

Drug Use and Dosing in Chronic Kidney Disease

Yahaya Hassan,¹Pharm D, Rowa'J Al-Ramahi,¹MSC, Noorizan Abd Aziz,¹Pharm D, Rozina Ghazali,²MBBS, MRCP

Abstract

One of the most important drug-related problems in patients with chronic kidney disease (CKD) is medication dosing errors. Many medications and their metabolites are eliminated through the kidney. Thus, adequate renal function is important to avoid toxicity. Patients with renal impairment often have alterations in their pharmacokinetic and pharmacodynamic parameters. The clearance of drugs eliminated primarily by renal filtration is decreased by renal disease. Therefore, special consideration should be taken when these drugs are prescribed to patients with impaired renal function. Despite the importance of dosage adjustment in patients with CKD, such adjustments are sometimes ignored. Physicians and pharmacists can work together to accomplish safe drug prescribing. This task can be complex and require a stepwise approach to ensure effectiveness, minimise further damage and prevent drug nephrotoxicity.

Ann Acad Med Singapore 2009;38:1095-103

Key words: Dosage adjustment, Renal impairment, Stepwise approach

Introduction

Chronic kidney disease (CKD) is an important therapeutic problem. There is an increasing realisation that renal impairment is under-diagnosed, and this has led to attempts to improve both the detection and management of patients with impaired renal function.¹ The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation established a classification of CKD that has been accepted and used worldwide. This classification defines CKD as a Glomerular filtration rate (GFR) <60 mL/min/1.73 m² or a GFR ≥ 60 mL/min/1.73 m² together with the presence of kidney damage for more than 3 months. Based on this definition, the K/DOQI has recommended a classification of CKD that is divided into 5 stages (Table 1).²

Effect of Chronic Kidney Disease on Drug Pharmacokinetics

Patients with renal impairment often have alterations in their pharmacokinetic parameters such as drug absorption, distribution, protein binding, biotransformation and renal excretion.^{3,4} Thus elimination of many drugs is dependent on renal filtration, secretion and reabsorption. Glomerular filtration is impaired by renal disease or ageing. Therefore,

the clearance of drugs eliminated primarily by this mechanism is decreased, and this should be considered when these drugs are prescribed to patients with impaired renal functions. Patients with severe renal insufficiency can experience accumulation of metabolites which can contribute to pharmacologic activity or toxicity. Patients can also have an altered pharmacodynamic response to a given drug because of the physiologic and biochemical changes associated with progressive renal insufficiency.^{5,6}

Effects on Absorption

Increased gastric pH is a common manifestation in CKD and its aetiology is multifactorial. Ammonia formation in the gut, secondary to conversion of salivary urea by urease enzymes, is one explanation for increased pH. The administration of phosphate binders, antacids, H₂-receptor antagonists, and proton-pump inhibitors in this patient population is common. For medications that are best absorbed in an acidic environment, drug dissolution and ionisation are often reduced by increased gastric pH, resulting in reduced bioavailability. Examples include furosemide, ketoconazole and ferrous sulfate.⁴⁻⁶ Conversely, it has been shown that the administration of magnesium

¹ Clinical Pharmacy Programme, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

² Department of Medicine, Penang Hospital, Penang, Malaysia

Address for Correspondence: Dr Yahaya Hassan, Clinical Pharmacy Programme, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden 11800, Penang, Malaysia.

Email: yahaya@usm.my

Table 1. Chronic Kidney Disease Staging and Clinical Action Plan

Stage	Description	GFR mL/min/1.73m ²	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment. Treatment of comorbid conditions. Slowing progression. CVD risk reduction.
2	Kidney damage with mild ↓ GFR	60-89	Estimating progression.
3	Moderate ↓ GFR	30-59	Evaluating and treating complications.
4	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy.
5	Kidney failure (ESRD)	<15 (or dialysis)	Replacement (if uraemia present).

* Includes actions from preceding stages

CVD: cardiovascular disease; ESRD: end-stage renal disease; GFR: glomerular filtration rate

hydroxide and sodium bicarbonate, can enhance the absorption of some weakly acidic molecules (e.g., ibuprofen, glipizide, glyburide, tolbutamide) by increasing their water solubility and subsequent absorption. Also, the ingestion of cation-containing antacids (e.g., calcium, magnesium), aluminum hydroxide, sodium polystyrene sulfonate and iron may reduce drug absorption because of chelation with other medications, resulting in the formation of insoluble compounds. The fluoroquinolones and tetracyclines are 2 medication classes that are highly susceptible to chelate formation in patients with renal insufficiency.⁴⁻⁷

Many patients with renal insufficiency suffer from gastroparesis, which can result in delayed gastric emptying, and this may prolong the time to reach maximum drug concentrations. However these delays generally do not affect the overall extent of absorption.⁵⁻⁷ This might be important for some drugs such as short acting sulfonylureas.⁴ Bowel wall oedema has also been cited as a potential cause of diminished oral absorption in CKD patients.^{3-5,7}

Several medications undergo significant metabolism in the gastrointestinal tract, including cyclosporine and tacrolimus. Renal insufficiency is associated with decreased intestinal CYP450 activity. This altered activity is thought to be secondary to diminished CYP450 gene expression. CKD-induced reductions in intestinal CYP450 biotransformation have a profound effect on drug absorption by increasing overall oral absorption.^{5,7} Vomiting and diarrhoea are common in CKD patients and this can reduce the amount of drug absorbed.^{3,4}

Effects on Distribution

CKD-induced alterations in protein binding are associated with many clinical implications. Medications that are acidic, such as barbiturates, cephalosporins, furosemide, penicillins, phenytoin, salicylates, valproate and warfarin are most severely affected by reduced protein binding. Acidic drugs are bound to albumin, plasma concentrations of which are often decreased in uremic patients. Hypoalbuminemia and altered plasma protein binding due to the competition for

binding sites by other drugs, metabolites, and accumulating endogenous substances may displace medications from plasma protein binding sites leading to increased levels of free concentrations of drugs. Conversely, alkaline drugs (e.g., propranolol, morphine, oxazepam, vancomycin) bind primarily to non-albumin plasma proteins, such as α 1-acid glycoprotein. α 1-acid glycoprotein is an acute-phase protein whose plasma concentrations are often elevated in renal dysfunction. For this reason, plasma concentrations of alkaline drugs in CKD patients may be reduced (e.g., propranolol).³⁻⁷

Attempts to achieve therapeutic drug concentrations in the CKD population without dose adjustments are often associated with higher free acidic drug concentrations and potentially drug-related toxicities. Increased free drug concentrations, however, may also result in an increased fraction of drug that undergoes biotransformation, decreasing pharmacologic activity.

Besides reduced plasma protein binding, volume of distribution (Vd) may also be affected by altered tissue binding. For most medications, changes in tissue binding are probably irrelevant. The major exception is digoxin. Digoxin's Vd is reduced by half in patients with stage 5 CKD. This reduction in Vd results in increased digoxin serum concentrations if the loading dose is not reduced.^{5,7}

CKD-induced changes in body composition, such as increased total-body water and adipose tissue and decreased muscle mass, can have a profound effect on hydrophilic drugs (e.g., pravastatin, fluvastatin, morphine, codeine). Oedema and ascites is expected to increase the Vd of hydrophilic compounds such as vancomycin. This change in Vd may result in reduced serum concentrations. Contrarily, muscle wasting and increased adipose tissue may reduce Vd and increase serum concentrations of hydrophilic medications.⁴⁻⁶

Effects on Metabolism

Renal dysfunction significantly alters hepatic biotransformations; these can increase, decrease or remain unchanged.^{4,7}

In general, phase I hydrolysis and reduction reactions are slowed in CKD. Phase II metabolic reactions are also affected by renal dysfunction. Acetylation (e.g., dapsone, hydralazine, isoniazid, procainamide), glucuronidation (e.g., acetaminophen, morphine, lorazepam, oxazepam, naproxen), sulfation (e.g., acetaminophen, minoxidil, dopamine, albuterol), and methylation (e.g., dobutamine, dopamine, 6-mercaptopurine) are all slowed in patients with CKD. Slowed phase I and II metabolic reactions result in increased serum drug concentrations.

A factor of drug biotransformation that cannot be overlooked is the kidney as a site for drug metabolism. Ordinarily, the kidneys have nearly 15% of the metabolic function of the liver, with most of the metabolic enzymes located in the renal cortex. Renal metabolism is obviously reduced during cases of renal insufficiency.

Understanding the metabolic pathways of all medications administered to a patient with renal insufficiency is a necessity. Reduction in the overall metabolic rate results in increased parent compound concentrations, potentially increasing the prevalence of adverse events.⁵⁻⁷

Effects on Elimination

Renal excretion of medications is dependent on glomerular filtration rate, renal tubular secretion and reabsorption. The glomerular elimination of drugs depends on several factors, including the molecular weight and protein binding. Drugs bound to albumin are not filtered. In this situation, the filtration rate of these drugs is directly proportional to their free plasma concentrations. In CKD, medication elimination by glomerular filtration is decreased, resulting in a prolonged free drug elimination half-life. Although protein binding decreases the glomerular filtration of some drugs, the renal tubular secretion of these medications may be increased. Highly protein-bound medications are actively secreted into the proximal convoluted tubules, ensuring they are excreted. In CKD, however, the secretion of drugs eliminated by this active transport system is reduced. Another factor affecting active tubular secretion of drugs is that this is a transport-mediated process and, with higher drug levels, the secretion reaches a limit leading to an increased elimination half-life. Also, competition between drugs for secretion can reduce their excretion. This is a common phenomenon seen with the co-administration of penicillin and probenecid.^{5,6}

In healthy kidneys, the renal clearance of many drugs is slow because they are substantially reabsorbed from the distal portion of the nephron. As expected, reductions in medication reabsorption are observed in patients with CKD, resulting in increased urinary concentrations of renally eliminated medications, such as aspirin and lithium.

One aspect of renal excretion that is often overlooked is the elimination of drug metabolites. Biologically active or toxic

metabolites of parent compounds may accumulate in patients with CKD. The opioid analgesic meperidine undergoes biotransformation to normeperidine. Normeperidine, which is renally eliminated, has little opioid activity. As it accumulates secondary to renal dysfunction, it lowers the seizure threshold. Similarly, the active metabolite of midazolam, alphahydroxymidazolam, can accumulate in CKD patients. Accumulation of this metabolite has resulted in excessive sedation. Additionally, biologically inactive metabolites may have an indirect effect on drug-plasma protein binding and receptor affinity.^{3,5}

Drug-related Problems in CKD Population

Drug-related problems are common in patients with renal insufficiency and haemodialysis patients. Such patients are at higher risk as they require complex therapeutic regimens with 5 or more medications and 12 or more medication doses per day that require frequent monitoring and dosage adjustment, and they usually have other concurrent diseases including diabetes mellitus, hypertension, coronary artery diseases and infections. They are usually non-compliant with medications. Several studies have established that the incidence of adverse drug events is much higher in patients with chronic kidney diseases than those without renal insufficiency.^{4,5,8,9}

Drug-related problems can result in an increase in morbidity and mortality, as well as an increase in the cost of healthcare. Inappropriate use of medications can increase adverse drug effects that may be reflected by excessive length of hospital stay, and excessive healthcare utilisation and cost.¹⁰⁻¹² Large numbers of adverse drug reactions are predictable and often preventable. Preventable adverse drug events are often a result of medication errors.^{13,14} Prescribing errors often occur because the prescribers do not have immediate access to all the needed information related to the drugs or the patient.¹⁵

Dosage Adjustment According to Renal Function

One of the most important drug-related problems in patients with renal impairment is medication dosing errors.^{8,16,17} Many medications and their metabolites are eliminated through the kidneys and thus adequate renal function is important to avoid toxicity. The proper dosing of medications for patients with renal impairment can maximise therapeutic efficacy and minimise toxicity.¹⁶ Proper dosing can also have an economic impact on the health system. Studies have shown that an adverse drug event increases the length of hospitalisation and consequently increases cost.¹⁸ Dosage adjustment can result in avoidance of costs associated with drug-related toxicity and in cost savings in terms of drug costs.^{19,20} Despite the importance of dosage adjustment among patients with renal impairment, such adjustments are rarely made.²¹⁻²⁴ A major reason for

inappropriate dosage adjustment is the underestimation of potential adverse consequences.

Several studies have indicated that dosing errors and the risk of toxicity are common among patients with renal impairment.^{14,17,21-23,25} In a review to assess compliance with dosing guidelines in patients with chronic kidney disease, the non-compliance rate in studies conducted in hospitals ranged from 19% to 67%.¹⁶

Appropriate drug selection and dosing in chronic kidney disease patients is important to avoid unwanted effects of drugs and to ensure optimal patient outcomes. Efforts to reduce dosing errors have the ability to lower the rate of adverse drug events, reduce the cost and improve the overall delivery of healthcare. The question remains of how to address this problem to improve the quality of healthcare delivered to patients. Two strategies have been suggested to assist practitioners in monitoring and adjusting drug therapy in patients: computerised dosing programmes and clinical pharmacist dosing services.^{16,26}

Computerised Dosing Programmes

Computerised clinical decision support alerts have been able to reduce the number of medication orders and administration of medications that are contraindicated due to renal insufficiency. Computerised guided medication dosing for inpatients with renal insufficiency has shown improved dose and frequency choices. Both were limited by non-compliance with the recommendation from the physicians.^{25,27} A systematic review of studies examining computer support for determining optimum drug dose has shown benefits from computer use, a barrier of adopting this system may be the lack of access to computers and electronic medical records.²⁸ In an attempt to solve this problem, a computerised system for prescribing and recording the administration of drugs which can be accessed from the patient's bedside using portable wireless terminals was developed. It was implemented in a renal unit and has contributed to safety and patient care.¹⁵ Computerised dosing programmes are promising; the major barrier to widespread adoption of these approaches is financial.

Clinical Pharmacist Dosing Services

Pharmacists have shown an impact in improving medical management in other areas. Clinical pharmacy interventions and involvement in disease management by community pharmacists have the potential to provide a valuable contribution to healthcare and decrease the overall healthcare cost.^{29,30} Clinical pharmacy services provided to hospitalised patients have demonstrated an economic impact with improved patient health outcomes.^{18,31} Having a pharmacist in a rounding team in the intensive care unit (ICU) and general medicine units have been shown to

reduce preventable adverse drug events.^{32,33} A pharmacist's clinical services in the coronary care unit (CCU) allowed for significant estimated reductions in total drug costs.³⁴ In general, it is highly recommended to have a clinical pharmacist in inpatient settings to improve the quality, safety and efficacy of healthcare, especially in the management of high-risk patients as patients with chronic kidney disease. The immediate concurrent feedback strategy implemented by a clinical pharmacist increased the proportion of doses of renally eliminated drugs adjusted to renal functions, decreased drug costs and had the potential to prevent adverse drug reactions.³⁵ Pharmacist recommendations in patients requiring dialysis have been welcomed by physicians and have positively affected the quality of care. The role of the pharmacist in ensuring appropriate drug dosing in patients with CKD and haemodialysis patients has proven to be useful and is highly encouraged.^{8,9,36}

Drug Prescribing in Patients with CKD

Based on the current data, we can conclude that in order to improve prescription in CKD patients, it would be necessary to have collaboration between all healthcare providers. The large number and the continuously increasing medications list makes it difficult for medical staff to remain updated on dosage adjustment issues. Since clinical pharmacists are well trained in pharmacokinetics, mechanisms of drug interactions and pharmacodynamics, they can assist physicians to adjust drug dosages in patients with chronic kidney disease.^{36,37} The involvement of a pharmacist at the point of prescription of a drug by a physician is the most effective. The time for decision-making is very important.^{26,38} Physicians and pharmacists can work together to have safe drug prescribing that can be complex and requires stepwise approach (Fig. 1) to ensure effectiveness, minimise further damage and prevent drug nephrotoxicity. The following recommendations can be useful:

(i) Have a Detailed Initial Assessment

The first step is to have a detailed initial assessment. This should include previous drug exposure, allergies and toxicity, the patient's current medications including over the counter drugs, body weight and height, extracellular fluid volume to evaluate possible chances on volume of distribution (increased by oedema, ascites, pleural effusion and decreased by volume depletion), in addition to laboratory data for renal function parameters, tests of liver functions and albumin concentration.^{3,4,6}

(ii) Evaluate the Degree of Renal Impairment

The second step is to evaluate the degree of renal impairment. The evaluation of GFR is the most reliable index and surrogate marker of overall kidney function.

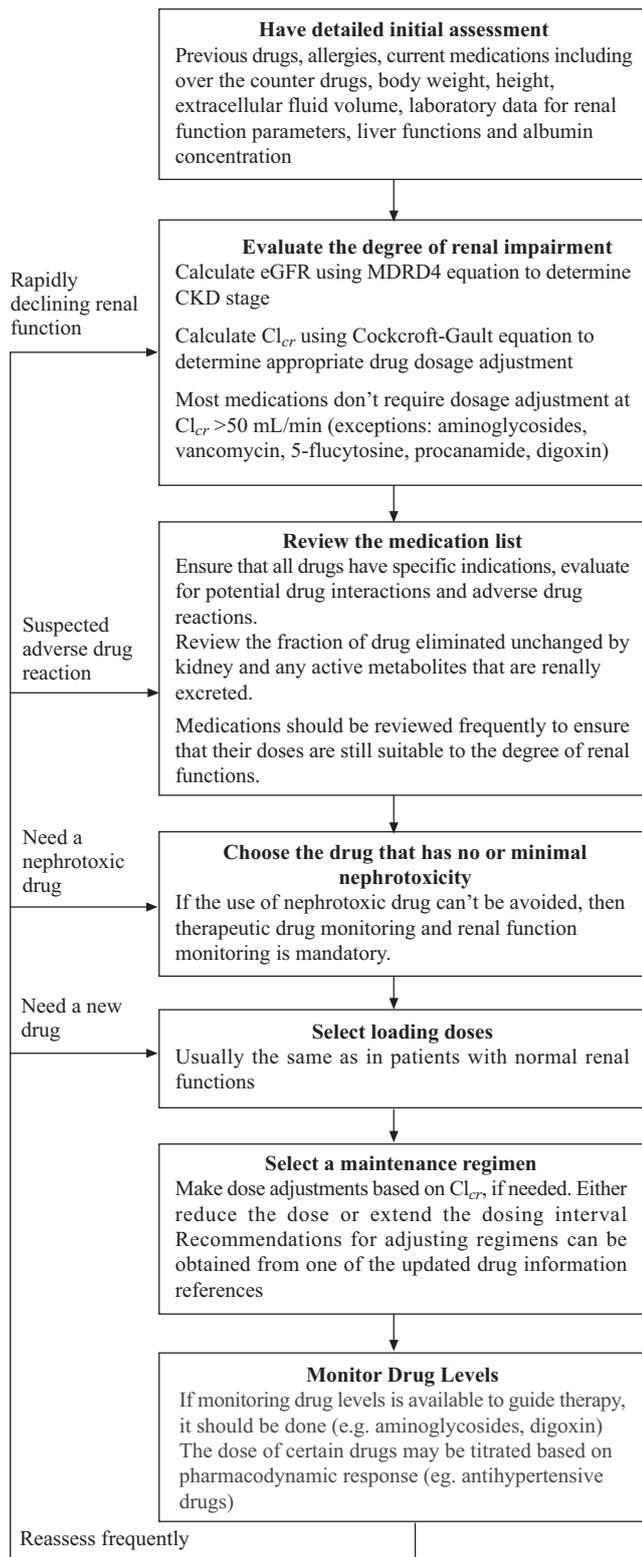


Fig. 1. Stepwise approach for adjusting drug dosages for patients with renal impairment.

Direct measurement of GFR using exogenous filtration markers such as iothalamate or inulin is the preferred, but is the most costly means. The measurement or estimation of creatinine clearance has been extensively used even though creatinine is a crude index of kidney function. Measured creatinine clearance requires serum and urine creatinine concentration determinations and the collection of a timed urine collection. It is not recommended for routine evaluation of kidney function.³⁹ The preferred equations for estimating creatinine clearance and glomerular filtration rate are Cockcroft-Gault equation and the abbreviated 4-variable Modification of Diet in Renal Disease Study Equation (MDRD4) equation which will be discussed here:

Creatinine Clearance (Cl_{cr})

The most practical approach for assessing kidney function in the majority of clinical settings is estimation of creatinine clearance. It seems that there is an underestimation or lack of knowledge of the importance regarding creatinine clearance in determining appropriate medication dose. It is important that creatinine clearance be calculated and documented for all patients for dose calculation. Using serum creatinine level as the only indicator of renal function is not accurate. Even though it is well known that serum creatinine concentrations are influenced by diet (e.g., vegetarian diet and creatine supplements), body mass (e.g., amputation and malnutrition) and some drug therapies (e.g., cimetidine and trimethoprim), the fact that it is an endogenous compound makes a great advantage. The equation depends on serum creatinine concentration and associated measurement limitations, plus tubular secretion of creatinine which results in overestimation of GFR by up to 20% in individuals with stages 2-4 CKD. Despite these limitations, the Cockcroft-Gault equation remains the most appropriate method to determine drug dosage individualisation based on kidney functions in clinical settings.³⁹

Cockcroft-Gault equation⁴⁰ is given as follows:

If male:

$$\text{Creatinine Clearance } (Cl_{cr}) = \frac{(140 - \text{age}) \times \text{weight}}{72 \times S_{cr}}$$

If female:

$$\text{Creatinine Clearance } (Cl_{cr}) = \frac{(140 - \text{age}) \times \text{weight}}{72 \times S_{cr}} \times 0.85$$

Where Cl_{cr} is expressed in millilitres per minute, age in years, weight in kilograms and serum creatinine (S_{cr}) in milligrams per decilitre.

If SI units (µmol/litre) are used instead of conventional units (mg/dL), the calculation is based on the relationship: 88.4 µmol/litre = 1 mg/dL.

If the patient is obese, the formula for ideal body weight is used as shown:

$$IBW \text{ male} = 50kg + (2.3kg \times \text{number of inches over 5 feet})$$

It can be adjusted to *BSA* where Cl_{cr} (mL/min/1.73m²) = [Cockcroft-Gault equation] x 1.73m²/*BSA*

$$BSA = (\text{weight in kg})^{0.425} \times (\text{height in cm})^{0.725} \times 0.007184$$

Estimated GFR using MDRD Equation

The traditional approach of estimating creatinine clearance and using it as a continuous variable of kidney function is now being replaced by estimation of GFR as a categorical variable for CKD staging. An abbreviated version of the MDRD (MDRD4) equation was introduced in 2000, and has demonstrated excellent precision and accuracy in the prediction of GFR. This equation is referred to as eGFR.³⁹

The MDRD4 study equation⁴¹ is given as follows:

If male:

$$eGFR = 186 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times 1.212 \text{ if the male is black}$$

If female:

$$eGFR = 186 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times 0.742 \times 1.212 \text{ if the female is black}$$

Where *eGFR* is expressed in millilitres per minute per 1.73m², age in years and serum creatinine (*S_{cr}*) in milligrams per decilitre.

The validity of this equation for clinical use in all patient settings and use as a guide for drug dosage adjustment is controversial. This equation has not been validated in children, pregnant women, the elderly (>70 years) and racial or ethnic subgroups other than Caucasians and African Americans. Because the eGFR equation provides less

Table 2. Medication That Can Cause Drug-induced Renal Dysfunction and Sites of Toxicity

Pre-renal Injury	Ciprofloxacin	Glomerular Injury
ACE inhibitors	Cyclosporine	Captopril
Angiotensin II receptor blockers	Diuretics	Foscarnet
Amphotericin B	Gold	Gold
COX-2 inhibitors	Indinavir	Interferon α
Cyclosporine	Lithium	Lithium
Diuretics	Methyldopa	Mefenamate
Interferon	NSAIDs	Mercury
Interleukin-2	Omeprazole	NSAIDs
NSAIDs	Penicillamine	Pamidronate
Radiocontrast media	Penicillins	Pencillamine
Tacrolimus	Phenobarbital	
Vasodilators	Phenytoin	Obstructive Nephropathy
	Propylthiouracil	Intratubular Obstruction
Intrinsic Renal Injury	Radiocontrast media	Acyclovir
Acute Tubular Necrosis	Ranitidine	Foscarnet
Aminoglycosides	Rifampin	Gancyclovir
Amphotericin B	Sulfonamides	Indinavir
Cisplatin	Triamtrene	Methotrexate
Cocaine	Valproic acid	Sulfonamides
Dextran	Vancomycin	Triamterene
Foscarnet	Warfarin	Ureteral Obstruction
Fosfamide	Vascular Effects	Atenolol
Hydroxyethyl starch	<i>Thrombotic Microangiopathy</i>	Dihydroergotamine
Immunoglobulin	Bleomycin	Ergotamine
Lithium	Cisplatin	Hydralazine
Mannitol	Clopidogrel	Methyldopa
Outdated Tetracycline	Cocaine	Methylsergide
Pentamidine	Conjugated estrogens	Pindolol
Radiocontrast media	Cyclosporine	
Sucrose	5-Fluorouracil	Chronic Renal Failure
Allergic Interstitial Nephritis	Gemcitabine	Chronic analgesic abuse
Acetaminophen	Interferon	Cisplatin
Acyclovir	Mitomycin C	Cyclosporine
Allopurinol	Quinine	Ifosfamide
Aminoglycosides	Tacrolimus	Lithium
Amphotericin B	Ticlopidine	Mesalamin
ACE inhibitors	<i>Cholesterol Emboli</i>	Nitrosourea
Aztreonam	Heparin	Tacrolimus
Carbamazepine	Streptokinase	
Cephalosporins	Tissue plasminogen activators	
Cimetidine	Warfarin	

precise estimates of GFR in patients with normal kidney function and stage 1 and 2 CKD, it is recommended that reporting eGFR results be reserved for patients with eGFR <60 mL/min/1.73m².³⁹

The MDRD4 Study equation, which estimates GFR, is more accurate than creatinine clearance determined from estimating formulas like Cockcroft-Gault or timed urine collection for identifying and staging CKD. To date, for dosing purposes there has been no comparison of the clinical impact on drug dose adjustment between current practice (mainly Cockcroft-Gault) and the MDRD4 study equation. When calculating appropriate drug doses we can't generally deviate from the Cockcroft-Gault equation because we are locked into whatever the pharmaceutical manufacturers recommend. In the future, manufacturers may provide new dosing guidelines based on estimated GFR using the MDRD4 equation.^{42,43}

(iii) Review the Medication List

This is to ensure that all drugs have specific indications and to evaluate for potential drug interactions and adverse drug reactions. For patients with CKD, medications should be reviewed frequently to ensure that their doses are still suitable to the degree of renal functions and to avoid toxicity especially in patients with rapidly declining kidney function.^{4,6,37}

(iv) Choose the Drug that has no or Minimal Nephrotoxicity

In chronic renal failure, the remaining functional nephron units work harder to compensate for the loss of other nephrons. These residual nephrons are more susceptible to nephrotoxic injury due to their increased workload.³⁷

If the use of nephrotoxic drug cannot be avoided, then therapeutic drug monitoring and renal function monitoring is mandatory.⁴ Examples of medications that can cause drug-induced renal dysfunction and sites of toxicity are in Table 2.⁴⁴⁻⁴⁷

(v) Select Loading Doses

These are usually the same as in patients with normal renal functions except for drugs that have a large Vd that is reduced in renal failure as digoxin and aminoglycosides that should be administered with 25% reduction in their loading dose when volume contraction is present. Consider loading dose increase in the presence of significant ECF volume excess for compounds with Vd approximating total body water. Loading dose can be calculated by the following formula {Loading dose = $Vd \times IBW \times Cp$ } where Vd is the volume of distribution (litres per kg), IBW is the ideal body weight (kg), and Cp is the desired plasma concentration (mg per litre).³⁻⁶

(vi) Select a Maintenance Regimen

Table 3. Examples of Drugs that Require Dosage Adjustment or Better to be Avoided in Renal Impairment

ACE inhibitors: captopril, enalapril, lisinopril, perindopril, ramipril
Analgesics: aspirin, morphine, meperidine, NSAIDs, tramadol
Antiarrhythmic agents: N-acetylprocainamide, procainamide
Antibiotics: aminoglycosides, aztreonam, cephalosporins, fluoroquinolones, imipenem, meropenem, nitrofurantoin, penicillins, sulfonamides, vancomycin
Anticoagulants: enoxaparin, tirofiban
Antiepileptics: gabapentin, topiramate, vigabatrin
Antifungals: fluconazole, flucytosine Itraconazole, terbinafine
Anti-gout drugs: allopurinol, colchicine
Antihistamines (H1- blockers): acrivastine, cetirizine, loratidine
Antihistamines (H2-blockers): cimetidine, famotidine, ranitidine
Antineoplastic agents: bleomycin, carboplatin, etoposide, fludarabine, hydroxyurea, methotrexate, nitrosourea
Antiviral drugs: aciclovir, amantadine, didanosine, famciclovir, foscarnet, ganciclovir, lamivudine
Beta-blockers: acebutolol, atenolol, nadolol, sotalol
Diuretics: acetazolamide, amiloride, mannitol, spironolactone, thiazides, triamterene
Fibrates: bezafibrate, clofibrate
Hypoglycaemic agents: acarbose, insulin, metformin, sulfonylureas
Muscle relaxants: alcuronium, metocurine, tubocurarine
Others: digoxin, metoclopramide, pentoxifylline, tranexamic acid

Recommendations for adjusting regimens can be obtained from one of the updated drug information references, the following examples can be useful: the American Hospital Formulary System Drug information,⁴⁸ Martindale: the Complete Drug Reference,⁴⁹ British National Formulary,⁵⁰ Drug Information Handbook,⁵¹ Drug Prescribing in Renal Failure,⁵² and Physician Desk Reference (PDR).⁵³ Unfortunately, different references might give different recommendations, but this should not be a reason to ignore dosage adjustments. We should remember that these recommendations provide only general guidelines for dosing adjustments and must be adapted to a specific patient's situation. Table 3 includes examples of some drugs that require dosage adjustment in renal impairment.

(vii) Monitor Outcomes

Varying the dose or dosing interval for medications may not be sufficient to guarantee therapeutic efficacy and avoid toxicity. If monitoring drug levels is available to guide therapy, it should be done. For some drugs with a narrow therapeutic index and renal elimination (e.g., aminoglycosides, digoxin), dosage regimen adjustments based on serum concentrations are useful. The dose of

certain drugs may be titrated based on pharmacodynamic response. This is appropriate for drugs that have a clear dose response relationship. Antihypertensive drugs, vasopressors and certain antiarrhythmic drugs fall into this category. Clinical pharmacists who have developed confidence and skill in using pharmacokinetics as a clinical tool, will be able to participate in this interdisciplinary approach to individualised patient care.^{3,37}

REFERENCES

- Macgregor MS, Boag DE, Innes A. Chronic kidney disease: evolving strategies for detection and management of impaired renal function. *Q J Med* 2006;99:365-75.
- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Available at: http://www.kidney.org/professionals/KDOQI/guidelines_ckd/toc.htm. Accessed 4 March 2009.
- Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. *West J Med* 1992;156:633-8.
- Kappel J, Calissi P. Safe drug prescribing for patients with renal insufficiency. *CMAJ* 2002;166:473-7.
- Gabardi S, Abramson S. Drug dosing in chronic kidney disease. *Med Clin North Am* 2005;89:649-87.
- Perazella MA, Parikh C. Pharmacology. *Am J Kidney Dis* 2005;46:1129-39.
- Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am J Kidney Dis* 2003;42:906-25.
- Manley HJ, Cannella CA, Bailie GR, St Peter WL. Medication-related problems in ambulatory hemodialysis patients: A pooled analysis. *Am J Kidney Dis* 2005;46:669-80.
- Manley HJ, Debra K, Drayer DK, Richard S, Muther RS. Medication-related problem type and appearance rate in ambulatory hemodialysis patients. *BMC Nephrology* 2003;4:10.
- Fijn R, Bemt VD, Chow M, De Blaey CT, De Jong-Van den Berg LT, Brouwers JR. Hospital prescribing errors: epidemiological assessment of predictors. *Br J Clin Pharmacol* 2002;53:326-31.
- Fattinger K, Roos M, Verge'eres P, Holenstein C, Kind B, Masche U, et al. Epidemiology of drug exposure and adverse drug reactions in two swiss departments of internal medicine. *Br J Clin Pharmacol* 2000;49:158-67.
- Bonk ME, Krown H, Matuszewski K, Oinonen M. Potentially inappropriate medications in hospitalized senior patients. *Am J Health Syst Pharm* 2006;63:1161-5.
- Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a south Indian hospital – their severity and cost involved. *Pharmacoepidemiol Drug Safe* 2003;12:687-92.
- Van Dijk EA, Drabbe NR, Kruijtbosch M, De Smet P. Drug dosage adjustments according to renal function at hospital discharge. *Ann Pharmacother* 2006;40:1254-60.
- Nightingale PG, Adu D, Richards NT, Peters M. Implementation of rules based computerized bedside prescribing and administration: intervention study. *BMJ* 2000;320:750-3.
- Long CL, Raebel MA, Price DW, Magid DJ. Compliance with dosing guidelines in patients with chronic kidney disease. *Ann Pharmacother* 2004;38:853-8.
- Blix HS, Viktil KK, Moger TA, Reikvam A. Use of renal risk drugs in hospitalized patients with impaired renal function – an underestimated problem? *Nephrol Dial Transplant* 2006;21:3164-71.
- Dooley MJ, Allen KM, Doecke CJ, Galbraith KJ, Taylor GR, Bright J, et al. A prospective multicentre study of pharmacist initiated changes to drug therapy and patient management in acute care government funded hospitals. *Br J Clin Pharmacol* 2003;57:513-21.
- Bonapace CR, White RL, Friedrich LV, Bosso JA. Differences in antimicrobial drug exposures in patients with various degrees of renal function based on recommendations from dosing references. *Pharmacotherapy* 2002;22:1097-104.
- Preston SL, Briceland LL, Lomaestro BM, Lesar TS, Bailie GR, Drusano GL. Dosing adjustment of 10 antimicrobials for patients with renal impairment. *Ann Pharmacother* 1995;29:1202-7.
- Salomon L, Deray G, Jaudon MC, Chebassier C, Bossi P, Launay-Vacher V, et al. Medication misuse in hospitalized patients with renal impairment. *Int J Qual Health Care* 2003;15:331-5.
- Pillans PI, Landsberg PG, Fleming AM, Fanning M, Sturtevant JM. Evaluation of dosage adjustment in patients with renal impairment. *Intern Med J* 2003;33:10-3.
- Yap C, Dunham D, Thompson J, Baker D. Medication dosing errors for patients with renal insufficiency in ambulatory care. *Jt Comm J Qual Patient Saf* 2005;31:514-21.
- Salomon L, Levu S, Deray G, Launay-Vacher V, Brucker G, Ravaud P. Assessing residents' prescribing behavior in renal impairment. *Int J Qual Health Care* 2003;15:235-40.
- Chertow GM, Lee J, Kumperman GJ, Burdick E, Horsky J, Seger DL, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001;286:2839-44.
- Mangino PD. Role of the pharmacist in reducing medication errors. *J Surg Oncol* 2004;88:189-94.
- Galanter WL, Didomenico RJ, Polikaitis A. A trial of automated decision support alerts for contraindicated medications using computerized physician Order entry. *J Am Med Inform Assoc* 2005;12:269-74.
- Walton R, Dovey S, Harvey E, Freemantle N. Computer support for determining drug dose: systematic review and metaanalysis. *BMJ* 1999;318:984-90.
- Munroe WP, Kunz K, Israel CD, Potter L, Schonfeld WH. Economic evaluation of pharmacist involvement in disease management in a community pharmacy setting. *Clin Ther* 1997;19:113-23.
- Hawksworth GM, Corlett AJ, Wright DJ, Chrystyn H. Clinical pharmacy interventions by community pharmacists during the dispensing process. *Br J Clin Pharmacol* 1999;47:695-700.
- Kaboli PJ, Hoth AB, Meclimon BJ, Schnipper JL. Clinical pharmacists and inpatient medical care. *Arch Intern Med* 2006;166:955-64.
- Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-70.
- Kucukarslan SN, Peters M, Mlynarek M, Nafziger DA. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Arch Intern Med* 2003;163:2014-8.
- Gandhi PJ, Smith BS, Tataronis GR, Mass B. Impact of a pharmacist on drug costs in a coronary care unit. *Am J Health Syst Pharm* 2001;58:497-503.
- Falconnier AD, Haefeli WE, Schoenenberger RA, Surber C, Martin-Facklam M. Drug dosage in patients with renal failure optimized by immediate concurrent feedback. *J Gen Intern Med* 2001;16:369-75.
- Joy MS, DeHart RM, Gilmartin C, Hacheg DM, Hudson JQ, Pruchnicki M, et al. Clinical pharmacists as multidisciplinary health care providers in the management of CKD: A joint opinion by the nephrology and ambulatory care practice and research networks of the American college of clinical pharmacy. *Am J Kidney Dis* 2005;45:1105-18.

37. Kilian R, Kliniken L. Drugs, renal failure and the clinical pharmacist. *Eur J Hosp Pharmacy* 2004;2:18-23.
38. Hodgkinson B, Koch S, Nay R, Nichols K. Strategies to reduce medication errors with reference to older adults. *Int J Evid Based Healthc* 2006;4:2-41.
39. Pharmacotherapy Self-assessment Program, Nephrology. Book 2. 6th ed. American College of Clinical Pharmacy, 2007.
40. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
41. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). *J Am Soc Nephrol* 2000;11:155A.
42. Spruill WJ, Wade WE, Cobb HH. Estimating glomerular filtration rate with a modification of diet in renal disease equation: implications for pharmacy. *Am J Health Syst Pharm* 2007;64:652-60.
43. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function -measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473-83.
44. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. *Nat Clin Pract Nephrol* 2006;2:80-91.
45. Guo X, Nzerue C. How to prevent, recognize, and treat drug-induced nephrotoxicity. *Cleve Clin J Med* 2002;69:289-312.
46. Taber S, Mueller B. Drug-associated renal dysfunction. *Crit Care Clin* 2006;22:357- 74.
47. Wells BG, DiPiro JT, Schwinghammer T, Hamilton C. *Pharmacotherapy Handbook*. 6th ed. McGraw-Hill Medical, 2005.
48. McEvoy GK, Miller J, Snow EK, Welsh OH, Litvak K, editors. *American Hospital Formulary System (AHFS) Drug Information* 2008. Bethesda: American Society of Health System Pharmacists, 2008.
49. Sweetman SC, editor. *Martindale: The Complete Drug Reference*. 35th ed. London: Pharmaceutical Press, 2007.
50. Joint Formulary Committee. *British National Formulary*. 56th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2008.
51. Lacy CF, Armstrong LL, Goldman MP, Lance LL. *Drug Information Handbook*. 17th ed. International. Cleveland: American Pharmaceutical Association, 2008.
52. Aronoff GR, Berns JS, Brier ME, Golpher TA, Morrison G, Singer I, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*, 5th ed. Philadelphia: American College of Physicians, 2007. Available at: <http://www.kdp-baptist.louisville.ed>. Accessed 4 March 2009.
53. Medical Economics Staff. *Physician's Desk Reference (PDR)*. 62th ed. Thomson, 2008.