Nephrology: 3. Safe drug prescribing for patients with renal insufficiency

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Case

Ms. J is a 33-year-old woman with type 1 diabetes mellitus who weighs 65 kg. She presents with an infected ulcer on her right foot. She is febrile, has obvious lymphangitic spread to her knee, palpable groin nodes and an elevated leukocyte count with a neutrophilic shift. Her complications of diabetes include proliferative retinopathy, peripheral neuropathy and nephropathy. The patient's serum creatinine before this recent illness was 150 μmol/L. You have chosen to prescribe a fluoroquinolone and metronidazole intravenously. Are antibiotic dose adjustments required for this patient? How would you rapidly calculate creatinine clearance?

The number of people with end-stage renal disease (ESRD) in Canada is increasing. In 1999, 142 individuals per million population were receiving renal replacement therapy, which is an increase from 83 per million population in 1990.[1] The leading cause of ESRD is diabetes (30%) followed by renal vascular disease, including hypertension (20%). Over the past decade, the number of older Canadians (aged ≥ 65 years) with ESRD has more than doubled.[1] Unfortunately, the number of people who have some degree of renal insufficiency, but have yet to need renal replacement therapy, is not fully known. Those groups at risk for developing renal impairment include individuals with diabetes, elderly people, those with hypertension, certain ethnic groups (i.e., Aboriginal people) and individuals with atherosclerotic disease elsewhere, autoimmune and genetic diseases, or a family history of renal disease. The third National Health and Nutrition Examination Survey (NHANES III) estimated that 14.7 million people in the United States had renal insufficiency.[2] Based on these data, one could estimate that there are about 1.5 million Canadians with renal insufficiency.

On average, patients with renal insufficiency are taking at least 7 different medications to manage not only their underlying disease (such as diabetes) but also the symptoms related to their renal impairment (i.e., problems with mineral metabolism, anemia).[3,4] The frequency of adverse drug reactions increases with the number of medications used, the degree of renal dysfunction, the age of the patient and the number of comorbid conditions.[5,6] As the kidney is a major organ of drug elimination, some knowledge of basic pharmacologic principles and a systematic approach to patients with renal insufficiency are necessary to ensure safe and effective patient care.

Diagnosis of renal insufficiency

All patients who are at risk for renal insufficiency should have their renal function assessed as part of their periodic health examination. At the very least, serum creatinine should be tested, recognizing that measuring serum creatinine alone will fail to diagnose abnormal function in 35% of people aged 40–49 years and 92% of people more than 70 years old.[7] A more accurate reflection of renal function is creatinine clearance. Guidelines for the investigation of newly diagnosed renal insufficiency exist elsewhere.[8] For patients with established renal insufficiency, a thorough history-taking, physical examination and certain basic laboratory tests are essential to identify individuals who may require adjustments to their medication.

The patient's history should include a record of current medications, including over-the-counter drugs, recreational drugs, alcohol use, and drug sensitivities or allergies, and comorbid conditions such as diabetes, liver disease or congestive heart failure. The physical examination should include measurement of height, weight and extracellular volume status (blood pressure and heart rate with orthostatic changes, jugular venous pulse, edema, ascites, lung crackles) and a search for signs of chronic liver disease.

The history and physical examination will frequently point to factors that can affect drug pharmacokinetics, including alterations in drug absorption and bioavailability, distribution, metabolism and excretion (Table 1).[9-12]

Determination of a patient's 24-hour creatinine clearance by urine collection, or by estimation using the Cockcroft–Gault formula (Table 2),[13] will confirm the degree of suspected renal insufficiency and frequently assist with safer drug prescribing.

Management

Once a physician has identified a patient with renal insufficiency and has recognized which of a drug's pharmacokinetic factors may be affected, a stepwise approach is important when prescribing drug therapy. This will help ensure the effectiveness of medication, avoid or minimize further kidney damage, and prevent drug nephrotoxicity

(Table 3).[14] It is important to note that these steps provide a framework for dosage adjustments and must be modified on an individual basis.

The number of adverse drug reactions experienced by patients with renal insufficiency can be decreased if drugs are used for specific indications, potentially nephrotoxic drugs are avoided, medication lists are continuously updated and there is an awareness of potential drug interactions. Response to drug therapy may be variable, and adverse drug reactions may occur quickly. Some of the more common drugs that require or do not require dose modification in patients with renal insufficiency are listed in Table 4.[15,16] Information about commonly used drugs that require special consideration in this group of patients is provided in Table 5.[3,6,15,16]

Complementary products, which are variably called herbal medicines, naturopathic remedies and phytomedicines, are becoming very popular. The practitioner should have some basic knowledge of the potential interactions with prescribed medications or simple adverse consequences in the patient with renal insufficiency. Some examples of herbal products that should be avoided by patients with renal insufficiency are listed in Table 6. Comprehensive accounts of herbal medicines may be found elsewhere.[17–21]

Case revisited

Using the Cockcroft–Gault formula for creatinine clearance, you calculate Ms. J's creatinine clearance to be 48 mL/minute (0.8 mL/second), which is reduced. You decide that the dose of metronidazole does not require any alteration, because it is hepatically metabolized. The recommended dose is 500 mg orally or intravenously every 8 hours. However, the dose of the fluoroquinolone taken intravenously needs to be reduced and after consulting the

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Table 1: Effect of renal insufficiency on drug pharmacokinetics

Absorption and bioavailability[9,10]
Bioavailability is defined as the percentage of an administered drug dose that reaches the central circulation. It is limited by first-pass hepatic metabolism and:

Gastrointestinal transit time:	Diabetic or uremic gastroparesis, or both, can alter rates of absorption of drugs such as short-acting sulfonylureas.
Gastric pH:	Medications that alter gastric acidity, such as histamine$_2$ blockers, can reduce the absorption of drugs such as iron and ketoconazole.
Gastrointestinal tract edema:	Edema caused by congestive heart failure, liver cirrhosis or nephrotic syndrome can slow drug absorption (i.e., absorption of furosemide).
Vomiting and diarrhea:	Common in renal failure, these reduce the amount of drug absorbed.
Antacids or cholestyramine:	Commonly taken by patients with renal failure, these can decrease the absorption of warfarin and digoxin.

Drug distribution[6,11,12]
Volume of distribution (Vd) is defined as the amount of drug in the body divided by the plasma concentration. Vd can be altered by:

Lipid v. water solubility:	Edema or ascites may increase Vd for protein-bound or water-soluble drugs such as vancomycin (possibly requiring a larger loading dose to achieve therapeutic drug concentrations).
Plasma protein drug binding:	Uremic states can alter plasma protein binding, affecting acidic drugs like phenytoin, valproic acid and ASA. Hypoalbuminemia and altered plasma protein binding can result in an increase in free or unbound concentrations of drugs such as phenytoin. Because assays for phenytoin measure total plasma concentrations and not the free fraction, patients with renal impairment who are taking this drug may have adequate seizure control at subtherapeutic concentrations, or conversely may show signs of toxicity at phenytoin concentrations within the usual therapeutic range.
Tissue protein drug binding:	Tissue protein binding is reduced in uremic states, which can decrease the Vd for drugs like digoxin.

Metabolism[6,11]
Metabolism can be affected by:

Hepatic biotransformations:	These can be increased, decreased or unchanged by renal insufficiency, and doses of metabolized drugs such as propranolol and dihydrocodeine should be adjusted accordingly.

Excretion[6,11]
Excretion is the most important pharmacokinetic factor altered in renal insufficiency by:

Glomerular filtration, tubular secretion, reabsorption:	Net renal excretion of a drug is a composite of these 3 factors. Generally it is assumed that all 3 decline in a parallel manner. Creatinine clearance is, therefore, the guiding factor for drug dosage.

Table 2: Cockcroft–Gault formula for creatinine clearance (CrCl)[13]

Men: $\text{CrCl (mL/min)} = \dfrac{(140 - \text{age [yr]}) \times \text{weight (kg)}}{\text{SCr (μmol/L)} \times 0.81}$

Women: $\text{CrCl (mL/min)} = 0.85 \times \text{CrCl (men)}$

This formula is for adults with stable renal function and takes into account increased creatinine production with increasing weight and decreased creatinine production with increasing age. It will overestimate the true glomerular filtration rate (GFR), but it is important to appreciate that in most clinical settings exact knowledge of the true GFR is not required. Creatinine clearance formulas for pediatric care and for individuals with unstable renal function can be found in Lam and colleagues.[3] There are many variations of the Cockcroft–Gault formula. The one presented here is simply the one we use.

Ranges of normal and decreased creatinine clearance (SI units):

Normal renal function		
Men	95–145 mL/min	(1.58–2.42 mL/s)
Women	75–115 mL/min	(1.25–1.92 mL/s)
Mild renal insufficiency*	50–70 mL/min	(0.83–1.17 mL/s)
Moderate renal insufficiency*	25–50 mL/min	(0.42–0.83 mL/s)
Severe renal insufficiency*	< 25 mL/min	(< 0.42 mL/s)

Note: SCr = serum creatinine.
*Please note that there is considerable controversy regarding what constitutes mild, moderate and severe renal insufficiency. It is also important to note that creatinine clearance declines by 1 mL/min per year (0.02 mL/s per year) after the age of 40 years. Therefore, these guidelines are for women and men aged < 65 years.

Compendium of Pharmaceuticals and Specialties[14] product monograph, you give ciprofloxacin 400 mg intravenously every 24 hours. An order is written for a repeat test of Ms. J's serum creatinine in 48 hours. Her medication list is reviewed, and no drug interactions are identified.

Comment

Safe drug prescribing for patients with renal insufficiency can be complex, but with the application of a stepwise approach the difficulties can be minimized. When in doubt, appropriate information for dosing guidelines should be sought in recently published monographs or texts.

Key points

- Identify those patients at risk for renal insufficiency
- Measure serum creatinine and either calculate or measure creatinine clearance
- Consider whether the patient's medications should be altered because of the patient's renal insufficiency
- Adjust drug doses if required
- Use the least nephrotoxic drug possible
- Monitor drug levels and renal function
- Keep up-to-date medication lists and be aware of complementary medicines

Table 3: Stepwise guide to adjusting drug dosages for patients with renal insufficiency

Step 1	Take history and perform physical examination	Record current medications, including over-the-counter drugs, recreational drugs, alcohol use. Drug allergies and sensitivities should be noted. Physical examination should include the following: height, weight, extracellular volume status (jugular venous pulse, blood pressure and heart rate with orthostatic changes, edema, ascites, lung crackles) and look for signs of chronic liver disease.
Step 2	Determine the degree of renal insufficiency	Measure serum creatinine. Order 24-hour urine collection or calculate creatinine clearance.
Step 3	Review the medication list	Ensure that all drugs are still required and that new medications have specific indications. Evaluate for potential drug interactions.
Step 4	Choose less nephrotoxic drugs	If the use of nephrotoxic drugs cannot be avoided without patient morbidity or mortality, then therapeutic drug monitoring or monitoring of renal function is mandatory.
Step 5	Select loading doses	These are usually the same for patients with both normal and abnormal renal function.
Step 6	Select a maintenance regimen	Either reduce the dose of the drug and maintain the usual dosing interval or maintain the drug dose and extend the interval. Recommendations for adjusting regimens can be obtained in the *Compendium of Pharmaceuticals and Specialties* (CPS)[14] product monographs. Remember to titrate the dose of the drug to patient effect, if applicable. For example, antihypertensives are dosed based upon blood pressure control, whereas antimicrobials are not adjusted according to response.
Step 7	Monitor drug levels	Monitor drug levels if monitoring is available to guide further therapy.
Step 8	Reassess	Reassess the patient to evaluate drug effectiveness and the need for ongoing therapy. If nephrotoxic drugs are used, remember to check the patient's serum creatinine and creatinine clearance again.

Table 4: Dose modification for patients with renal insufficiency

Drugs requiring dose modification		Drugs not requiring dose modification
All antibiotics	**EXCEPT**	Cloxacillin, clindamycin, metronidazole, macrolides
Antihypertensives		**Antihypertensives**
Atenolol, nadolol, angiotensin-converting-enzyme inhibitors		Calcium channel blockers, minoxidil, angiotensin receptor blockers, clonidine, α-blockers such as prazosin
Other cardiac medications		**Other cardiac medications**
Digoxin, sotalol		Amiodarone, nitrates
Diuretics		**Narcotics**
AVOID potassium-sparing diuretics in patients with creatinine clearance < 30 mL/min (< 0.5 mL/s)		Fentanyl, hydromorphone, morphine (may require dose modification if given in a palliative care setting)
Lipid-lowering agents		**Psychotropics**
HMG–CoA reductase inhibitors, benafibrate, clofibrate, fenofibrate		Tricyclic antidepressants, nefazodone, other selective serotonin reuptake inhibitors
Narcotics		**Hypoglycemia medications**
Codeine, meperidine		Repaglinide, rosiglitazone
Psychotropics		**Miscellaneous**
Lithium, chloral hydrate, gabapentin, trazodone, paroxetine, primidone, topiramate, vigabatrin		Proton pump inhibitors
Hypoglycemia medications		
Acarbose, chlorpropamide, glyburide, gliclazide, metformin, insulin		
Miscellaneous		
Allopurinol, colchicine, histamine$_2$ receptor antagonists, diclofenac, ketorolac, terbutaline		

Table 5: Special considerations for drug use by patients with renal insufficiency

Meperidine	Metabolite normeperidine is neurotoxic and may cause seizures
NSAIDS	Decrease diuretic response and increase propensity to hyperkalemia if taken with potassium-sparing diuretics and angiotensin-converting-enzyme inhibitors
Chlorpropamide	Has increased half-life when taken by patients with renal insufficiency and prolongs hypoglycemia
Metformin	Should not be used if creatinine clearance < 50 mL/min (< 0.83 mL/s) because it can cause life-threatening lactic acidosis
Insulin	There is decreased renal clearance of exogenously administered insulin and, therefore, potential for increased hypoglycemic reactions as creatinine clearance declines.
Aminoglycosides Vancomycin	Dosage adjustment is required, because these drugs will rapidly accumulate in renal insufficiency and are potentially nephrotoxic. Therapeutic drug monitoring is recommended.
Cimetidine Triamterene Trimethoprim	Inhibit tubular secretion of creatinine and therefore cause a rise in serum creatinine, which is reversible when these drugs are discontinued[17]

Table 6: Herbal products that may cause renal problems

Aristolochic acid	Contained in Virginian and Texas snakeroot or in Chinese herbs like *Stephania tetranda* and *Magnolia officinalis*. It causes rapidly progressive fibrosing interstitial nephritis and renal failure. It is also linked to urothelial malignancy.
Barberry	Possibly causes interstitial nephritis
Buchu	Causes renal irritation
Chinese herbal drugs	Contain a variety of herbs, and often aristolochic acid
Juniper	Causes renal fibrosis
Licorice	Is associated with sodium and water retention, hypokalemia and hypertension
Noni juice	Also known as the Och plant (India), Nono (Tahiti), Nonu (Samoa), Nhau (Southeast Asia) and Chinese fruit (Australia), it is associated with hyperkalemia.

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Additional resources

National Kidney Foundation Web site. Available: www.kidney.org (accessed 2002 Jan 16).

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