CHAPTER 3

RENAL DRUG DOSING CONCEPTS

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Chronic kidney disease (CKD) is a progressive consequence of systemic diseases such as diabetes and hypertension as well as localized kidney injury as the result of glomerulonephritis. Over 500,000 patients in the United States have stage 5 CKD, which is also categorized as end-stage renal disease (ESRD). Each year, for the last several decades, up to 100,000 patients have developed ESRD and over 80,000 have died.[1] Chronic renal replacement therapy, whether peritoneal or hemodialysis (HD), was life-sustaining for over 600,000 patients in 2011 at a total cost of over $49 billion USD. A significant portion of patients who receive a kidney transplant continue on to develop CKD. Most stage 1 to 4 CKD patients are initially identified in primary care clinics, while others are identified in acute care environments. Population-based studies, such as NHANES, report that the prevalence of CKD is increasing dramatically, with more than 50% of U.S. adults aged 30 to 64 expected to develop CKD in their lifetime.[2]

Kidney failure can also appear abruptly, with some patients presenting with acute kidney injury (AKI) in emergency departments, clinical wards, or intensive care units.[3] The majority of AKI cases are attributed to drug therapy or renal hypoperfusion in hospitalized patients, which often requires continuous renal replacement therapies (CRRT). Regardless of the cause of acute or chronic renal impairment, these patients are at increased risk of accumulating drugs, toxic metabolites, and other nephrotoxins. For any drug that relies extensively on the kidney for elimination from the body (i.e., renal clearance > 30% of total clearance) and drug concentrations in blood or plasma are clearly associated with a pharmacodynamic effect (success, failure, or toxicity), dose adjustments are necessary when renal function is considerably reduced. The aim of this chapter is to describe dosing strategies for patients with CKD, AKI, and those receiving renal replacement therapies on an intermittent and/or continuous basis.

CLINICAL ASSESSMENT OF KIDNEY FUNCTION

The indices of glomerular and tubular function most widely utilized clinically include daily urinary protein excretion rate (glomerular), urine albumin-creatinine ratio (glomerular), fractional excretion of sodium (tubular), and serum creatinine concentration (glomerular and tubular). Creatinine is excreted by glomerular filtration and tubular secretion, making creatinine clearance (CrCl) a composite index of renal function that has been strongly associated with the total and renal clearance of many drugs that are eliminated by the kidney and is the primary index of renal drug dosing in FDA product labeling.

In patients with CKD stages 1 through 5 (pre-dialysis), the Cockcroft-Gault (CG) equation (see Chapter 2) is commonly used to estimate CrCl in the presence of stable kidney function. Newer equations that estimate GFR (eGFR), such as the CKD-EPI equations, are most appropriately used for identifying CKD and staging their degree of CKD severity.[4] Although the Modification of Diet in Renal Disease (MDRD) equation was initially adopted into automated systems for reporting GFR in clinical settings, it has been shown to be largely inaccurate at GFR > 60 mL/min and has since been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Neither of these eGFR equations has been consistently demonstrated to be equivalent to CG or measured CrCl when adjusting drug doses for renal impairment.[5,6] Recent studies by the Food and Drug Administration (FDA) and others showed that eGFR equations yield significantly higher estimates of kidney function, and significantly different dose calculations, when compared to CG equation, particularly in elderly individuals and those receiving narrow therapeutic index drugs such as enoxaparin.[5-9] Thus, renal dosing practices should remain consistent with the original pharmacokinetic studies of a particular drug in CKD, which to date generally involves estimation of CrCl.

Quantification of renal function in patients with AKI, where renal function and serum creatinine values are rapidly changing, is a challenging situation. Here, numerous equations for estimating CrCl based on two non-steady-state serum creatinine values have been proposed. See Chapter 2 for further discussions of appropriate use of equations to quantify renal function in various situations and patient populations. For critically ill patients with AKI receiving CRRT, estimation of both residual renal function (CrCl) and CRRT clearance are required for dose individualization (see section on dosing strategies).[10,11]

MECHANISMS OF DRUG CLEARANCE

Renal elimination

The process of renal drug elimination is a composite of glomerular and tubular functions, with the amount of drug cleared by the kidney (A_c) described by the following equation:

$$A_c = A_{filt} + A_{sec} - A_{reabs} \quad \textbf{(Eq. 1)}$$

Initially, unbound drug is filtered through the glomerulus (A_{filt}) into the proximal tubular fluid. When in the tubule, filtered drug may then be passively or actively reabsorbed (A_{reabs}) back into the bloodstream. This reabsorptive process is rare and occurs primarily in distal segments for unionized drugs at low urine flow rates. Drugs may also undergo active tubular secretion (A_{sec}), where unbound drug in plasma is transported into the tubular cell. This process of secreting drugs into the urine is mediated by transporters such as the organic anionic transporter (OAT), organic cationic transporter (OCT), or p-glycoprotein (P-GP). These transporters act in an efflux and uptake manner and are located along the basolateral and apical membranes of the proximal tubule.[12-14] The pathways work together to form an extremely efficient process of detoxification, resulting in renal clearance values that can exceed GFR, and in some cases approach renal plasma flow, which can be observed with para-aminohippurate and several penicillins. As filtration capacity (measured as GFR) progressively diminishes in CKD, some experimental data suggest that tubular secretory mechanisms may maintain their functionality, thereby providing significant renal clearance for some drugs even in the presence of severe glomerular damage.[15]

Kidney diseases can affect both glomerular and tubular function, leading to reduced overall drug elimination. As destruction of nephrons progresses, it has traditionally been believed that the function of all segments of the remaining nephrons is affected equally.[16] Based on this assumption, the rate of drug excretion in the normal or diseased kidney can be estimated by GFR or CrCl, which are predominantly measures of glomerular function.[17] The total renal clearance of a drug from the body also depends on (1) the fraction of the drug eliminated unchanged by the normal kidney, (2) the renal mechanisms involved in drug elimination, and (3) the degree of functional impairment of each of these pathways. The fraction of unchanged drug eliminated renally (f_e) and an assessment of the relationship between renal function and the drug's parameters, such as half-life (t½), total clearance (CL), and renal clearance (CL_{Renal}), can be used to individualize drug therapy. Ideally, renal drug clearance is determined by quantifying the amount of drug excreted in urine relative to the area under plasma drug concentration versus time curve (AUC) of drug in plasma, and renal function is measured using a GFR method such as iohexol or iothalamate clearance.[18] More commonly, the relationship between CrCl and drug clearance (CL) is evaluated in a large patient population with varying renal function, as follows:

$$CL = (A \times CrCl) + B \quad \textbf{(Eq. 2)}$$

$$k = (A \times CrCl) + B \quad \textbf{(Eq. 3)}$$

where A is the slope of the linear relationship between CrCl and either CL or k (the elimination rate constant), and B is the nonrenal CL (CL_{NR}) or nonrenal k (k_{NR}), respectively. This drug-specific information can then be used to design dose adjustment strategies in patients with renal insufficiency to minimize drug toxicity and optimize therapeutic efficacy.