



Drug Dosage Adjustments in Chronic Kidney Disease: The Pharmacist's Role

An important issue in drug therapy is dosage adjustment in chronic kidney disease (CKD). Many drugs need to be adjusted depending on a person's kidney function; it is the pharmacist's duty to ensure a patient is taking the optimal dose. Pharmacists in Saskatchewan will soon have the opportunity to access patients' lab values, allowing them to estimate kidney function. In practice, it is not feasible to check the kidney function of every patient. Identification of the most vulnerable patient demographic and which drugs require dosage adjustments is critical for optimal pharmacotherapy.

What is Chronic Kidney Disease ?

CKD is defined as the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) for three months or longer.¹ The degree of renal insufficiency and the severity of kidney disease are generally reflected in the decline of GFR. The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) established a classification of CKD that has been accepted and used worldwide.² The five stages of classification, along with a description of each stage, are shown in Table 1.

Table 1: Chronic Kidney Disease Staging¹		
Stage	Description	GFR (ml per minute per 1.73 m²)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with a mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

While many diseases can lead to CKD, diabetes (30%) and renal vascular disease such as hypertension (20%) account for the majority of cases.³ Other risk factors for CKD include old age, autoimmune disease, urinary stone, certain ethnic groups (ie. First Nation's, South Asians, Pacific Islanders), family history of kidney disease, vascular disease (such as CAD, CVD, PVD) and recovery from acute kidney failure.⁴ Several formulas have been developed for estimating GFR, all of which have limitations. The most commonly used are the Cockcroft-Gault (CG) and the 4-variable Modification of Diet in Renal Disease (MDRD4).⁴ The NKF however is now recommending the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation⁵, although there is some debate on whether or not it is more accurate than the MDRD⁶. Recently, a meta-analysis reported a weight-corrected ("no weight") CG formula provided the best estimate of measured GFR.⁷ (See Figure 1)

Figure 1: Weight-corrected ('No weight') Cockcroft-Gault Equation^{4,7}

$$\text{CLCr (ml/s/70kg)}^* = \frac{(140 - \text{age}) \times 1.5 (\times 0.85 \text{ if female})}{\text{SCr (umol/L)}}$$

*For ml/min/70kg, multiply by 60

Table 2: Equations for estimating GFR ⁵		
Equation	Variables	Comments
Cockcroft-Gault (CG)	Age, weight, sex, serum creatinine level	Dosage adjustment recommendations are generally based on pharmacokinetic studies utilizing this equation. Several variations – original equation overestimates GFR
Modification of Diet in Renal Disease (MDRD4)	Age; sex; race; and serum creatinine level	Underestimates GFR when GFR > 60 ml/min/1.73m ²
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)	Age; sex; race; and serum creatinine level	More accurate than MDRD for estimating GFR in patients with normal kidney function, Stage I & II CKD
On-line calculators	http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm http://www.nkdep.nih.gov/lab-evaluation/gfr-calculators/adults-SI-units.shtml http://www.globalrph.com/multiple_crcl.htm	

Adjusting Drug Dosages in CKD

Dosing adjustments are generally not required until CrCl falls below 1 mL/s/70 kg (GFR 60 ml/min/1.73m²).⁴ Most labs now report an estimated GFR (eGFR) as well as serum creatinine levels. The equation used to calculate eGFR varies among labs. Saskatoon Health Region currently uses the CG equation but will soon switch to the MDRD4. ***For most patients, the reported eGFR is accurate enough for initial drug dose adjustment regardless of which equation is used.***^{4,8} Subsequent doses should be titrated based on patient response and/or serum levels.⁴

Other factors to be considered in adjusting doses:

- Usual methods of GFR estimation are not accurate for children, elderly, pregnant women, or weight extremes.^{4,5,8}
 - Options for obese patients (> 30 % over ideal body weight): use the CG equation and lean body weight; increase the no weight CrCl by a factor of 0.3 – 0.4 or use the Salazar-Corcoran equation.^{5,6,7} (Online calculator available at <http://www.globalrph.com/crcl.htm>.)
 - Usual methods of creatinine clearance overestimate kidney function in the elderly. Dosing in this age group must be based on individual risk versus benefit analysis and clinical judgment.^{8,10} New methods to more accurately estimate kidney function in the elderly are being developed but require validation.¹⁰
 - Modified equations for calculating kidney function in children have been developed and are available at:
<http://www.globalrph.com/specialpop.htm>
http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm
- Dosing changes can involve dose reduction, increasing the interval between doses, or both.^{4,11}
 - Loading doses generally do not require adjustment.
 - When a rapid effect is needed (e.g. severe pain, serious infection), patient response rather than renal function is the most important consideration.

- Dose reduction results in more consistent drug concentrations, but increases risk of toxicity if the interval between doses is not long enough to allow for elimination.
- Increasing the interval between doses reduces the risk of toxicity but may increase the risk of subtherapeutic effect if concentrations fall below the effective level.

What Drugs need Dosage Adjustments?

There is an extensive list of drugs that either require dosage adjustment and / or should not be used by patients with CKD because of lack of benefit or nephrotoxicity.¹ The mnemonic BANDD CAMP (seen in Table 2) can be used to recognize several categories of drugs which may be of concern in CKD. For a comprehensive list of drugs and specific recommendations for dosage adjustments based on CrCl, see e-Therapeutics⁺ Appendices: Dosage Adjustment in Renal Impairment (available at www.shirp.ca).⁴

Table 2: Drug Classes Requiring Dosage Adjustment/ in CKD ¹⁻⁵			
	Drug Class	Adjust Dose	Avoid in Stages 4 and 5 of CKD
B	Beta Blockers	Acebutolol, atenolol, bisoprolol, nadolol, sotalol	Sotalol
A	ACE inhibitors /ARBs*	All ACE inhibitors	Olmesartan
N	NSAIDS**, Opioids	Codeine, morphine, oxycodone, tramadol	All NSAIDS, meperidine
D	Diuretics	Potassium sparing diuretics, thiazide diuretics	Potassium sparing diuretics, thiazide diuretics
D	Diabetic medications	Gliclazide, acarbose, insulin, gliptins	Glyburide, metformin, exanotide
C	Cholesterol medications	Pravastatin, rosuvastatin; fibrates	
A	Antimicrobials (Dose reductions are often delayed for 24-48 hours to allow for aggressive dosing/drug to reach steady state)	<i>Antibiotics:</i> Most antibiotics EXCEPT cloxacillin, clindamycin, metronidazole, erythromycin, azithromycin <i>Antifungals:</i> fluconazole, itraconazole <i>Antivirals:</i> acyclovir, famciclovir, valacyclovir	Nitrofurantoin
M	Miscellaneous	Allopurinol, colchicine, digoxin, H ₂ RAs***	New anticoagulants
P	Psychotropics	Lithium; gabapentin, pregabalin, topiramate, vigabatrin; bupropion, duloxetine, paroxetine, venlafaxine	

*ARBs – angiotensin II receptor blockers; **NSAIDs – nonsteroidal anti-inflammatory drugs; ***H₂RAs – Histamine-2 receptor antagonists

Steps for the pharmacist:

1. Identify patients at risk of CKD (eg. patients with diabetes, hypertension, or glomerulonephritis).
2. Ask the patient about kidney function and check the patient's lab report if accessible. If additional information is necessary, contact the patient's doctor.
3. Identify which medications might require dosage adjustments in CKD. (Hint: use the BANDD CAMP mnemonic).
4. Check medication profile for drug interactions which could affect serum levels of renally- excreted drugs (e.g., p-glycoprotein inhibitors) and/ or decrease renal function (e.g., nephrotoxic drugs).

5. Determine the dose adjustments needed for all relevant medications. Recommendations for dose adjustment based on renal function are provided in manufacturers' drug monographs, e-Therapeutics+, Lexi-Comp, Micromedex, etc.
6. Communicate recommendations for adjustments to the patient's medication to the doctor.
7. Set up a monitoring plan for the patient. Further dose adjustments may be necessary depending on the patient's response.

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