to be altered in CKD.[13] The liver and intestinal mucosa are the major sites for the biotransformation of drugs and drug metabolites by phase II enzymes (Figure 1). It should be noted that the products of phase I and phase II metabolism are not always pharmacologically inactive or less toxic than the parent drug.

Drug transporters also have a critical role in controlling drug exposure. Transporters are transmembrane proteins facilitating the passage of both drugs and other xenobiotics across biological barriers encountered during drug absorption, tissue distribution, and excretion. Transporters, such as drug-metabolizing enzymes, are expressed differentially across body tissues and are characterized as either uptake or influx transporters (transport into the cellular barrier) or efflux transporters (transport out of the cellular barrier). The importance of transporters in governing the intestinal absorption of drugs and nutrients and renal tubular secretion or reabsorption of drugs or their metabolites is increasingly being recognized. On the other hand, the role of hepatic sinusoidal transporters in regulating the access of drug substrates to the hepatocellular enzymes and that of canalicular transporters in biliary excretion of drugs and/or their conjugate metabolites are not as widely appreciated. Recent studies in experimental models of CKD have demonstrated altered expression and/or activities of intestinal and hepatic drug transporters that could modulate the respective intestinal absorption and hepatic uptake and metabolism of drugs.[7,14,15]

## DRUG METABOLISM IN CKD

More than 75 commonly used drugs have been reported to exhibit altered non-renal clearance in patients with CKD (see Table 1 for compilation). Most of these drugs are eliminated by CYP-mediated, oxidative metabolism (summarized in Figure 2). Only a few are subject to primary phase II metabolism, namely *O*-glucuronidation (diacerein, morphine, oxprenolol, and zidovudine) and *N*-acetylation (isoniazid and procainamide). In almost all cases, reduced non-renal clearance, along with an increase in oral bioavailability in some cases (especially for drugs that undergo first-pass metabolism in the intestinal mucosa and/or liver), was observed in CKD. A case in point is the diminished non-renal clearance of nimodipine, which could result in as much as a 7-fold increase in its AUC,[16] although the increase in drug exposure is usually more modest (1.5–3.0-fold), variable across patients, and dependent upon the degree of renal impairment and the dialysis regimen in patients near or at the end stage of renal disease. Increased clearance has been reported for a handful of drugs, including phenytoin, fosinopril, cefpiramide, nifedipine, bumetanide, and sulfadimidine.[17,18] At least in the case of phenytoin, the apparent acceleration in non-renal clearance is attributed to reduced binding of phenytoin to albumin in uremic serum, resulting in a higher fraction of circulating drug being available for uptake and metabolism by the liver.

A number of mechanisms have been hypothesized for the impairment of drug metabolism in CKD, particularly metabolic pathways mediated by CYP enzymes. The supporting evidence is drawn largely from experimental studies in animal models of acute and chronic renal failure. The proposed mechanisms include the following: alterations in gene transcription and protein translation, reduced CYP expression due to inhibition of hemoprotein biosynthesis and/or increased enzyme degradation, depletion of cofactors (e.g., supply of nicotinamide adenine dinucleotide phosphate (NADPH)), and direct competitive inhibition of CYP enzyme by circulating uremic constituents.[13,18]

Supply of δ-aminolevulinic acid is recognized as a rate-limiting step in the hepatic synthesis of CYP hemoproteins. Total microsomal CYP content is consistently reduced in various experimental models of renal failure, and mitochondrial δ-aminolevulinic synthetase activity is depressed in the two-step 5/6th nephrectomy model in rats.[19] Leber *et al.*[20] reported that intraperitoneal supplementation of δ-aminolevulinic acid in rats after subtotal nephrectomy normalized the level of CYP in the liver, but it did not reverse the reduction in CYP activities; hence, interference of