Drug Dosing in the Elderly Patient with Chronic Kidney Disease

By Ali Olyaei

Chronic kidney disease (CKD) is a relatively common condition among older Americans. An estimated 26 million people in the United States are reported to have CKD. As the population of Americans 65 and older grows, so does the incidence of CKD. Evidence now indicates that kidney disease and aging carry a significant risk for cardiovascular complications and sudden death.

The progressive physiological changes with the aging process are inevitable: Aging-associated changes in carbohydrate metabolism and vascular atherosclerosis markedly increase the risk of developing diabetes and hypertension, and these high incidences of comorbid conditions may also lead to a higher incidence of cardiovascular events. Aging, directly or indirectly, has an effect on renal function and the handling of the most commonly used drugs in the geriatric population. The elderly with CKD are at a greater risk for adverse drug reactions and have a higher potential for drug–drug interactions (1, 2).

The pharmacokinetics and pharmacodynamics of most drugs are altered due to functional or anatomical changes of the renal system. These structural and functional changes are mostly multifactorial, resulting from the loss of kidney mass and exposure to precipitating factors leading to renal injury. These factors can include clinical nephrotoxins, electrolyte abnormalities, heart failure, and environmental insults.

In early adulthood, the average weight of a kidney is 250 g (±25 g); by age 75, kidney weight decreases to 200 g (±25 g). This loss of mass is most noticeable at the cortex level and much less in the medulla section. Glomeruli are also affected, with biopsies indicating a thickening basement membrane with hyalinization of renal arterioles. The incidence of biopsy-proven glomerulosclerosis increases from 1 to 2 percent in early adulthood, as opposed to roughly 30 percent by age 80+. Chronic vascular disease and inflammatory stages of CKD also contribute to tubular atrophy and interstitial fibrosis in the aging kidney. Other potential causes for loss of renal function could be due to aging-related vascular calcification, the release of endothelin-1 and nitric oxide synthase, free reactive oxygen species, and metabolic syndrome. Medication issues, including polypharmacy with the development of CKD, should also be considered for increased risk of morbidity and mortality (3).

Pharmacokinetics is the study of drug absorption, distribution, metabolism, and elimination. The drug dosing and adverse drug reactions observed in the aging CKD population is a complex combination of pharmacokinetic and pharmacodynamic variation from aging and CKD. Pathological or physiological adaptation of aging and CKD affects the pharmacokinetic behavior of most drugs. Therefore, health care providers must design a pharmacotherapeutic regimen for each patient to avoid unnecessary toxicity and initiation of dialysis. *N Engl J Med* 2009; 361:1539–1547.

References
10. Jean Holley, MD, is clinical professor of medicine at the University of Illinois at Urbana-Champaign.
Drug Dosing

Continued from page 19

There appears to be no constant alteration in pharmacokinetics of most commonly used drugs. Unfortunately, most tables and protocols for drug dosing in renal impairment do not incorporate many elements of pharmacokinetic changes associated with CKD. These data are driven solely according to the renal elimination process (4).

### Table 1. Influence of aging on pharmacokinetics

<table>
<thead>
<tr>
<th>Organ</th>
<th>Age-related changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Decreased GFR, renal blood flow, and tubular function</td>
</tr>
<tr>
<td>Liver</td>
<td>Decreased liver size and liver blood flow</td>
</tr>
<tr>
<td>Skin</td>
<td>Decreased hydration of stratum corneum, decreased skin surface lipids, and decreased skin microcirculation</td>
</tr>
<tr>
<td>Body</td>
<td>Decreased lean body mass, total body water, and body fat</td>
</tr>
</tbody>
</table>

### Absorption

There appears to be no constant alteration in drug absorption in the elderly population or patients with CKD. However, oral iron therapy, calcium supplements, phosphate binders, gastroparesis, nausea, and vomiting related to uremia significantly alter the absorption of most drugs. For drugs requiring a rapid plasma concentration such as a loop diuretic or a narcotic analgesic, requiring a rapid plasma concentration such as a loop diuretic or a narcotic analgesic, there is a much higher rate for hypertensive and diabetic patients. The glomerular filtration rate (GFR) is a good overall index of kidney function in both healthy patients and those with CKD.

**Metabolism**

Most drugs are excreted unchanged through the kidney, or metabolized through phase I or II reactions. Phase I reactions involve drug oxidation, reduction, and hydrolysis. Cytochrome P-450 also plays an important role in phase I reactions. Phase II metabolism involves glucuronidation, sulfation, acetylation, and methylation. Both aging and CKD reduce the hepatic clearance of many drugs. Phase I reactions are substantially decreased with aging, which has a smaller effect on phase II reactions. Liver mass is approximately 20 to 40 percent lower in elderly patients, with significantly reduced liver blood flow. Uremia may also influence the expression of the cytochrome P-450 isoenzyme system so that patients with CKD cannot metabolize drugs completely. Elderly patients with CKD may achieve a higher plasma concentration or even toxic concentrations of pharmacologic agents when they are prescribed at approved dosages.

Many drugs that metabolize, inhibit, or induce the cytochrome P-450 system and adverse drug reactions due to potential enzyme inhibition are common in older patients with CKD. Despite all of these fluctuations in pharmacokinetic properties due to drug metabolism, clinically, there is no quantitative approach to adjusting drug dosage according to liver function in older patients or patients with CKD. As a result, drug-induced liver injury is more common in the elderly (5).

### Elimination

Reduced renal function may prolong drug half-life and increase the risk of toxicity. To avoid drug toxicity, an accurate estimate of renal function is essential. As mentioned, kidney function generally declines with age. Renal blood flow, tubular function, and filtration are significantly reduced by 70 to 80 years of age. Risk factors for developing drug-induced kidney disease include female gender, age, dehydration, CKD, diabetes, cardiovascular disease, and end stage liver disease. Despite many hopes, there is no reliable clinical predictor of nephrotoxicity in elderly patients. In general, after the age of 30, creatinine clearance (CrCl) declines by 1 mL/min/year with a much higher rate for hypertensive and diabetic patients. The glomerular filtration rate (GFR) is a good overall index of kidney function in both healthy patients and those with CKD.

Clinically, the measurement of GFR is difficult and cumbersome, and has traditionally been estimated using age, weight, serum creatinine, race, and gender. Several methods of estimating GFR have been recommended. CrCI is the most common method, using the Cockcroft and Gault (CG) equation. The CG equation was developed in 1976 from a study of 249 Caucasian males, with and without CKD. Both men and women, all with CKD. The four-point equation is as follows:

\[
\text{GFR} = 141 \times \min (\text{Scr} / 1.33 \times \text{max(Scr/Cr)}), 1 \times 0.995 \times \text{Age}^{0.18} \times \text{SUN}^{−0.19} \times \text{Alb}^{−0.01}\]

*Scr = serum creatinine concentration (mg/dL), Age = age of the patient (years), SUN = serum urea nitrogen (mg/dL), Alb = serum albumin concentration (g/dL).

In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was released. The CKD-EPI equation is a modified MDRD equation with a more accurate estimate of renal function in patients with CKD for both impaired renal function and patients with GFR >60 mL/min. The CKD-EPI equation takes into account age, creatinine, gender, and race and is calculated as follows:

\[
\text{GFR} = \frac{186.3 \times \text{SerumCr}−0.99}{\text{Age}^{−0.15} \times \text{SUN}^{−0.15} \times \text{Alb}^{−0.25}}
\]

where Scr = serum creatinine (mg/dL).

Other methods to measure GFR include a 24-hour urine collection, which is inconvenient for most patients, or the measurement of cystatin C (an endogenous marker), which has not been validated for drug dosing. These calculations can be downloaded from a number of mobile medical applications from http://www.qxmd.com/calculate-online/nephrology or http://nephr.com for iPhone, iPad, and BlackBerry. It has been speculated that the MDRD method of GFR estimation may improve precision, reduce variation in estimating kidney function, and lead to more consistent drug dosing. However, for most drugs, MDRD equations have not been validated. All of these methods are often found to under- or overestimate renal function. For drug dosing in patients with CKD or the elderly, and in particular for patients with mild renal insufficiency, the MDRD and CKD-EPI equations provide less reliable estimations of renal function than the CG equation, and all three methods lack precision.

### Prescribing in the elderly with CKD

Pharmacotherapy drug response in the elderly is associated with significant inter- and intraindividual variability. Medication management in the elderly with chronic kidney disease is a challenging task. Pharmacokinetic and

### Table 2. Influence of chronic kidney disease on pharmacokinetics

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Kidney disease effects</th>
<th>Incorporated into drug dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug absorption</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>++</td>
<td>No</td>
</tr>
<tr>
<td>Intestinal and first pass metabolism</td>
<td>+</td>
<td>No</td>
</tr>
<tr>
<td>Distribution</td>
<td>++</td>
<td>No</td>
</tr>
<tr>
<td>Elimination</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal</td>
<td>+++</td>
<td>Yes</td>
</tr>
<tr>
<td>Nonrenal</td>
<td>++</td>
<td>No</td>
</tr>
</tbody>
</table>

In 1999, the Modification of Diet in Renal Disease (MDRD) equation was introduced to estimate renal function in patients with CKD. This study was conducted in both men and women, all with CKD. MDRD is less accurate in patients with GFR >60 mL/min; however, it is a more accurate measurement of GFR than CG in patients with GFR <60 mL/min. There are two methods of estimation: four-point (age, gender, race, creatinine) and six-point (age, gender, creatinine, BUN, albumin, race). The four-point equation is as follows:

\[
\text{GFR} = 186.3 \times \text{SerumCr}−1.154 \times \text{age}−0.203 \times 1.212 \times (\text{if patient is black}) \times 0.742 \times (\text{if female})
\]

The MDRD equation for estimating GFR using the six-point method can be calculated as:

\[
\text{GFR} = (\text{Scr} \times 1.73)^{0.89} \times \text{Age}^{0.177} \times \text{SUN}^{0.018} \times 0.762 \times (\text{if patient is female}) \times 1.180 \times (\text{if patient is black})
\]

where Scr = serum creatinine concentration (mg/dL), Age = age of the patient (years), SUN = serum urea nitrogen (mg/dL), and Alb = serum albumin concentration (g/dL).

pharmacodynamic variability associated with aging and CKD should be incorporated into the treatment plan for optimal therapy. A clinical treatment plan should include the type and severity of kidney disease, comorbid conditions, level of renal function, drug interactions, and cost. There are no simple rules for drug dosing in CKD that can be applied to the elderly population. If possible, for most medications, the advice is: “Start slow and go slower.” If possible, providers should follow these steps:

1. Take a careful medical and drug history
2. Consider adverse drug reactions or potential contraindications
3. Give a loading dose to reach therapeutic drug concentration rapidly
4. Adjust a maintenance dose according to renal function
5. Adjust schedule according to renal function
6. Consider therapeutic drug monitoring if possible (Table 3)
7. Detect drug interactions and adverse drug interactions

**Conclusion**
Pharmacotherapy in the elderly with CKD remains a challenging task. Rational drug therapy for elderly patients with CKD requires an adequate knowledge of disease status, comorbid conditions, and the pharmacokinetic and pharmacodynamic properties of the selected drug. Understanding the time course of drug effects (absorption, distribution, metabolism, and elimination) is vital for avoiding drug toxicity while optimizing the clinical outcome.

**References**
7. Stevens LA, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m². *Am J Kidney Dis* 2010; 56:486–495.

Aly Olyaei, PharmD, is professor of medicine and pharmacotherapy in the division of nephrology and hypertension at Oregon State University.

### Table 3. Therapeutic drug monitoring in chronic kidney disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic range</th>
<th>When to draw sample</th>
<th>How often to draw levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (gentamicin, tobramycin, amikacin)</td>
<td>Gentamicin and tobramycin: Trough: 0.5–2 mg/L, Peak: 5–8 mg/L Amikacin: Trough: 20–30 mg/L, Peak: &lt;10 mg/L, 0.5–3 mg/L</td>
<td>Trough: immediately prior to dose, Peak: 30 min after a 30- to 45-min infusion, Obtain random drug level 12 hours after dose</td>
<td>Check peak and trough with third dose; For therapy &gt;72 hours, levels not necessary; Repeat drug levels weekly or if renal function changes</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4–12 µg/mL</td>
<td>Trough: immediately prior to dosing                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>After initial dose; Repeat drug level in 1 week or if renal function changes</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>150–400 ng/mL</td>
<td>Trough: immediately prior to dosing                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.8–2.0 mg/mL</td>
<td>12 hours after maintenance dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>5–7 days after first dose for patients with normal renal and hepatic function; 15–20 days in anephric patients</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1–5 µg/mL</td>
<td>8 hours after iv infusion started or changed                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>After initial dose; Repeat drug level in 1 week or if renal function changes</td>
</tr>
<tr>
<td>Lithium</td>
<td>Acute: 0.8–1.2 mmol/L, Chronic: 0.6–0.8 mmol/L</td>
<td>Trough: before a.m. dose at least 12 hours since last dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Phenytoin, free phenytoin</td>
<td>15–40 µg/mL</td>
<td>Trough: immediately prior to dosing                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Check 2 weeks after first dose or change in dose, Follow-up level in 1–2 months</td>
</tr>
<tr>
<td>Procarbazine, N-acetyl procarbazine (a procarbazine metabolite)</td>
<td>4–10 µg/mL, Trough: 4 µg/mL, Peak: 8 µg/mL, 10–30 µg/mL</td>
<td>Trough: immediately prior to dosing                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>5–7 days after first dose or after change in dose</td>
</tr>
<tr>
<td>Quinidine</td>
<td>1–5 µg/mL</td>
<td>Trough: immediately prior to next dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>10–20 µg/dL</td>
<td>Trough: immediately prior to next dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Tacrolimus (FK506)</td>
<td>10–15 mg/L</td>
<td>Trough: immediately prior to next dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Theophylline po or aminophylline iv</td>
<td>15–20 µg/mL</td>
<td>Trough: immediately prior to next dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Daily for first week, then weekly</td>
</tr>
<tr>
<td>Valproic acid (divalproex sodium)</td>
<td>40–100 µg/mL</td>
<td>Trough: immediately prior to dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>Check 2–4 days after first dose or change in dose</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Trough: 5–15 mg/L, Peak: 25–40 mg/L</td>
<td>Trough: immediately prior to dose                                                                 else Repeat drug levels weekly or if renal function changes</td>
<td>With third dose (when initially starting therapy, or after each dosage adjustment) For therapy &gt;72 hours, levels not necessary; Repeat drug levels if renal function changes</td>
</tr>
</tbody>
</table>

**Note:** For therapy <72 hours, levels not necessary; Repeat drug levels weekly or if renal function changes.

To detect drug interactions and adverse drug reactions or potential contraindications, see Table 3. For infection complications, however, health care providers need to be more aggressive about providing optimal care while reducing adverse drug reactions.