



Therapeutic Brief

30

www.veteransmates.net.au

Topic 30: Know your patient's renal function – an important prescribing consideration

Over half of Australians older than 65 years have an estimated glomerular filtration rate (GFR) of less than 60mL/min.¹ On average, GFR declines by about 10mL/min every 10 years after 40 years of age.^{2,3} Up to 90% of renal function can be lost before symptoms become evident.⁴ For many medicines a decline in renal function can profoundly impact upon the safety and efficacy of treatment.

Analysis of the DVA health claims database indicates that 27% of veterans aged 85 years or older did not have a claim for a blood test in the year prior to receiving a medicine that requires renal function monitoring.⁵

Understanding your patient's current renal function is critical when prescribing medicines that are renally excreted. The dose of these medicines will often require adjustment for patients with renal impairment, but the need for dose adjustment is not always recognised.^{6,7} Reduced renal function may cause medicines or their metabolites to accumulate and result in toxicity, especially if the medicine has a narrow therapeutic index (e.g. digoxin, lithium).⁸ Some medicines that undergo hepatic metabolism may also

re-enter systematic circulation before being excreted as polar metabolites or conjugates by the kidney. Doses can be adjusted by reducing the dose, extending the dosing interval, or both.⁹ Alternatively, the medicine may be ceased if after a review it is deemed unnecessary.

Renal function monitoring should also be considered in patients using a medicine that may impair renal function or cause nephrotoxicity (e.g. NSAIDs, ACE inhibitors, angiotensin receptor blockers). Patients with pre-existing renal impairment may be particularly susceptible to nephrotoxicity.¹⁰ Note that no medicine or complementary therapy has been proven to protect against age-related renal function decline.

Inside

- 2 Monitor renal function
- 2 Medicines that accumulate in renal impairment
- 4 Medicines that can reduce renal function or cause nephrotoxicity
- 4 Other medicines that require renal function monitoring
- 4 Further information

Key points

- > Older patients and those with diabetes are at increased risk of renal impairment which may cause medicines to accumulate or cause toxicity.
- > Medicines that are renally excreted may require dose reduction to avoid potential adverse effects.
- > Check renal function has been assessed in patients who have recently started a renally excreted or nephrotoxic medicine, or who have not had a renal function test in the past 12-months.
- > Pathology laboratories provide an estimated GFR (eGFR) in test reports which can be used to assist in medicine dosing decisions. The Cockcroft-Gault equation is a method that can be used to estimate renal function for the purpose of calculating medicine doses.



Monitor renal function

Renal function monitoring is important regardless of how long a medicine has been used. The medicine may require dose adjustment as the patient ages. Conversely, dose reduction based on the presumption of impairment may result in sub-therapeutic dosing in patients with normal renal function.¹¹

Consider renal function assessment when¹²:

- > conducting a periodic review to assess possible age-related decline in GFR;
- > patient experiences dehydration;
- > prescribing a new renally excreted or nephrotoxic medicine;
- > patient experiences symptoms suggestive of toxicity or an adverse drug reaction; or
- > patient has had a recent hospitalisation.

How to estimate renal function

Request a test which includes serum creatinine (e.g. urea, electrolytes and creatinine) from the pathology laboratory. The patient's estimated GFR (eGFR) is provided as part of standard pathology reporting and is based on the Modification of Diet in Renal Disease (MDRD) equation. This equation uses the serum creatinine results, adjusts for specific patient factors but assumes a person is of average body size (body surface area of 1.73m²).⁹ The eGFR can be used to assist in medicine dosing decisions.¹³ The Cockcroft-Gault equation is a method using serum creatinine to estimate renal function and calculate doses.^{12,14-16} Most prescribing software packages include calculators which use this equation.

Note that serum creatinine itself is not a reliable indicator of renal function, and should not be used in isolation. Additionally, no calculated (eGFR or Cockcroft-Gault based) estimate of renal function is relevant for people receiving dialysis. Both estimations produce less reliable results with extremes of age and body weight, and when serum creatinine is rapidly changing.

Medicines that accumulate in renal impairment

There are a number of commonly used and/or problematic medicines that require renal function monitoring in the general practice setting (See table 1). For patients with renal impairment, potential adverse effects can be prevented by avoiding these medicines, adjusting the dose, or considering an alternative.¹¹ Guidance about dosing according to GFR is available in the Australian Medicines Handbook (AMH) and Product Information. When monitoring medicines that can accumulate in renal impairment, it should be noted that some fixed-dose combination medicines contain one or more active ingredients that are renally excreted (e.g. metformin-glibenclamide) and that **some medicines that accumulate in renal impairment are also nephrotoxic.**

Allopurinol

Allopurinol has a renally excreted active metabolite that may accumulate in patients with renal impairment.^{9,17}

For most older people a maintenance dose of 100mg/day will be sufficient.^{12,18}

For patients with a GFR less than 10mL/min an initial dose of 100mg on alternate days is recommended, or the medicine should be avoided.

Bisphosphonates

Australian guidelines suggest that bisphosphonates should not be used for osteoporosis in patients with a GFR less than 30-35mL/min.¹² The United States Food and Drug Administration recently alerted clinicians to the risk of renal failure associated with zoledronic acid, especially in patients co-prescribed diuretics or other potentially nephrotoxic medicines.¹⁹ The other osteoporosis medicines strontium ranelate and teriparatide are not

recommended in patients with a GFR less than 30mL/min.¹² Denosumab may be an appropriate alternative in renal impairment.

Dabigatran

Accumulation of dabigatran in patients with renal impairment may lead to major bleeding events and death.²⁰ The Therapeutic Goods Administration advises that renal function should be assessed in all patients before starting dabigatran.²¹ It should not be used in patients with a GFR less than 30mL/min. For patients taking dabigatran, renal function should be assessed in situations where a decline in renal function is suspected (e.g. low blood volume, dehydration, concurrent use of certain medicines) and in older patients or those with moderate renal impairment, renal function should be assessed at least once per year.²¹

Table 1: Medicines that may accumulate and require renal function monitoring^{a,12}

Analgesics	Genitourinary	Blood	Endocrine	
codeine	solifenacin ^b	dabigatran	glibenclamide	
hydromorphone	sildenafil	enoxaparin	glimepiride	
morphine	tadalafil	rivaroxaban	gliptins (saxagliptin, sitagliptin, vildagliptin)	
oxycodone	tolterodine ^b		metformin	
tramadol	vardenafil ^b			
Neurological	Psychotropic	Cardiovascular	Gastrointestinal	Musculoskeletal
baclofen	acamprosate	ACE-inhibitors ^c	H2-antagonists	allopurinol
gabapentin	amisulpride	angiotensin receptor blockers ^c		bisphosphonates
galantamine	benzodiazepines	atenolol		colchicine
levetiracetam	bupropion	bisoprolol		strontium ranelate
memantine	desvenlafaxine	digoxin		teriparatide
methysergide	duloxetine	fenofibrate		
paliperidone	lithium			
pramipexole	reboxetine			
pregabalin	venlafaxine			
topiramate				
varenicline				

^a this list does not include antibiotic, antifungal or antiviral medicines, or those medicines predominately used in hospital settings

^b not available on the PBS/RPBS

^c use in renal impairment may increase the risk of hyperkalaemia; monitor potassium levels

Digoxin

Renal function monitoring is required for patients using digoxin because it has a narrow therapeutic index and prolonged elimination half-life in older people.²² The dose should be reduced to avoid accumulation in older people. For patients with a GFR from 10-25mL/min, a daily maintenance dose of 62.5-125 micrograms is recommended and for patients with a GFR less than 10mL/min, a daily maintenance dose of 62.5 micrograms is recommended.¹² In situations where renal function is impaired or rapidly changing, the trough serum digoxin concentration should be monitored closely.

Metformin

Metformin may accumulate in people with renal impairment increasing the risk of lactic acidosis, a rare but potentially fatal adverse drug reaction.

The risk may be highest when a patient experiences another hypoxemic condition (e.g. acute myocardial infarction, severe infection, respiratory disease, liver disease).¹⁰ Australian guidelines recommend a maximum daily dose of 2g for patients with a GFR from 60-90 mL/min, and 1g for patients with a GFR from 30-60 mL/min.¹² **Metformin is not recommended for patients with a GFR less than 30mL/min.**

Sulphonylureas

Patients with renal impairment are at increased susceptibility to hypoglycaemia associated with sulphonylureas and their metabolites. **Short-acting sulphonylureas (e.g. glicazide, glipizide) are preferred in patients with renal impairment.**^{9,12} Glipizide does not have an active metabolite and dose reduction is generally not considered necessary in renal impairment.

Opioids

Renal function monitoring should be considered for patients using opioids as a dose reduction is usually necessary in patients with renal impairment. Many opioids (e.g. codeine, tramadol, morphine, and hydromorphone) have active metabolites that can accumulate in patients with renal impairment causing central nervous system and respiratory adverse effects.²³ The dose of oxycodone should also be reduced in patients with a GFR less than 30mL/min. Extended release products (e.g. controlled release oxycodone) may be unsuitable for patients with renal impairment, and immediate release products may need to be dosed less frequently. Fentanyl and buprenorphine may be suitable in renal impairment.^{12,24} 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 which require monitoring (See table 2). Guidance about monitoring renal function for toxicity is available in the AMH and Product Information. This advice is specific for each individual medicine and reflects the nature of the renal function related precaution.

ACE-inhibitors and angiotensin receptor blockers

ACE-inhibitors or angiotensin receptor blockers inhibit the renin-angiotensin-aldosterone system which can lead to an acute decline in GFR of up to 15% from baseline.¹⁰ It is recommended that renal function and electrolytes should be measured before starting an ACE-inhibitor and reviewed after 1-2 weeks.¹² An acute decline in GFR is not necessarily a reason to discontinue treatment if the benefits outweigh the risk (particularly for those with severe

congestive cardiac failure).²⁵ Dose adjustment may also be necessary as renal impairment affects the excretion of most ACE-inhibitors.¹² The risk of hyperkalaemia is also increased in patients with renal impairment.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The rate of acute renal failure (ARF) is up to three times higher in NSAID users compared to non-users.²⁶ The risk of ARF is further increased among concomitant users of NSAIDs with either loop diuretics or ACE inhibitors/angiotensin receptor blockers.^{26,27} Decline in GFR associated with NSAIDs may improve following treatment cessation.²⁸ Selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) have a similar adverse renal effect profile to non-selective NSAIDs.²⁹ The alternative analgesic paracetamol is considered safe to use in patients with renal impairment.

Table 2: Medicines associated with renal function decline or nephrotoxicity^{10,12}

- ACE-inhibitors^a
- angiotensin receptor blockers^a
- bisphosphonates
- frusemide^b
- H₂-antagonists
- NSAIDs/Cox-2 inhibitors
- penicillamine
- proton-pump inhibitors

^a use in renal impairment may increase the risk of hyperkalaemia; monitor potassium levels

^b higher doses are often required in renal impairment and may cause decline in renal function; monitor electrolytes



Other medicines that require renal function monitoring

A number of other medicines (e.g. amiloride, eplerenone, and spironolactone) may increase the risk of hyperkalaemia when used in patients with renal impairment. Clinicians are advised to monitor renal function and potassium levels when prescribing these medicines.¹² As the use of calcitriol in patients with renal impairment may increase the risk of hypercalcaemia, hyperphosphataemia, and nephrocalcinosis, plasma calcium and phosphate levels should be monitored.

Spironolactone

Due to the risk of hyperkalaemia, consider renal function monitoring for patients using spironolactone. This is particularly the case if spironolactone is used together with ACE-inhibitors and angiotensin receptor blockers, NSAIDs or in patients with diabetes.⁹ It is recommended that the serum potassium and GFR should be closely monitored. Spironolactone is best avoided in patients with a GFR less than 30mL/min.

Consider a medicines review* for patients with renal impairment. The accredited pharmacist can:

- help identify the possible need for dose reduction of renally excreted medicines
- help provide patient education if medicine doses have changed.

When referring a patient, providing the pharmacist with recent laboratory test results, including eGFR and serum creatinine will assist in the generation of a more meaningful report.

* either a Home Medicines Review (HMR) or a Residential Medication Management Review (RMMR)



Further information:

- Kidney Health Australia www.kidney.org.au
- Royal College of Pathologists of Australasia Manual www.rcpamannual.edu.au

Full reference list available at: www.veteransmates.net.au



Topic 30

Know your patient's renal function – an important prescribing consideration

Full reference list for Therapeutic Brief

- Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: The AusDiab kidney study. *J Am Soc Nephrol* 2003; 14: S131–8.
- Stevens LA, Coresh J, Greene T, et al. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354: 2473–83.
- Porush JG, Faubert PF. Renal disease in elderly patients. *Rev Clin Gerontol* 1997; 7: 299–307.
- Australian Institute of Health and Welfare. An overview of chronic kidney disease in Australia. 2009. Available at: <http://www.aihw.gov.au/publication-detail/?id=6442468245> Accessed October 26, 2011.
- DVA Health Claims Database. University of South Australia. Quality Use of Medicines and Pharmacy Research Centre. Accessed June, 2011.
- Rahimi AR, Kennedy K, Thomason M, et al. Improper renal dosing in long-term care facilities. *South Med J* 2008; 101: 802–5.
- Hanlon JT, Wang X, Handler SM, et al. Potentially inappropriate prescribing of primarily renally cleared medications for older veterans affairs nursing home patients. *J Am Med Dir Assoc* 2011; 12: 377–83.
- Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004; 57: 6–14.
- Faull R, Lee L. Prescribing in renal disease. *Aust Prescr* 2007; 30: 17–20.
- Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. *Am Fam Physician* 2007; 75: 1487–96.
- Chakrabarti S, Chattopadhyay I. Measuring renal function in old age. *Rev Clin Gerontol* 2008; 18: 257–67.
- Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd.
- Kidney Health Australia. 2011. Available at: <http://www.kidney.org.au/HealthProfessionals/eGFRClinicalTools/tabid/632/Default.aspx> Accessed December 10, 2011.
- Royal College of Pathologists of Australasia. RCPA Manual. 2010. Available at: <http://www.rcpamanual.edu.au/> Accessed November 27, 2011.
- National Prescribing Service. Automatic eGFR reporting – its role in screening for kidney disease and drug-dosing decisions. 2008. Available at: http://www.nps.org.au/_data/assets/pdf_file/0009/59967/Automatic_eGFR_reporting_151_its_role_in_screening_for_kidney_disease_and_drug-dosing_decisions_-_RADAR_Aug_08_To_print.pdf Accessed September 29, 2011.
- Hanlon JT, Aspinall SL. Renal function equations to use to guide prescribing of primarily renally cleared medications for older adults. *J Am Med Dir Assoc* 2011; Aug 10 [Epub ahead of print].
- Fravel MA, Ernst ME. Management of gout in the older adult. *Am J Geriatr Pharmacother* 2011; 9: 271–85.
- Australian Government Department of Veterans' Affairs. Veterans' MATES Therapeutic Brief 21: Revisiting gout management in your veteran patients. 2009. Available at: www.veteransmates.net.au Accessed November 28, 2011.
- United States Food and Drug Administration. Reclast (zoledronic acid): drug safety communication - new contraindication and updated warning on kidney impairment. 2011. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm270464.htm> Accessed October 31, 2011.
- Legrand M, Mateo J, Aribaud A, et al. The use of dabigatran in elderly patients. *Arch Intern Med* 2011; 171: 1285–6.
- Therapeutic Goods Administration. Dabigatran (Pradaxa) & the risk of bleeding: new recommendations for monitoring kidney function. 2011. Available at: <http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm> Accessed November 7, 2011.
- Cheng JW, Rybak I. Use of digoxin for heart failure and atrial fibrillation in elderly patients. *Am J Geriatr Pharmacother* 2010; 8: 419–27.
- Böger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. *Palliat Med* 2006; 20: S17–23.
- Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract* 2010; 20: 428–50.
- Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? *J Am Geriatr Soc* 2002; 50: 1297–300.
- Huerta C, Castellsague J, Varas-Lorenzo C, et al. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis* 2005; 45: 531–9.
- Loboz KK, Shenfield GM. Drug combinations and impaired renal function - the 'triple whammy'. *Br J Clin Pharmacol* 2004; 59: 239–43.
- Delmas PD. Non-steroidal anti-inflammatory drugs and renal function. *Br J Rheumatol* 1995; 34(Suppl1): 25–8.
- Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. *J Intern Med* 2003; 253: 643–52.