Prescribing for older people with chronic renal impairment

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Background

Renal function is an important prescribing consideration. On average, glomerular filtration rate declines by about 10 mL/min every 10 years after the age of 40. Renal impairment may cause medicines to accumulate or cause toxicity, especially if the medicine has a narrow therapeutic index.

Objective

To present an overview of prescribing considerations in the primary care setting for patients with chronic renal impairment.

Discussion

Serum creatinine considered in isolation is not a reliable indicator of renal function. The estimated glomerular filtration rate provided in pathology reporting can alert prescribers to possible renal impairment and the need to consider dose adjustments. The Cockcroft-Gault equation should be used to adjust medicine doses. Renal function monitoring is recommended for patients using medicines that can impair renal function or cause nephrotoxicity (eg. NSAIDs, ACEIs, ARBs).

Keywords

renal insufficiency; aged; pharmaceutical preparations/ administration and dosage

CPD

The Australian Diabetes, Obesity and Lifestyle (AusDiab) study found that over half of those aged more than 65 years were estimated to have a glomerular filtration rate (GFR) of less than 60 mL/min.[1] On average, GFR declines by about 10 mL/min every 10 years after the age of 40.[2,3] While this means renal impairment is common in older age, renal impairment is an independent risk factor for cardiovascular disease and all cause mortality,[4,5] and should not be viewed as a routine part of ageing.[6] Monitoring is important, as up to 90% of renal function can be lost before clinical symptoms of renal failure become apparent.[7] Renal impairment can impact the safety and efficacy of medicine treatment, and is often implicated in medicine-related hospitalisations.[8]

It is important to have an estimate of a patient's renal function before prescribing medicines that are renally excreted or that impair renal function or cause nephrotoxicity, such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Some medicines that can accumulate in renal impairment are also nephrotoxic. Patients with pre-existing renal impairment may be more susceptible to nephrotoxicity[9] and contrast-induced nephropathy.[10] Renal function testing should also be performed when there are signs or symptoms suggestive of toxicity or an adverse reaction, after recent hospitalisation, or during/after episodes of dehydration.

Renal function monitoring is important, regardless of how long a medicine has been used, as dose adjustments may be necessary as the patient ages. Conversely, dose reductions on the presumption of impairment without confirmation may result in subtherapeutic dosing in patients with normal renal function.[11] No medicines, including those marketed as complementary medicines, have been proven to directly protect against renal function decline. However, blood pressure control and blockade of the renin-angiotensin system may retard the decline of renal function in those with pre-existing disease, especially diabetes.[12,13]

How to estimate renal function

Measurement of serum creatinine alone is not a reliable indicator of renal function and should not be used in isolation for the purpose of prescribing medicines safely. Before prescribing, it is advised to have a recent estimate of the patient's GFR by testing for serum creatinine (eg. urea, electrolytes and creatinine). All Australian pathology practices report estimated GFR (eGFR) in conjunction with serum creatinine. Most pathology laboratories now calculate eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula rather than the Modification of Diet in Renal Disease equation.[6] The eGFR can alert prescribers to possible renal impairment and the need to consider dose adjustments of medicines.

The Therapeutic Goods Administration currently recommends using the Cockcroft-Gault (CG) equation to adjust medicine doses.[14] At present, most dosing recommendations in renal impairment are based on the manufacturer's data obtained using either measured GFR or the CG equation.[6] The CG equation uses serum creatinine – adjusted for gender, weight and age – to calculate an estimate of creatinine clearance.[15] Most prescribing software packages include calculators for the CG equation. No calculated estimate of renal function (eGFR or CG based) is relevant for people receiving dialysis. Both the CKD-EPI and CG equations produce less reliable results in situations (including malnutrition) with extremes of age and body weight, and when serum creatinine is rapidly changing.[6,16]

Medicines that accumulate in renal impairment

Renal impairment may cause medicines or their metabolites to accumulate. This may result in toxicity, especially if the medicine has a narrow therapeutic index (eg. digoxin, lithium).[17] Potential adverse effects can be prevented by reducing the dose, extending the dose interval, or by prescribing an alternative medicine that is less likely to accumulate.[18] If after review a medicine is deemed unnecessary, it may be ceased.

A number of medicines commonly prescribed in general practice may require dose modification on the basis of renal function monitoring (*Table 1*). Evidence suggests that the need for dose adjustment in renal impairment is not always recognised.[19,20] In addition, some hepatically metabolised medicines re-enter systematic circulation before excretion, as polar metabolites or conjugates that are ultimately excreted by the kidneys. Fixed-dose combination products may also contain one or more active ingredients that are renally excreted (eg. metformin-glibenclamide). The *Australian Medicines Handbook* and product information are sources of guidance about dosing in renal impairment.[15]

Allopurinol

Allopurinol has a renally excreted active metabolite that accumulates in renal impairment and may cause adverse effects if the dose is not adjusted.[18,21] For most older people, a maintenance dose of 100 mg/day is sufficient.[22] An initial dose of 100 mg on alternate days is recommended for patients with a GFR <10 mL/min,[15] or if possible, the medicine should be avoided altogether in this situation.

Bisphosphonates

Most bisphosphonates are generally not recommended for treating osteoporosis in patients with a GFR <30–35 mL/min.[15] The United States Food and Drug Administration has warned about the risk of renal failure associated with zoledronic acid, especially in patients co-prescribed diuretics or other potentially nephrotoxic medicines.[23] The alternative osteoporosis medicines, strontium ranelate and teriparatide, are also not recommended in patients with a GFR <30 mL/min.[15]

Dabigatran

Accumulation of dabigatran in renal impairment may lead to major bleeding and death.[24] Renal function should be assessed in all patients before starting dabigatran, and the medicine is not suitable for patients with a GFR <30 mL/min.[25] For patients taking dabigatran, renal function should be assessed in situations where a decline in renal function is suspected (eg. hypovolaemia, dehydration, concurrent use of nephrotoxic medicines). In older patients or those with moderate renal impairment, renal function should be assessed at least once per year.[25]

Digoxin

Digoxin has a narrow therapeutic index and prolonged elimination half life in older people.[26] For patients with an eGFR of 10–30 mL/min, a daily maintenance dose of 62.5–125 µg is recommended and for patients with a GFR <10 mL/min, a maintenance dose of 62.5 µg once daily or on alternate days is recommended.[15] Trough serum digoxin concentrations should be monitored, particularly when renal function is impaired or rapidly changing. Alterations in serum potassium, magnesium and calcium can also influence the effect of digoxin on the myocardium, and these electrolytes should also be monitored periodically.

Metformin

Accumulation of metformin increases the risk of lactic acidosis, especially in the context of other circumstances where there may be hypoxaemia (eg. acute myocardial infarction, severe infection, respiratory disease, liver disease).[9] Australian guidelines recommend a total maximum daily dose of 2000 mg for patients with a GFR of 60–90 mL/min, and 1000 mg for patients with a GFR of 30–60 mL/min.[15] Metformin is not recommended for patients with a GFR <30 mL/min.

Sulphonylureas

Renal impairment increases susceptibility to hypoglycaemia associated with sulphonylureas and their metabolites. Short-acting sulphonylureas (eg. glicazide, glipizide) are preferred for patients with renal impairment.[15,18] Glipizide does not have an active metabolite and dose reduction is not usually necessary in renal impairment.

Table 1. Medicines that may accumulate and require renal function monitoring*

Analgesics	**Genitourinary**	**Anticoagulant**	**Endocrine**
Codeine	Solifenacin#	Dabigatran	Glibenclamide
Hydromorphone	Sildenafil	Enoxaparin	Glimepiride
Morphine	Tadalafil	Rivaroxaban	Gliptins (saxagliptin, sitagliptin, vildagliptin)
Oxycodone	Tolterodine#		Metformin
Tramadol	Vardenafil		
Neurological	**Psychotropic**	**Cardiovascular**	**Gastrointestinal**
Baclofen	Acamprosate	ACEIs†	H_2-antagonists
Gabapentin	Amisulpride	ARBs†	
Galantamine	Benzodiazepines	Atenolol	**Musculoskeletal**
Levetiracetam	Bupropion	Bisoprolol	Allopurinol
Memantine	Desvenlafaxine	Digoxin	Bisphosphonates
Methysergide	Duloxetine	Fenofibrate	Colchicine
Pramipexole	Lithium		Strontium ranelate
Pregabalin	Paliperidone		Teriparatide
Topiramate	Reboxetine		
Varenicline	Venlafaxine		

* This list does not include antibiotic, antifungal or antiviral medicines, or those medicines predominately used in the hospital setting

Not available on the PBS/RPBS

† Use in renal impairment may increase the risk of hyperkalaemia; monitor potassium levels

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Opioids

Dose reduction of opioids is usually necessary in patients with renal impairment. Many opioids (eg. codeine, tramadol, morphine, hydromorphone) have active metabolites that can accumulate and cause central nervous system or respiratory depression.[27] The initial dose of oxycodone should be reduced in patients with a GFR <30 mL/min.[15] Extended release products (eg. controlled release oxycodone) may be more difficult to titrate to appropriate clinical effect in those with renal impairment, and immediate release products may need to be dosed less frequently. Fentanyl and buprenorphine may be suitable in renal impairment.[28] However, fentanyl patches should not be prescribed to patients who are opioid naive.

Medicines that can reduce renal function or cause nephrotoxicity

There are also a number of commonly used medicines that can impair renal function or cause nephrotoxicity (*Table 2*). These include ACEIs, ARBs and NSAIDs. Acute interstitial nephritis is a very rare adverse effect of proton pump inhibitors (PPIs); but the high volume of PPI prescribing means that PPIs are a leading cause of acute interstitial nephritis in Australia.[29]

Guidance about monitoring renal function for toxicity is available in resources including the *Australian Medicines Handbook* and product information.

ACEIs and ARBs

Even without pre-existing risk factors, ACEIs or ARBs can cause an acute decline in GFR.[9] It is recommended to measure renal function and electrolytes when initiating these medicines, and the tests should be repeated after 1–2 weeks.[15] An acute decline in GFR is not necessarily a reason to discontinue treatment.[30] If the acute decline in GFR is less than 25% below the baseline and stabilises within 2 months then the medicine should be continued. Paradoxically, those with an acute decline in GFR may derive the greatest benefit in terms of renoprotection. If the acute decline in GFR is greater than 25% below baseline then the medicine should be stopped and investigations for bilateral renal artery stenosis performed.[31] Dose adjustment may also be necessary, as renal impairment affects the excretion of most ACEIs.[15] Renal impairment also increases the risk of hyperkalaemia.

NSAIDs

The rate of acute renal failure (ARF) is up to three times higher in NSAID users compared to non-users.[32] The decline in GFR associated with NSAIDs may improve following treatment cessation.[33] Selective cyclooxygenase-2 (COX-2) inhibitors have a similar adverse renal effect profile to non-selective NSAIDs,[34] and caution is still required with these agents. The risk of ARF is further increased when NSAIDs are used together with either loop diuretics or ACEIs/ARBs.[32,35] The combination of diuretics, NSAIDs/COX-2 inhibitors and ACEIs/

Table 2. Medicines associated with renal function decline or nephrotoxicity

ACEIs*
ARBs*
Bisphosphonates
Frusemide#
H_2-antagonists
NSAIDs/COX-2 inhibitors
Penicillamine
Proton pump inhibitors†

* Use in renal impairment may increase the risk of hyperkalaemia; monitor potassium levels

\# Higher doses are often required in renal impairment and may cause decline in renal function; monitor electrolytes

† Acute interstitial nephritis is a very rare adverse effect of proton-pump inhibitors

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ARBs is referred to as the 'triple whammy' and should be avoided.[35] Paracetamol is considered suitable to use in patients with renal impairment.

Other circumstances that require consideration of renal function

Monitoring renal function and serum potassium is recommended when prescribing medicines that increase the risk of hyperkalaemia in patients with renal impairment (eg. amiloride, eplerenone, spironolactone).[15] Monitoring of serum potassium and GFR is recommended in patients taking spironolactone due to the risk of hyperkalaemia. The risk is highest if spironolactone is used with ACEIs, ARBs, NSAIDs, or in patients with diabetes.[18] Spironolactone is best avoided in patients with a GFR <30 mL/min. Potassium supplements should be used with caution in renal impairment, particularly if used in combination with potassium-sparing diuretics or ACEIs. Use of calcitriol in renal impairment is associated with an increased risk of hypercalcaemia, hyperphosphataemia, calciphylaxis and nephrocalcinosis.

Renal impairment may also increase the risk of bleeding, independent of the effects of concurrent medication.[36] Vigilance is needed with prescribing medicines that can increase the risk of bleeding.

Practice points

- Older patients, those with diabetes and those using nephrotoxic medicines are at increased risk of renal impairment.
- Medicines that are renally excreted may accumulate and cause toxicity. Dose reduction may be necessary to avoid potential adverse effects.
- Check renal function before and soon after prescribing a renally excreted or nephrotoxic medicine.
- Use the Cockcroft-Gault equation to adjust medicine doses. The eGFR can be used to alert prescribers to the possibility of renal impairment and prompt consideration of medicine dose adjustments.

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Competing interests: None.

Provenance and peer review: Commissioned; externally peer reviewed.

Acknowledgements

This article is adapted and reproduced from the Veterans' MATES Therapeutic Brief 30. The Australian Government Department of Veterans' Affairs Veterans' MATES Program is provided by the Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia in association with Discipline of General Practice, University of Adelaide; Discipline of Public Health, University of Adelaide; Repatriation General Hospital, Daw Park; NPS – Better choices, Better Health; Australian Medicines Handbook; and Drug and Therapeutics Information Service. Veterans' MATES Program materials are available at www.veteransmates.net.au.

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This work has been produced with the assistance of funding provided by the Australian Government Department of Veterans' Affairs, which has approved the content of this article. However, the views expressed do not necessarily represent the views of the Minister for Veterans' Affairs or the Australian Government Department of Veterans' Affairs. The Commonwealth does not give any warranty nor accept any liability in relation to the contents of this work.

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