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A Synopsis of Clinical Pharmacokinetic Alterations in Advanced CKD

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Abstract

Unrecognized alterations in pharmacokinetics, which quantitatively describes the time course of drug disposition in the body, may lead to clinically significant changes in systemic exposure and corresponding response to drugs in patients with chronic kidney disease (CKD). Clinicians must take pharmacokinetic changes into consideration when selecting and dosing medications in CKD patients in order to optimize the risk:benefit ratio. Pharmacokinetic changes in absorption, distribution and renal clearance are well characterized and generally predictable for most drugs. Conversely, changes in nonrenal clearance are less well understood and corresponding clinical implications are still being elucidated. This review provides a synopsis of alterations in each of these pharmacokinetic parameters observed in patients with advanced CKD.

Pharmacokinetics quantitatively describes the individual steps that determine drug disposition in the body, namely absorption from an extravascular site of administration, distribution to various tissues, and elimination from the body. The latter is typically described within the context of nonrenal clearance pathways comprised of drug metabolism and transport, or renal excretion of parent drug and metabolites. The decline in kidney function associated with advanced kidney disease leads to a decrease in the systemic clearance of renally cleared drugs, which requires a corresponding dose reduction to avoid toxicity. As a result, drug dosage adjustment guidelines, which are based on the premise that systemic clearance primarily reflects renal clearance and is proportional to kidney function (e.g., creatinine clearance), are commonly used (1,2).

Still, response to drug therapy is often less predictable and the frequency of adverse drug events and other medication related problems is higher in patients with kidney disease than in those with normal kidney function (3,4). Contributing factors undoubtedly include well-known alterations in absorption, distribution, and nonrenal metabolism and transport of drugs in addition to altered renal excretion in the setting of kidney disease. Numerous comprehensive and critical reviews of these topics have been published previously, including several that specifically address pharmacokinetic alterations and corresponding

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dosing strategies during intermittent hemodialysis and other renal replacement therapy modalities (5–17). This review provides a brief synopsis of clinically relevant pharmacokinetic alterations observed in patients with advanced chronic kidney disease (CKD).

Absorption

A drug's bioavailability represents the extent of absorption from an extravascular site of drug administration, or in quantitative terms the fraction of the administered dose that reaches the systemic circulation. It is influenced by numerous factors including the route of delivery, rate of administration, and physiologic changes at the site of administration and throughout the complex pathways that drugs often traverse before reaching the systemic circulation. For example, an orally administered drug formulation undergoes dissolution when exposed to acidic gastric contents, exposing it to enterocytes lining the lumen of the gut wall. Most drugs then undergo some combination of passive diffusion, active transport across the intestinal barrier, or presystemic metabolism in enterocytes (18). The parent drug and any metabolites formed enter the portal circulation and pass through the liver, where they may be excreted unchanged in the bile or metabolized before entering the systemic circulation (i.e., undergo first-pass effects) (19).

Patients with CKD often exhibit pathophysiological changes in the gastrointestinal (GI) tract that can impact drug absorption. For example, delayed gastric emptying caused by gastroparesis may be observed in patients with diabetes (6,20). Decreased GI motility may affect the time required to reach the maximal plasma concentration, but typically does not impact bioavailability and the maximal plasma concentrations (C_{max}) achieved.

On the other hand, bioavailability of many drugs may be influenced by increased gastric pH and concurrent drug administration (8). High salivary urea concentrations may result in conversion of urea to ammonia by gastric urease (8). The subsequent increase in gastric pH may alter the dissolution or ionization properties of a drug, leading to changes in bioavailability. Antacids, H_2 -receptor antagonists, and proton-pump-inhibiting agents also may modify bioavailability by affecting gastric pH and to a lesser extent gut motility. Antacids and vitamin supplements may dramatically reduce the bioavailability of some drugs by the formation of insoluble salts or metal ion chelates (21,22).

GI edema has been cited as a potential cause of altered drug absorption, particularly in CKD patients with concomitant cirrhosis or congestive heart failure. For example, the bioavailability of furosemide may decrease from 50% to 10% in these patients (15). Lastly, decreased first-pass metabolism in the intestine and liver may significantly influence oral drug bioavailability (23). This may be incorrectly interpreted as being caused by decreased elimination rather than increased bioavailability (10).

Distribution

A drug's volume of distribution (V_D) reflects the extent of distribution throughout the body. It quantitatively describes the amount of drug in the body (A) relative to the measured concentration in some compartment, usually plasma (C_p), as follows:

$$V_D = A/C_p$$

V_D does not represent an actual anatomic volume; it is a virtual space reflecting the apparent volume of plasma into which a given dose would have to be distributed to achieve the observed plasma concentration (24). V_D provides no information on the specific tissues into which the drug has distributed, but it is useful to assess the extent of drug distribution to extravascular tissues. V_D is affected by several physiologic variables, including plasma protein binding, tissue binding, and total-body water, each of which may be altered in the setting of kidney disease (5,10).

Protein binding limits drug distribution, as only unbound or free drug, which represents the pharmacologically active moiety, is able to traverse cellular membranes and distribute outside the vascular space. Many drugs have been reported to exhibit altered protein binding in kidney disease (8,25,26). Acidic and basic drugs bind mainly to albumin and 1-acid glycoprotein (AAG), respectively. Protein binding of many acidic drugs, including penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin, is reduced in patients with kidney disease, which typically is attributed to hypoalbuminemia, qualitative changes in the conformation of the protein-binding site, and competition for binding sites by other drugs, metabolites, and endogenous substances (i.e., organic acids) (6,7,27). AAG is an acute-phase protein and its plasma concentrations are often elevated in patients with kidney disease. However, binding of basic drugs to AAG generally appears to be unaffected in patients with CKD (28). Changes in plasma protein binding may result in alterations in V_D . However, changes in plasma protein binding alone often will not have significant clinical implications because an increase in the fraction of unbound drug may result in a corresponding increase in both V_D and systemic clearance, resulting in no net change in drug exposure (10,29).

V_D also may be affected by altered tissue binding of drugs in patients with kidney disease, although like changes in protein binding, this is relatively rare and limited to few drugs, such as pindolol, ethambutol, and most notably digoxin (10). The V_D of digoxin is decreased by up to 50% in patients with stage 5 CKD, leading to elevated serum concentrations if the loading dose is not adjusted accordingly (6). Lastly, changes in total-body water content can have a major effect on V_D . Hydrophilic drugs may exhibit increased V_D in patients with CKD because of fluid retention. V_D increases as extracellular fluid volume increases, resulting in decreased serum concentrations. Alterations in extracellular fluid volume will have the greatest effect on hydrophilic drugs with low to moderate V_D (i.e., <0.7 L/kg), such as aminoglycosides and cephalosporins (7,15).

Elimination

Elimination of a drug from the body is characterized in pharmacokinetic terms as total systemic clearance (CL), which is equivalent to the sum of all individual and simultaneously occurring organ clearances. Typically, CL is defined simply as the sum of renal excretion or clearance (CL_R) and nonrenal clearance (CL_{NR}), as follows (19):

$$CL = CL_R + CL_{NR}$$

The incorporation of CL_{NR} into the equation reflects the fact that few drugs are eliminated entirely unchanged by the kidney, with most drugs undergoing a combination of renal and nonrenal clearance. Each of these may be altered in patients with kidney disease.

Renal Excretion

Kidney function is the most predictable and quantifiable determinant of drug clearance from the body. Reduction in kidney mass, the number of functioning nephrons, renal blood flow, glomerular filtration rate (GFR), and/or the rate of tubular secretion account for the decreased renal excretory capacity observed as kidney disease progresses. The clinical consequences of impaired kidney function on the elimination of renally cleared drugs have been appreciated for almost 60 years, since Kunin published a series of seminal studies documenting prolonged antibiotic half-lives in patients with impaired kidney function along with the relationships between drug half-lives and creatinine clearance (30–32).

Although the first tables of renal dose adjustment recommendations were published about a decade later (33,34), Dr. Luzius Dettli is often credited for being the first to systematically approach the issue of drug dosing in the setting of impaired kidney function (13,35). Indeed, the ‘Dettli Method’ bases drug dosing recommendations on the linear relationship between the elimination rate constant of renally cleared drugs and a patient’s creatinine clearance (36–38). It facilitated the use of *a priori* estimates of CL and corresponding dosing requirements to individualize therapy based on kidney function, and is the foundation upon which dosing nomograms for renally cleared drugs are established even today.

Dettli defined the equation of the linear relationship as follows (36):

$$k = k_{NR} + \alpha \cdot CrCl$$

where k is the overall elimination rate constant based on a first-order one compartment model, k_{NR} is the nonrenal elimination rate constant, and α is a constant relating the renal drug elimination rate constant to the creatinine clearance (CrCl). This approach assumes that the overall elimination rate constant (or CL) declines linearly with CrCl, and that the nonrenal elimination rate constant (or CL_{NR}) remains constant as kidney function declines. While the first assumption generally holds true for drugs that are predominantly renally cleared, the second assumption is flawed, as the functional expression of numerous drug metabolizing enzymes and drug transporters is reduced in patients with kidney disease (39).

Nonrenal Clearance

Our understanding of the effect of kidney disease on CL_{NR} is comparatively less than CL_R , but it has received much attention in recent years (16,39–41). CL_{NR} encompasses all routes of drug elimination, excluding renal excretion of unchanged drug, and includes hepatic and extrahepatic metabolism and transport pathways. It is mediated largely by the concerted actions of cytochrome P450 (CYP) metabolic enzymes, such as CYP3A, and transporters

including P-glycoprotein (Pgp), organic anion-transporting polypeptides (OATPs), and multidrug resistance-associated proteins in the gastrointestinal tract and hepatobiliary system. The CL_{NR} of numerous drugs that are known substrates of these pathways is reduced in patients with kidney disease (41,42). Unfortunately, identification of specific nonrenal drug-metabolizing enzymes and transporters that are affected in humans is difficult because of the complex interplay between them and the involvement of multiple organs.

In the intestine, the combined actions of drug metabolizing enzymes and uptake and efflux transporters are important determinants of a drug's bioavailability (43). Orally administered drugs may be actively transported across the apical membrane, and then metabolized to a more polar compound by drug metabolizing enzymes. The drug and/or metabolite may then be either actively effluxed back across the apical membrane into the gut lumen or translocated across the basolateral membrane into the portal circulation. Alterations in the function of enzymes and transporters involved in this process may affect oral bioavailability and thus systemic drug exposure (43). For example, the bioavailability of several drug substrates of CYP3A is increased in CKD, and one frequently cited hypothesis is reduced CYP3A-mediated intestinal metabolism (39,44). However, the results of recent clinical studies refute this proposed mechanism. The intestinal bioavailability of midazolam and erythromycin is not altered in patients with end-stage renal disease (45,46). Both drugs are CYP3A substrates, and erythromycin is also transported by OATP and Pgp, suggesting that these pathways are not impacted in the intestine.

The liver is the principal site of CL_{NR} *in vivo*. Similar to the intestine, drug clearance in the liver is the net result of metabolic enzyme activity and the activity of drug transport proteins responsible for cellular uptake and efflux. Following administration and entry of drugs and metabolites into the portal circulation, they may undergo active uptake across the sinusoidal membrane of the hepatocyte, followed by metabolism, then efflux across the canalicular membrane into the bile for excretion. Again, alterations in the function of any of the pathways involved may affect hepatic clearance and thus systemic drug exposure.

Activity of the highly expressed hepatic enzyme CYP3A has been reported to be lower in CKD, due to either downregulation or through direct inhibition by uremic toxins (47–49). Numerous reports of reduced systemic clearance of nonspecific CYP3A drug substrates in patients with CKD support this concept (39,40). However, recent clinical studies with midazolam, a specific CYP3A4 probe drug, showed no changes in the elimination half-life in patients with ESRD, with either unchanged or lower systemic clearance of the drug after oral (45) or IV administration (50), respectfully.

Although it is unclear whether CKD definitively alters CYP3A function in humans, it is now well established that alterations in transporters but not CYP3A, per se, may result in significant changes in the pharmacokinetics of CYP3A substrates that exhibit overlapping substrate specificity with transporters (e.g., erythromycin) (46). In fact, several studies have demonstrated a decrease in the apparent oral clearance of the transporter probe drug fexofenadine in CKD patients, suggesting that hepatic OATP uptake is reduced (45,50,51). Altered function of several other CYPs has also been reported in CKD patients. For instance, studies with the probe drug bupropion suggest that CYP2B6 activity is reduced

(52,53), and a 50% increase in the S/R-warfarin ratio in ESRD patients compared to healthy control subjects may suggest that hepatic CYP2C9 activity is decreased (54), though recent data generated using the probe drug flurbiprofen suggest otherwise (51).

Although not as extensively characterized as CYPs, several studies suggest that the function of other metabolic pathways also may be decreased in patients with CKD. For example, altered exposure of naltrexone (55) and decreased metabolic clearance of idarubicin (56) have been described in patients with CKD. Given the contribution of hepatic reductase enzymes to their elimination, these findings suggest that reduction of drugs may be altered in CKD. The clearance of morphine, which is primarily glucuronidated by the 2B7 and 1A3 isoforms of uridine diphosphate-glucuronosyltransferase (UGT), is significantly reduced in CKD compared to healthy volunteers (57). Zidovudine, an antiretroviral nucleoside reverse transcriptase inhibitor that is eliminated primarily by UGTs, has a significantly higher systemic exposure in patients with CKD than with normal kidney function, likely due to reduced hepatic metabolism (58). Lastly, clearance of isoniazid and procainamide, both substrates of N-acetyl-transferase (NAT), in patients with CKD is significantly reduced compared to healthy subjects (59,60). Collectively, these data suggest that drug substrates of CL_{NR} pathways may need to be dose adjusted in patients with advanced CKD in order to avoid excessive systemic exposure and to minimize the likelihood of toxicity.

Summary

Medications are critically important in the treatment of kidney disease, offering tremendous benefits to patients with CKD when used optimally. However, inherent risks associated with suboptimal use in this tenuous population create prescribing challenges. Clinicians must take into consideration the alterations in pharmacokinetics, which often require dosing adjustments and the careful selection of medications to optimize the risk:benefit ratio. Pharmacokinetic changes in absorption, distribution and renal clearance are well characterized and generally predictable. Conversely, changes in CL_{NR} are less well understood and corresponding clinical implications are still being elucidated. Recommendations by the FDA to characterize the pharmacokinetics of nonrenally cleared drugs will aid in our understanding in the future and will facilitate development of enhanced dosing recommendations in patients with CKD (61). Until then, clinicians should be cognizant of all possible alterations in pharmacokinetics and tailor pharmacotherapy accordingly in order to ensure that patients with CKD receive maximal benefits from drug therapy while minimizing potential adverse outcomes.

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