# Drug Dosing in the Elderly with Chronic Kidney Disease

By Rachel W. Flurie and Gary R. Matzke

Chronic kidney disease (CKD) is a prevalent disease in the United States that disproportionately affects the elderly. The national prevalence is approximately 15 percent and reaches nearly 50 percent in adults aged 70 years and older (1). CKD stages 1 and 2 are characterized by a GFR >60 mL/min/1.73 $m^2$, and dose adjustments are usually indicated only for drugs that have a narrow therapeutic index, such as aminoglycosides and vancomycin. CKD stages 3, 4, and 5 are characterized by progressively lower GFR—30 to 59, 15 to 29, and <15 mL/min/1.73$m^2$, respectively—and drug dose adjustment becomes particularly important for these patients.

Advancing age makes drug dosing challenging because elderly patients often experience adverse drug effects at lower exposure levels than do younger patients; have multiple comorbidities, such as obesity and diabetes, that may independently affect drug pharmacokinetics; and experience polypharmacy with its heightened risk of undesirable outcomes (2, 3). Despite the availability of drug dosage recommendations in the product information approved by the U.S. Food and Drug Administration (FDA), as many as 19 to 69 percent of drugs prescribed for elderly CKD patients exceed the recommended dose (4). Thus, it is crucial that clinicians 1) identify the renal function of the elderly CKD patient, 2) recognize the need for drug dose adjustment (i.e., most commonly due to alterations in drug pharmacokinetics), and then 3) prescribe the appropriate dosage regimen based on the FDA-approved product information or widely available resources (5–7).

## Determining a patient's kidney function

The first step is to assess or estimate the patient's kidney function. Traditionally, the estimation of creatinine clearance (eCrCl) has been the primary index of kidney function in clinical practice for drug dosing. During the past 10–15 years, many health systems and outpatient clinical laboratories have begun to report estimated GFR (eGFR) to enhance the identification and staging of patients with CKD, and some have proposed that eGFR replace eCrCl for drug dosing (8, 9). Multiple equations based on creatinine, and more recently, creatinine and cystatin C, have been developed to calculate eGFR. Currently, most clinical laboratories in the United States use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation because it provides a more accurate eGFR throughout the full range of kidney function. The reporting of eGFR by clinical laboratories has enhanced the identification of adult patients with CKD, but it has not significantly contributed to an improvement in drug dosage adjustment outcomes as one might have anticipated (4).

The pharmacokinetic data suggest that eGFR generally correlates with eCrCl and can be used for staging of CKD and for drug dose adjustment for patients when the eGFR, expressed as mL/min/1.73 $m^2$, is re-expressed in mL/min before drug references are consulted (9). This requires determination of the patient's weight and height, two clinical values that are not often accurately recorded (3). However, the CKD-EPI equation, which is preferred for CKD staging, overestimates kidney function in elderly patients relative to eCrCl, and the resultant discordance in dosing recommendations may be problematic (10, 11). Thus, if eGFR is used as reported, larger doses may be recommended, possibly leading to higher costs and increased risk of adverse drug effects. For drugs with a broad therapeutic index (e.g., antihypertensives or antidiabetics) this may not be clinically significant, and using eGFR may be acceptable. For drugs with a narrow therapeutic index, eCrCl is preferred. In cases where drug effectiveness is critical or the risk of toxicity is high and associated with serum concentrations (e.g., antibiotics, immunosuppressants, or antiepileptics), monitoring serum drug concentrations is recommended.

## Influence of age and CKD on drug pharmacokinetics

The absorption, distribution, metabolism, and excretion of many drugs are altered by impaired kidney function and aging and, when significant, are the foundation for the generation of drug dose adjustment strategies (Table 1) (12–15).

### *Absorption*

No consistent significant alterations in gut absorption have been reported in elderly CKD patients. The bioavailability of some drugs (e.g., levodopa, metoprolol, dextropropxyphene, felodipine, sertraline, and dihydrocodeine) is increased because of decreased presystemic gut and liver metabolism.

### *Distribution*

The volume of distribution of many hydrophilic drugs (e.g., aminoglycosides, penicillins, and cephalosporins) is increased as a consequence of reduced muscle mass, increased total body water, or reduced protein binding, which are often seen in elderly CKD patients. Decreased serum albumin is associated with increased unbound drug fraction and volume of distribution for phenytoin, furosemide, and ceftriaxone, among others. One should start with the typical dose and then monitor unbound drug concentrations or pharmacodynamic response to assure optimal patient outcomes.

### *Metabolism*

Drug metabolism may be reduced in elderly CKD patients as the result of reductions in liver blood flow and the intrinsic activity of cytochrome oxidative enzymes. Emerging clinical evidence suggests that accumulation of uremic toxins may be responsible for the activity of cytochrome oxidative enzymes and transporter proteins (13). Prediction of the degree of effect of aging or CKD on the metabolism of a particular drug is problematic because there is no quantitative correlation even among drugs within the same pharmacologic class.

### *Excretion*

For drugs that are predominantly (>30 percent of total clearance) eliminated by the kidneys, progressive reductions in GFR associated with CKD or aging can reduce renal clearance, and the resultant drug accumulation may lead to exaggerated effects or toxicity at normal doses. In addition to physiologic reductions in glomerular filtration, tubular secretion may be impaired and contribute to marked reductions in renal drug clearance. The elderly and those with CKD stages 3 to 5 are also more prone to acute kidney injury from drugs that cause direct damage or alter renal hemodynamics (e.g., aminoglycosides, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs) and are slower to recover from an insult. Given that the measurement of GFR or creatinine clearance is challenging and costly, eCrCl should be used to guide therapeutic decisions, and for drugs with a narrow therapeutic index, monitoring serum drug concentrations is recommended.

## Optimal prescribing for the elderly CKD patient

Drug prescribing for the elderly CKD patient starts with identification of the patient's kidney function and awareness of the known impact of aging and CKD on drug pharmacokinetics. A systematic approach to these variables, with FDA-approved dosage recommendations (available from multiple sources) for initial therapy, has the highest likelihood of achieving the patient's individual treatment goals (Table 2) (5–7). Drug dosing recommendations for the most frequently prescribed and

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**Table 1. Pharmacokinetic changes due to aging and chronic kidney disease**

| Pharmacokinetic Parameter | Age-Related Changes | Chronic Kidney Disease Changes | Impact on Drug Dosing* |
|---|---|---|---|
| Absorption | Reduced splanchnic blood flow; gastric acid production, gastric emptying rate, and absorptive surface | Decreased intestinal metabolism; decreased P-glycoprotein activity | Minimal for most drugs |
| Distribution | Increased body fat; decreased muscle mass; decreased total body water; decreased serum albumin; increased α1-acid glycoprotein | Decreased serum albumin; increased total body water | Moderate for some drugs (e.g., phenytoin, theophylline, digoxin, aminoglycosides) |
| Metabolism | Reduced hepatic mass; decreased hepatic blood flow; decreased hepatic metabolic activity | Decreased function of cytochrome oxidative 450 enzymes and drug transporter proteins | Moderate for some drugs (e.g., nortriptyline, morphine, warfarin) |
| Elimination (renal) | Reduced renal mass; decreased renal blood flow; decreased GFR; renal tubular atrophy | Decreased GFR; impaired tubular secretion and reabsorption; increased proteinuria | Major for drugs that are extensively renally eliminated (e.g., cimetidine, sitagliptin, lisinopril) |

***Minimal = no dosing impact anticipated; Moderate = some drugs may require monitoring and dose adjustment; Major = accurate dose adjustment and drug monitoring are required.**

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# Drug Dosing

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highest-cost drugs for Medicare beneficiaries and for other commonly prescribed medications in the elderly are listed in Table 3 (5, 6, 16).

The key to optimize elderly CKD patient outcomes is for clinicians to understand the rationale for drug dose adjustment and to use the appropriate resources to individualize therapy. The concomitant presence of obesity or malnutrition or of other chronic diseases that affect drug pharmacokinetics and response such as heart failure and liver disease further complicates therapy decisions and patient outcomes.

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**Table 2. Stepwise approach to drug dosing in the elderly patient with chronic kidney disease***

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|---|
| 1. Obtain pertinent patient medical history—comorbidities, comprehensive medication history, physical examination, laboratory data |
| 2. Assess renal function—eGFR for drugs with broad therapeutic index and eCrCl for drugs with narrow therapeutic index |
| 3. Review current medications—consider the risk of adverse effects, need for dose adjustment, and contraindications (e.g., www.uptodate.com or www.epocrates.com) |
| 4. Individualize the medication regimen—consider goals of treatment, need for a loading dose, maintenance dosing |
| 5. Monitor drug efficacy/toxicity—patient signs and symptoms, therapeutic drug monitoring when applicable |
| 6. Revisit and revise—adjust medication regimen based on pharmacotherapeutic response and changes in renal function |

***Abbreviations: eCrCl = estimation of creatinine clearance; eGFR = estimated GFR.**

**Table 3. Dosing recommendations for selected drugs in elderly patients with chronic kidney disease***

| Drug | Dose Adjustment Recommendations† | | |
|---|---|---|---|
| | GFR = 30–50 mL/min | GFR = 10–30 mL/min | GFR <10 mL/min |
| Atenolol | 25–50 mg q24h | | 25 mg q24h |
| Cimetidine | reduce dose 50% | | reduce dose 75% |
| Ciprofloxacin | reduce dose 50% | reduce dose 50%; administer q18h | reduce dose 50%; administer q18–24h |
| Duloxetine‡ | usual dose | avoid use | |
| Famotidine | reduce dose 50% OR dose q36–48h | | |
| Gabapentin | 300 mg q12–24h | | 300 mg q48h |
| Glipizide | reduce dose 50% | | |
| Lenalidomide‡ | reduce dose 50% | reduce dose 75% OR reduce dose 25% and administer q48h | |
| Levofloxacin | reduce dose 50% OR administer q24–48h | | reduce dose 50%; administer q48h |
| Lisinopril† | reduce dose 25–50% | | reduce dose 50–75% |
| Metformin‡ | reduce dose 75% | | avoid use |
| Olmesartan | usual dose | use with caution | reduce dose 50% |
| Pregabalin | reduce dose 50% | reduce dose 75% | reduce dose 75–90% |
| Rosuvastatin‡ | usual dose | 5–10 mg q24h | |
| Saxagliptin | reduce dose 50% | | |
| Simvastatin‡ | usual dose | 5 mg q24h | |
| Sitagliptin‡ | reduce dose 50% | reduce dose 75% | |
| Solifenacin | usual dose | reduce dose 50% | |
| Sulfamethoxazole-trimethoprim | dose q12–18h | | dose q24h |
| Tolterodine | usual dose | reduce dose 50% | |

***Abbreviations: q12h = every 12 hours; q18h = every 18 hours; q24h = every 24 hours; q36h = every 36 hours; q48h every = 48 hours.**
**†May use eGFR or eCrCl to approximate GFR.**
**‡Included in the top 10 drugs by 2013 Medicare claims or costs.**