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KIDNEY COMPLICATIONS OF COMMONLY USED DRUGS – PART 2

Prescribing drugs for patients with impaired kidney function

In last week's How To Treat, part 1 of this series looked at the pathogenesis of drug-induced kidney function and the drugs responsible for renal complications. Part 2 concludes this week with advice on responding to suspected drug-induced kidney failure and on prescribing in the context of impaired kidney function.

SOME drugs require dose adjustment in patients with impaired kidney function, while others are best avoided altogether (table 1). The reasons for this fall into four groups:

■ **Drugs that lead to increased risk of nephrotoxicity in patients with chronic kidney disease, eg, gentamicin.** If unadjusted doses of aminoglycosides are administered

to patients with impaired kidney function, the risk of nephrotoxicity occurring is greatly increased.

■ **Drugs that are either exclusively or partially excreted by the kidney.** The

levels of these drugs accumulate in the circulation of patients with chronic kidney disease and lead to an exaggeration of their intended

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effect, eg, digoxin, atenolol, gabapentin, glibenclamide, enoxaparin and codeine (see Authors' case study, Use loop diuretics with caution, p32). The dose of digoxin (Lanoxin, Sigmaxin) must be reduced in the context of acute kidney failure or progressive chronic kidney disease to avoid digitalis toxicity. Glibenclamide (Daonil, Glimel, Glucovance), a commonly used sulfonylurea almost exclusively excreted by the kidney, may cause severe hypoglycaemia in patients with impaired kidney function.

■ **Drugs that are either exclusively or partially excreted by the kidney.** The levels of these drugs accumulate in the circulation of patients with chronic kidney disease and lead to complications unrelated to their intended effect, eg, metformin, aciclovir, allopurinol, colchicine, tetracycline, nitrofurantoin and fenofibrate. If unadjusted oral or parental doses of aciclovir (Acihexal, Acyclo-V, Lovir, Zovirax, Zyclir) are administered to patients with impaired kidney function, neurotoxicity frequently supervenes. Long-term daily doses of nitrofurantoin are frequently employed as antibiotic prophylaxis in patients with debilitating recurrent UTIs. Over time this can lead to severe, irreversible peripheral neuropathy in patients with chronic kidney disease.

■ **Drugs that require caution in patients with chronic kidney disease for a range of reasons,** eg, diuretics, ACE inhibitors, angiotensin-II-receptor antagonists (ARAs), NSAIDs and COX-2-selective NSAIDs (see Authors' case study, Use loop diuretics with caution p32).

Table 1: Commonly used drugs requiring caution, dose adjustments or avoidance in chronic kidney disease

Drug class	Common examples	Potential complications	Common solutions
Aminoglycosides	Amikacin, gentamicin, neomycin, tobramycin	Non-oliguric acute kidney failure, hypomagnesaemia	<ul style="list-style-type: none"> ■ Avoid if possible ■ Avoid concurrent loop-blocking diuretics ■ Reduce dose and increase dosing interval ■ Monitor levels and kidney function
Cardiac glycosides	Digoxin	Digitoxicity	<ul style="list-style-type: none"> ■ Reduce dose ■ Monitor levels (evening dosing facilitates this)
Beta blockers (renal excretion only)	Sotalol, atenolol	Cardiotoxicity	<ul style="list-style-type: none"> ■ Reduce dose ■ Observe for cardiotoxicity, eg, bradycardia ■ Use alternative beta blocker instead eg, metoprolol
Glycopeptides	Vancomycin	Acute kidney failure	<ul style="list-style-type: none"> ■ Increase dosing interval ■ Monitor levels and kidney function
Purine nucleoside analogue	Aciclovir	Acute kidney failure, neurotoxicity/acute confusional state/coma	<ul style="list-style-type: none"> ■ Ensure adequate hydration ■ Ensure slow infusion rate ■ Reduce dose and increase dosing interval ■ Monitor cognitive function and neurological status ■ Monitor kidney function closely
Anticonvulsant	Gabapentin	Neurotoxicity/acute confusional state	<ul style="list-style-type: none"> ■ Reduce dose ■ Monitor cognitive function and neurological status
Biguanide	Metformin	Lactic acidosis	<ul style="list-style-type: none"> ■ Avoid if GFR <40mL/min/1.73m² ■ Use hepatically excreted sulfonylurea instead, eg, gliclazide, glipizide
Loop diuretics	Bumetanide, ethacrynic acid, frusemide	Dehydration, hypokalaemia	<ul style="list-style-type: none"> ■ Monitor fluid status closely ■ Monitor potassium level and kidney function closely, particularly when concurrent use of ACE inhibitor and/or angiotensin-II-receptor antagonist or concurrent use of NSAID and/or COX-2-selective NSAID
Potassium-sparing diuretics	Amiloride, spironolactone, triamterene	Dehydration, hyperkalaemia	<ul style="list-style-type: none"> ■ Monitor fluid status closely ■ Monitor potassium level and kidney function closely, particularly when concurrent use of ACE inhibitor and/or angiotensin-II-receptor antagonist
ACE inhibitors	Captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril	Acute kidney failure, hyperkalaemia	<ul style="list-style-type: none"> ■ Introduce at low dose ■ Ensure adequate hydration ■ Temporarily withhold diuretics initially ■ Avoid concurrent NSAIDs (including COX-2-selective NSAIDs) initially ■ Monitor kidney function after 7-10 days ■ Monitor potassium level closely, particularly with concurrent use of potassium-sparing diuretics
Angiotensin-II-receptor antagonists	Candesartan, eprosartan, irbesartan, losartan, telmisartan	Acute kidney failure, hyperkalaemia	<ul style="list-style-type: none"> ■ Monitor kidney function after 7-10 days ■ Monitor potassium level closely, particularly with concurrent use of potassium-sparing diuretics
Sulfonylureas (renally excreted)	Glibenclamide, gliclazide, glimepiride	Hypoglycaemia	<ul style="list-style-type: none"> ■ Avoid use ■ Use hepatically excreted sulfonylurea instead, eg, gliclazide, glipizide
Low molecular weight heparins	Dalteparin, enoxaparin	Haemorrhage	<ul style="list-style-type: none"> ■ Reduce dose ■ Monitor factor Xa levels if indicated
Xanthine oxidase inhibitor	Allopurinol	Increased risk of severe 'allopurinol hypersensitivity syndrome'	<ul style="list-style-type: none"> ■ Reduce dose
Gout therapy	Colchicine	Myositis/rhabdomyolysis	<ul style="list-style-type: none"> ■ Avoid doses >600mg bd if GFR <50mL/min/1.73m² ■ Monitor for myopathy and elevated creatine kinase levels
Tetracyclines	Tetracycline	Severe catabolic state causing severe uraemia and hyperkalaemia	<ul style="list-style-type: none"> ■ Avoid if GFR <60mL/min/1.73m² ■ Use doxycycline or minocycline instead
Nitrofurantoin	Nitrofurantoin	Peripheral neuropathy	<ul style="list-style-type: none"> ■ Avoid long-term use if GFR <50mL/min/1.73m²
Opiates	Codeine, dextropropoxyphene, hydromorphone, morphine, oxycodone, pethidine, tramadol	Obtundation, respiratory compromise and coma	<ul style="list-style-type: none"> ■ Avoid if possible ■ Reduce dose and increase dosing interval ■ Monitor cognitive function and neurological status ■ Use buprenorphine, fentanyl or methadone analgesics instead
Fibrates	Fenofibrate, gemfibrozil	Myopathy/rhabdomyolysis	<ul style="list-style-type: none"> ■ Exercise caution in patients with reduced GFR ■ Monitor creatine kinase level and kidney function, particularly with concurrent use of statins and/or calcineurin inhibitors

Numerous antimicrobials require dose adjustments in chronic kidney disease. For further information see *Therapeutic Guidelines: Antibiotics, Version 12*. Appendix 2.11: www.tg.com.au/complete/tgc.htm

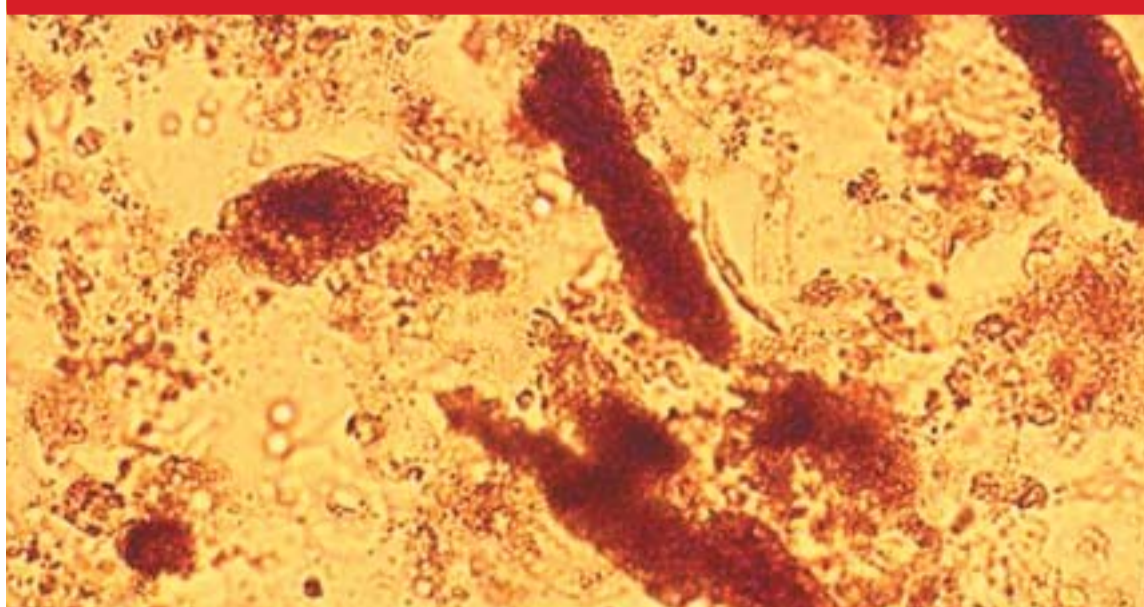
When you suspect drug-induced kidney failure

If doctors exercise a high index of suspicion in patients at highest risk, some cases of drug-induced kidney failure can be predicted, but most cases are detected as an 'incidental finding' when the patient is investigated or treated for unrelated conditions. These patients rarely have specific symptoms or signs but present with vague symptoms of malaise, lethargy, anorexia, nausea and perhaps oliguria (or polyuria).

The differential diagnosis of either acute or chronic kidney disease is extremely broad and relies on a meticulous history and thorough clinical examination supported by the interpretation of appropriate investigations. The pursuit of previous laboratory results to establish a temporal relationship between the prescription of a drug and the onset of abnormal blood results can be invaluable in reaching a diagnosis.

Patients are frequently unsure of precise details, making it necessary

Figure 1: Muddy brown casts of acute tubular necrosis. (From Johnson J, Feehally J. *Comprehensive Clinical Nephrology*, 2nd edn. Mosby, 2003. Reproduced with permission from Elsevier Ltd.)



to liaise with other physicians, pharmacist(s), family members and hospitals involved in the patient's

care. This can be very time consuming but is crucially important. Acute drug-induced kidney fail-

ure is frequently a diagnosis of exclusion, which can only be definitively confirmed by performing a percutaneous renal biopsy (see Authors' case study, The dangerous allergy, p31).

Important questions to ask include:

- Have you recently been prescribed any new medications?
- When were you prescribed these medications?
- Have you been taking any non-prescription drugs, vitamins, herbal remedies or alternative therapies?
- Have you previously been allergic to any medications?
- Have you been particularly thirsty?
- Has your mouth been dry?
- Have you been lightheaded when you stand up (postural hypotension)?
- Have you not felt like eating?
- Have you experienced nausea,

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- vomiting or hiccoughs?
 - Have you been tired and lethargic?
 - Have you noticed a rash?
 - Has your skin been particularly itchy (uraemic pruritus)?
- Clinical signs to illicit include:
- Severe hypertension or postural hypotension (measure erect and supine blood pressure).
 - Uraemic tinge.
 - Scratch marks (uraemic pruritus).
 - Oliguria/anuria.
 - Polyuria.
 - Rash.

Drug-induced kidney failure is frequently a diagnosis of exclusion.

- Signs of dehydration.

Drug-induced kidney failure is frequently a diagnosis of exclusion. It is imperative to consider alternative diagnoses and to perform selected investigations, including (when appropriate):

- FBC, urea and electrolytes, calcium/magnesium/phosphate, LFTs and C-reactive protein.
- Midstream urine for culture and sensitivity (to exclude infection).
- Spot urine albumin:creatinine ratio (defines stages 1 and 2 chronic kidney disease and proffers an

increased risk of cardiovascular disease).

- Spot urine microscopy for casts (figure 1) and dysmorphic red cells (the presence of dysmorphic red cells indicates a glomerular source of red cells and frequently suggests an underlying glomerulonephritis or vasculitis, which may be drug induced).
- Spot urine microscopy for eosinophilia (detected using Wright's stain or Hansel's stain suggests an underlying acute allergic tubulo-interstitial nephritis).

- Urine cytology (particularly important in patients with a history of analgesic abuse, who are at risk of underlying urinary tract malignancy).

- Antinuclear antibodies, antibodies to double-stranded (ds) DNA (high titres of dsDNA in the appropriate context suggest lupus nephritis).
- Antihistone antibodies (supports an underlying drug-induced lupus nephritis).
- Extractable nuclear antigens (suggest an underlying connective tissue disease).
- Hypocomplementaemia

C3/C4 (supports a diagnosis of lupus nephritis, post-infectious glomerulonephritis, mixed essential cryoglobulinaemia, membranoproliferative glomerulonephritis or cholesterol atheroembolic disease).

- Antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibodies, cryoglobulins (suggest an underlying vasculitis).
- Renal tract ultrasound (to rule out obstructive nephropathy, estimate kidney size and assess renal parenchymal echogenicity).
- Percutaneous renal biopsy.

Renin-angiotensin system inhibition in chronic kidney disease

MANY clinicians believe that an acute rise in plasma creatinine concentration precipitated by the introduction of an ACE inhibitor or ARA should prompt withdrawal of these drugs, because ACE inhibition can trigger acute kidney failure in the setting of bilateral renal artery stenosis (or unilateral renal artery stenosis in patients with a solitary kidney) (see figure 2).

Interestingly, only about one-third of such patients experience a rise in plasma creatinine concentration when challenged with an ACE inhibitor and/or ARA. What are the risks and what is the best approach to this common scenario?

Patients with chronic kidney disease, particularly those with proteinuria, benefit from maximal tolerated inhibition of the renin-angiotensin system achieved with ACE inhibitors alone, or in combination with, ARAs.

As well as lowering blood pressure, postulated mechanisms for this benefit include reduction of proteinuria, efferent arteriolar vasodilation leading to reduced intraglomerular pressure, and 'downstream' hormonal and cytokine effects that ultimately protect the kidneys.

The primary benefit is a reduced rate of progression of chronic kidney disease that is, preservation of kidney function over time. In recent years, chronic kidney disease has been established as one of the most important risk factors for cardiovascular and cerebrovascular disease, and ACE inhibitors and ARAs have also been demonstrated to reduce morbidity and mortality in the setting of MI and stroke.

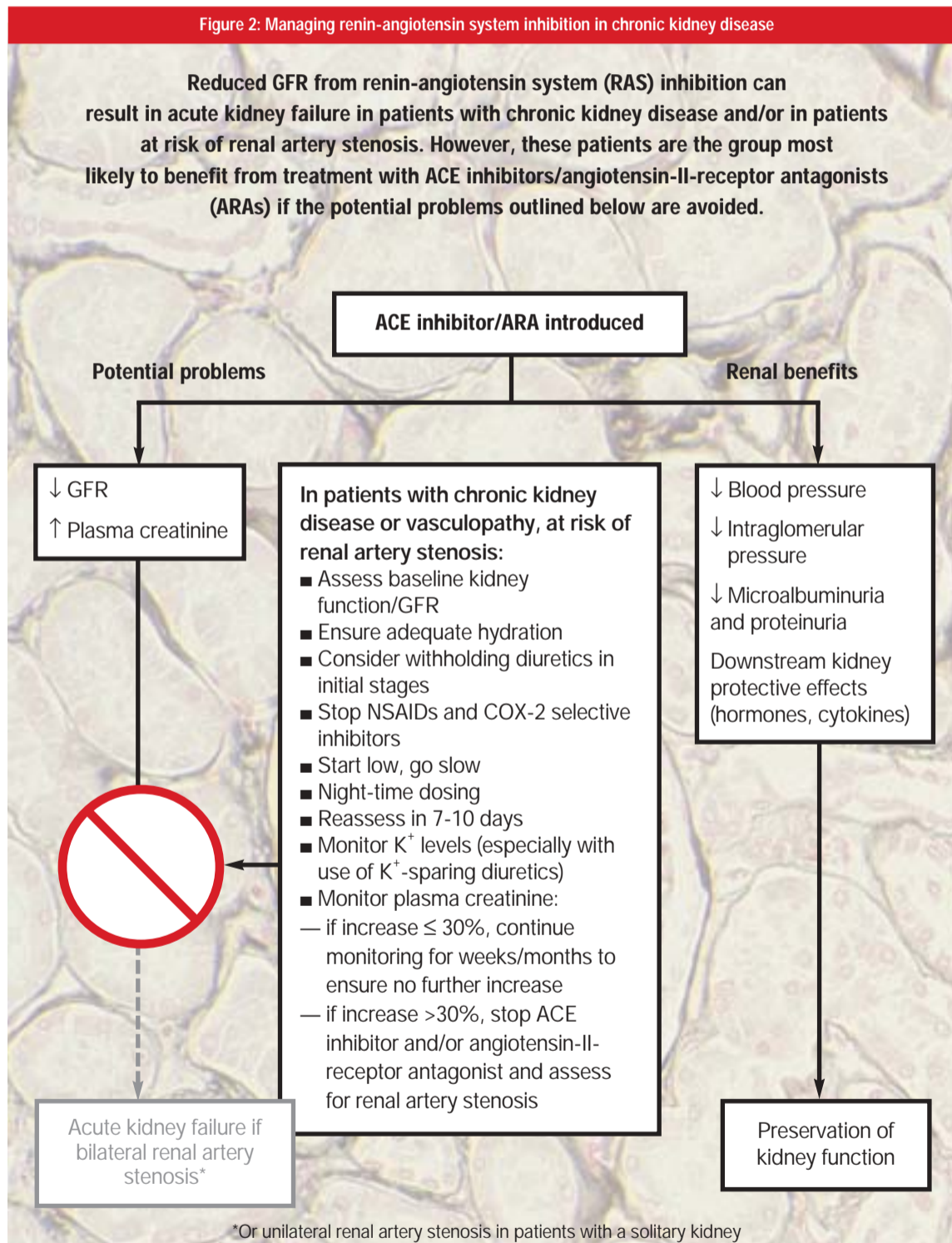
It follows that many patients with chronic kidney disease would benefit from inhibition of the renin-angiotensin system.

Should all patients who experience a rise in plasma creatinine concentration with introduction of these drugs be prevented from obtaining their benefits? Given their striking potential benefits, a sensible and systematic approach to the prescription of these drugs needs to be adopted.

As a general rule, all patients with confirmed chronic kidney disease should be challenged with one or both of these drugs, using the guidelines below and in table 1.

A few simple measures are useful when introducing an ACE inhibitor

Figure 2: Managing renin-angiotensin system inhibition in chronic kidney disease



- Assess baseline kidney function/GFR (see above).

- Ensure the patient is well hydrated.

- Consider temporarily withholding diuretics in the initial days.

- Withhold NSAIDs (including COX-2-selective NSAIDs) — ideally these drugs should be avoided in these patients.

- Always introduce ACE inhibitors and/or ARAs at low doses and titrate upwards if tolerated — this is particularly important in the elderly.

- Consider evening dosing of ACE inhibitors and/or ARAs to avoid falls associated with 'first-dose hypotension' — this is particularly important in the elderly.

- Reassess clinical status and urea and electrolytes within 7-10 days.

- Monitor potassium levels closely, particularly with concurrent use of potassium-sparing diuretics such as spironolactone (Aldactone, Spiractin).

Dosage adjustments are often suggested for ACE inhibitors in chronic kidney disease; however, there is little evidence to support such a recommendation. The only widely available ACE inhibitor metabolised and excreted by the liver, as opposed to the kidneys, is fosinopril (Monopril) but any theoretical advantage of this drug has never been confirmed.

It is reasonable to tolerate a 30% increase in plasma creatinine concentration in patients started on ACE inhibitors or ARAs. An increase of 30% or less should be monitored closely over the following weeks and months to ensure no further increase occurs. If the level increases over days to weeks, or the initial elevation is >30%, the drug should be stopped and the patient assessed for the presence of haemodynamically significant renal artery stenosis.

Our practice is to perform contrast CT renal angiography in a radiology practice equipped with a recent generation scanner and appropriate protocol, to ensure images of sufficiently high quality. Gadolinium MR renal angiography is required in patients at risk of contrast nephropathy (see below). No MBS item number is available for the latter, and patients will not be reimbursed the \$300-500 cost.

Australia has one of the highest rates of analgesic nephropathy in the world related to past use of Bex and Vincent's powders.



or ARA in patients with chronic kidney disease or those with vasculopathy and at risk of renal

artery stenosis, to minimise the risk of inducing a rise in plasma creatinine or a reduction in GFR:

Radiological contrast media and chronic kidney disease

CONTRAST-induced nephropathy is a leading cause of new-onset acute kidney failure in hospitalised patients. It is defined as an acute decline in kidney function after the administration of IV contrast in the absence of other causes.

Patients with normal kidney function rarely develop contrast-induced nephropathy, but incidence progresses with increasing plasma creatinine concentration (or decreasing GFR). For example, in patients with a plasma creatinine concentration of 180µmol/L, the estimated incidence of contrast-induced nephropathy is 20%, rising to 50% in patients with concentrations of 450µmol/L.

Contrast-induced nephrotoxicity ranges in severity from asymptomatic non-oliguric acute kidney failure to severe oliguric acute kidney failure requiring dialysis, with significantly increased morbidity and mortality. Table 2 shows how to minimise the risk of contrast-induced nephropathy.

In most cases not requiring dialysis, the plasma creatinine concentration peaks after 3-5 days and returns to baseline by 7-10 days. Because kidney impairment occurs rapidly after contrast administration, it is helpful to check the plasma urea, creatinine and electrolytes 3-5 days after the test.

In patients who have undergone interventional angiographic procedures, and in whom the plasma creatinine concentration fails

Table 2: Minimising the risk of contrast-induced nephropathy
<ul style="list-style-type: none"> Investigations requiring radiocontrast are usually planned in advance. Clear documentation of the patient's chronic kidney disease in correspondence and request forms will help 'flag' patients requiring prophylactic measures and allow interventionists to consider using smaller volumes of low-osmolar radiocontrast media, which are less nephrotoxic (but more expensive).
<ul style="list-style-type: none"> Encourage all patients, with the exception of those at risk of cardiac failure, to drink plenty of water on the day preceding, and on the day of, their investigation.
<ul style="list-style-type: none"> Drugs with the potential to contribute to contrast-induced nephropathy, such as ACE inhibitors, ARAs, NSAIDs (including COX-2-selective NSAIDs) and diuretics should be withheld on the day before, and on the day of, the procedure in all patients.
<ul style="list-style-type: none"> Because of the risk of lactic acidosis when contrast-induced nephropathy occurs in a patient with diabetes who is receiving metformin (Diabex, Diaformin, Glucophage), this drug should be withheld for 48 hours before exposure to radiocontrast and only reintroduced when it has been confirmed that contrast-induced nephropathy has not occurred.
<ul style="list-style-type: none"> Prehydration has been shown to be the most effective intervention to prevent contrast-induced nephropathy. Patients at high risk, and in whom no alternative to radiocontrast is available, should be prehydrated with a 0.9% normal saline infusion infused for 2-12 hours at 1.0 mL/kg/hour before the radiocontrast and continued for up to 12 hours after the radiocontrast, with careful observation of fluid balance.
<ul style="list-style-type: none"> In patients at mildly increased risk of contrast-induced nephropathy, in whom parenteral prehydration cannot be arranged, oral prehydration plus N-acetylcysteine (Mucomyst) 600mg bd orally on the day before, and on the day of, the procedure may help reduce risk (total of four doses). This should be mixed in orange juice to make it more palatable.

to normalise after 7-10 days, the possibility of cholesterol atheroemboli should be considered. Findings supporting this diagnosis include malaise, fever, livedo reticularis, eosinophilia, hypocomplementaemia and a progressive deterioration in kidney function up to four weeks after the procedure.

This condition is usually irreversible and requires long-term surveillance for complications of chronic kidney disease.

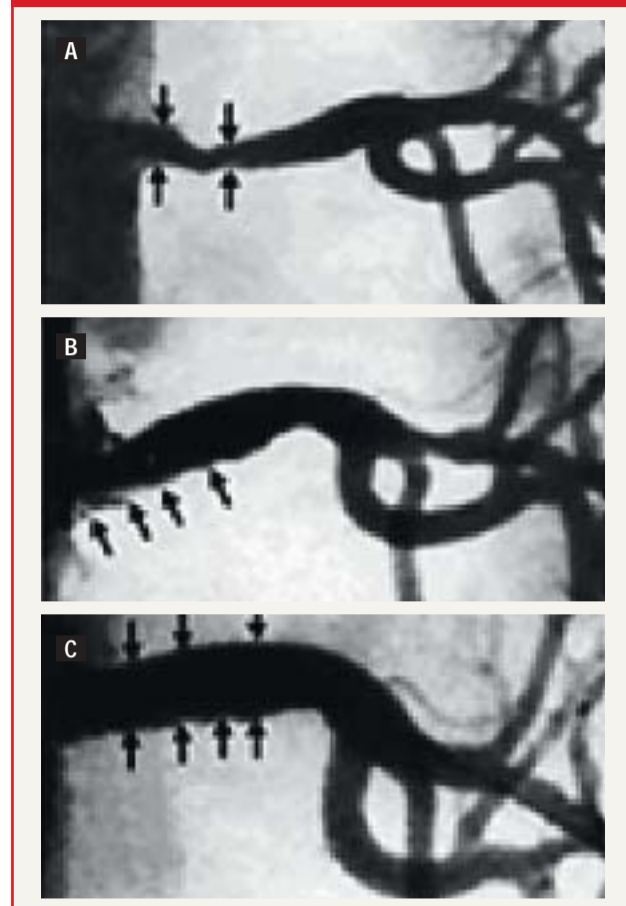
The most important risk factors for developing contrast-induced nephropathy are baseline chronic kidney disease and diabetes mellitus: patients with both conditions are at highest risk. The most important risk factors are outlined in table 3.

Table 3: Risk factors for contrast-induced nephropathy
<ul style="list-style-type: none"> Chronic kidney disease (the lower the GFR the greater the risk) Diabetes mellitus Congestive cardiac failure Hepatic cirrhosis Diuretic use and/or periprocedural volume depletion Hypertension Age >75 Multiple myeloma Concurrent use of ACE inhibitors, ARAs or NSAIDs (including COX-2-selective NSAIDs) Intra-arterial radiocontrast injection, eg, coronary angiography High doses of radiocontrast

When risk factors are present

Establishing baseline kidney function helps to quantify risk and determine which measures need to be implemented before administering radiocontrast. It is important to

Figure 3: A: Typical appearance of atherosclerotic renal artery stenosis, involving the ostium and proximal third of the left renal artery (arrows). B: After angioplasty there was residual stenosis, dissection and a pressure gradient (arrows). C: This resolved after placement of a Palmaz stent (arrows). (From: Safian RD, Textor SC. *New England Journal of Medicine* 2001; 344:431-42.)



consider whether the patient really needs the investigation and whether the risk:benefit ratio is justified in an individual patient.

Try to avoid radiocontrast in all patients with GFR <50mL/min/1.73m², particularly when other risk factors are also present. For example, gadolinium-enhanced MR angiography can be used, instead of contrast CT renal

angiography, to assess suspected renal artery stenosis (see table 2 and figure 3).

Omitting a left ventriculogram in patients undergoing coronary angiography significantly reduces the contrast load, and information about left ventricular function can be obtained by alternative non-invasive means such as transthoracic echocardiography.

Authors' case study

The dangerous allergy

TR, a previously fit and well 67-year-old retired librarian, presented to her family physician with a two-week history of anorexia and malaise. Her clinical history included mild hypertension, hyperlipidaemia and a diagnosis of gastro-oesophageal reflux disease made six weeks previously.

She had a low-grade fever, but physical examination was otherwise unremarkable. In particular, she had no rash. Dipstick urinalysis revealed protein +.

Her medications included atenolol 25mg daily, simvastatin 10mg at night and omeprazole 20mg at night. She had been maintained on these medications for three years with the exception of omeprazole, which had been prescribed six weeks before.

Numerous investigations were arranged:

- FBC revealed a mild normochromic normocytic anaemia not present at the time of a previous test two months before.
- Eosinophil count was normal.
- Plasma creatinine concentration was 200µmol/L, compared with



- 80µmol/L two months before.
- C-reactive protein was 84mg/L.
- ESR was 120mm/hour.
- Tests for antinuclear antibody, antineutrophil cytoplasmic antibodies, complement, anti-DNAse, serum and urine electrophoretogram and immuno-electrophoretogram were all normal.
- Midstream urine for culture and

- sensitivity revealed sterile pyuria.
- Spot urine microscopy was negative for casts and dysmorphic red cells.
- Early morning urines for acid-fast bacilli were negative.
- Renal tract ultrasound was entirely normal.
- In the absence of a definitive diagnosis and in light of the sever-

ity of the acute kidney failure, a percutaneous renal biopsy was performed. This revealed a prominent infiltrate of mixed inflammatory cells (lymphocytes, plasma cells, scattered eosinophils and isolated groups of neutrophils) in the cortical interstitium.

In view of the temporal relationship between this patient's presentation and the introduction of the proton-pump inhibitor, a diagnosis of omeprazole-induced acute allergic interstitial nephritis was made (see Pathogenesis, and figure 4 in part 1 of this article).

The patient was treated with high-dose oral corticosteroids and made a complete recovery, with a plasma creatinine concentration two months later of 88µmol/L.

Interpretation

The differential diagnosis of acute kidney failure is extremely broad and relies on a meticulous history and examination supported by the interpretation of appropriate investigations. The pursuit of 'old' baseline investigation results can be invaluable.

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Establishing a temporal relationship between the onset of abnormal investigation results and a potential renal injury is crucial to reaching a diagnosis. Timely use of more invasive investigations can be helpful.

Withdrawal of the culprit medication and institution of an alternative such as an H₂-receptor antagonist is crucial to prevent long-term chronic kidney disease. There is little evidence to support the use of corticosteroids in this setting; however, they are frequently employed in severe cases, as it is thought they may accelerate recovery.

Use loop diuretics with caution

The attentive daughter of TT, a frail, independently-living 80-year-old, requested her GP visit her mother at home because she had recently “taken to her bed”.

The patient’s clinical history included stage-4 chronic kidney disease with an estimated creatinine clearance of 21.6mL/min/1.73m², hypertension, ischaemic heart disease, AF, polymyalgia rheumatica and chronic debilitating pain in her cervical spine.

She had required hospitalisation three times in the past 12 months for management of recurrent congestive cardiac failure, although her main concern was always the unsightly swelling of her ankles.

During her most recent hospitalisation after a fall



secondary to postural hypotension, her frusemide had been discontinued. She then developed dyspnoea and severe bipedal oedema necessitating reintroduction of frusemide 40mg twice daily.

Her usual medications were digoxin 62.5µg daily, meto-

prolol 25mg twice daily, ramipril 1.25mg daily, spironolactone 12.5mg in the morning, frusemide 40mg in the morning/20mg at noon, prednisone 4mg daily and calcitriol 0.25µg at night. She had been maintained on these medications for 18 months with intermittent adjustments

of frusemide and prednisolone dosage.

Physical examination revealed a frail, drowsy, confused patient who weighed 55kg. She was afebrile, markedly dehydrated and hypotensive. Her respiratory rate was eight breaths/min. Her pupils were small but equal in size.

Blood and urine investigations showed a plasma creatinine concentration of 336µmol/L compared with 141µmol/L six weeks before. Surprisingly, a digoxin level taken eight hours after her last dose was within the normal range.

The precise cause of her clinical deterioration was unclear until her daughter found a half empty box of codeine phosphate/paracetamol (Dolaforte) 30/500mg next to her mother’s bed which had been prescribed for neck pain in the past. TT had self-medicated, taking two tablets every four hours for the preceding five days to treat an exacerbation of her neck pain.

A diagnosis of acute-on-chronic kidney failure secondary to dehydration was made and the patient was admitted to hospital for IV rehydration. Her urine output and creatinine concentration improved and her mental test score rapidly returned to her ‘baseline’ of 26/30.

Interpretation

With stage-4 chronic kidney disease, TT had self-medicated with an opiate anal-

gesic at doses appropriate for a person half her age and with normal kidney function. The opiate rapidly ‘accumulated’, leading to drowsiness and confusion.

This led to a reduced oral fluid intake which, when combined with the reintroduction of the loop diuretic (frusemide 40mg twice daily), led to a rapid downward spiral in her condition.

The elderly are at markedly increased risk of adverse drug reactions. This risk is dramatically increased in patients with chronic kidney disease combined with multiple comorbidities. In particular, managing symptoms and signs of patients with congestive cardiac failure can be extremely difficult.

Many are pre-occupied with dependent ankle swelling and constantly insist on ever greater doses of diuretics, frequently leading to intravascular fluid deficiency, reduced kidney perfusion and acute-on-chronic kidney failure.

A strict no-added-salt diet, fluid restriction and daily weighing is recommended. A relative or carer may need to monitor weight if the patient is unable to comprehend the importance of daily weighing.

Any marked change in weight from a pre-agreed ‘baseline’ should prompt an urgent review by the GP to assess fluid status, urea and electrolytes, and appropriate alteration of clinical management.

GP’s contribution



DR MARCELA COX
Leichhardt, NSW

Case study

GEORGE is an independent 76-year-old man who has a long-standing history of hypertension that is well controlled with amlodipine (Norvasc) 10mg and fosinopril/hydrochlorothiazide (Monoplus) 20/12.5mg.

He also has benign prostatic hypertrophy, with a bladder residual volume of about 100mL, which his urologist had been managing conservatively with regular reviews. George’s usual plasma creatinine concentration is about 160µmol/L and his calculated GFR is 38mL/min.

Last year George mentioned that his urinary frequency had increased and he had hourly nocturia. He was otherwise well, with no fever or loin pain. Examination showed his prostate to be unchanged and there was no evidence of acute urinary retention. A urinalysis showed blood, leucocytes and nitrites and an MSU grew *Escherichia coli*. George was started empirically on trimethoprim 300mg at night.

He returned for review four days later, feeling symptomatically improved and with reduced nocturia. However, his repeat creatinine test showed a rise to 900µmol/L, with a urea of 20mmol/L. His blood pressure was 145/90mmHg, he was not oliguric or clinically fluid overloaded.



When seen urgently by a renal physician, George’s repeat MSU showed the infection had cleared, and a repeat bladder ultrasound was unchanged. The trimethoprim was stopped and he was observed as an outpatient, with his plasma creatinine concentration returning to his normal baseline over the next three weeks.

Questions for the authors

How often does trimethoprim cause acute renal failure?

The precise incidence of acute kidney failure is not known; however, a temporary rise in plasma creatinine concentration is common (see next answer).

What is the mechanism of the renal

George was started empirically on trimethoprim... he improved... [but] his repeat creatinine test showed a rise to 900µmol/L.

dysfunction with this drug?

Trimethoprim can reversibly increase serum creatinine concentration and reduce creatinine clearance without decreasing GFR, both in people with normal renal function and in those with chronic kidney disease. The mechanism is by competitive inhibition of tubular

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secretion of creatinine and may not signify a deterioration in renal function.

Trimethoprim may also cause acute kidney failure by causing acute allergic tubulo-interstitial nephritis. Also, it is structurally related to the potassium-sparing diuretics, triamterene and amiloride, which can induce hyperkalaemia by interfering with renal potassium excretion.

What other antibiotics would one need to be careful with using in George?

Although rare, most antibiotics can cause acute allergic tubulo-interstitial nephritis; however, some drugs need particular mention in the context of George's management.

Avoid nitrofurantoin because of the risk of peripheral neuropathy in patients with GFRs <50mL/min/1.73m². Avoid aminoglycosides, if possible, because of the risk of direct tubular toxicity.

Always verify drug safety



and dosing using *Therapeutic Guidelines: Antibiotics*. Version 12. Appendix 2.11 (www.tg.com.au/complete/tgc.htm).

General questions for the authors

How common is the acute

allergic tubulo-interstitial nephritis reaction to proton-pump inhibitors?

The precise incidence of this reaction is not known; however, two recently published hospital-based series from Norwich and Sydney suggest PPIs are by far the

most common drugs to cause this entity.

Given that proton-pump inhibitors are frequently prescribed drugs in general practice, would you recommend routine review of creatinine concentration after

Be aware of the acute allergic tubulo-interstitial nephritis reaction to proton-pump inhibitors.

tion in all patients prescribed proton-pump inhibitors for early detection of what is probably a rare reaction.

Rather, we would recommend increased awareness of this potentially devastating reaction and advocate review of creatinine concentration in patients developing non-specific malaise, lethargy, nausea or weight loss in the weeks to months after introduction of a proton-pump inhibitor.

With regard to initiating ACE inhibitors, if the creatinine concentration is unchanged at the 7-10-day check, how frequently should renal function be monitored subsequently?

We would recommend surveillance of urea and electrolytes every 3-6-months thereafter, but this needs to be individualised. In the present era of widespread use of ACE inhibitors, ARAs and spironolactone, we would advocate repeat measurement of urea and electrolytes 7-10 days after each increase in dose of any of these medications.

their initiation and, if so, at what interval after starting?

Proton-pump inhibitors are the third most commonly prescribed class of drugs prescribed on the PBS. At this stage there is insufficient evidence to warrant routine review of creatinine concentra-



How to Treat Quiz

Kidney complications of commonly used drugs – part 2 — 14 April 2006

INSTRUCTIONS

Complete this quiz to earn 2 CPD points and/or 1 PDP point by marking the correct answer(s) with an X on this form. Fill in your contact details and return to us by fax or free post.

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1. Which TWO statements about drug-induced kidney failure are correct?

- a) It is usually detected because of a specific symptom
- b) Acute drug-induced kidney failure is frequently a diagnosis of exclusion
- c) The differential diagnosis of acute or chronic kidney disease is usually very narrow
- d) The temporal relationship between a drug and the onset of kidney failure can be vital in reaching the correct diagnosis

2. Jim, 45 and a new patient, presents for a check up. Pathology show a reduced estimated GFR (eGFR) and elevated plasma creatinine level. Which THREE questions are most relevant to discovering the cause of his kidney dysfunction?

- a) Have you recently been prescribed any new medications?
- b) Do you smoke?
- c) Have you been taking any non-prescription drugs, vitamins, herbal remedies or alternative therapies?
- d) Have you noticed a rash?

3. The cause of Jim's kidney dysfunction is unclear from the history. Which test results correctly suggest the stated cause (choose THREE)?

- a) Eosinophiluria on spot urine microscopy suggesting acute allergic tubulo-interstitial nephritis
- b) Presence of extractable nuclear antigens

suggesting an underlying connective tissue disease

- c) Albumin:creatinine ratio >3.4mg/mmol on two spot urine tests suggesting glomerulonephritis or vasculitis
- d) Abnormal urine cytology suggesting urinary tract malignancy

4. Gemma, 62, is a new patient. She has osteoarthritis, hypertension and signs of mild heart failure. She is taking a thiazide diuretic, glucosamine and intermittent NSAIDs. Pathology and imaging show stage-2 chronic kidney disease. You want to start her on an ACE inhibitor to improve her heart failure and preserve her renal function. Which TWO actions are you most likely to advise in the days before starting this medication?

- a) Transient cessation of Gemma's diuretic
- b) Strict fluid restriction for two days before starting therapy
- c) Stop use of all NSAIDs
- d) Switch from a thiazide to a potassium-sparing diuretic

5. How would you initiate therapy and monitor Gemma during the initial phase of therapy (choose TWO)?

- a) Begin with the maximum tolerated dose of ACE inhibitor
- b) Accept an elevation of 45% in her plasma creatinine concentration in the first 7-10 days of treatment
- c) Reassess clinical status and urea and elec-

trolytes within 7-10 days

- d) Start with a low dose at night

6. Marie, 56, has chronic kidney disease and was diagnosed with breast cancer five years ago. Investigations for back pain have shown metastases. Which THREE treatments should be used with caution or modified, given her kidney dysfunction?

- a) Codeine
- b) Paracetamol
- c) Parenteral bisphosphonates
- d) Selective COX-2 inhibitors

7. Marie develops severe headaches and you suspect a cerebral secondary. Her plasma creatinine concentration is 180µmol/L and she has stage-3 chronic kidney disease. What advice would you give Marie about investigation using a brain CT with contrast (choose TWO)?

- a) Marie should strictly limit her fluid intake on the day before the procedure
- b) Her risk of contrast-induced nephropathy is about 50%
- c) Prehydration is the most effective intervention to prevent contrast-induced nephropathy
- d) Deterioration in renal function usually shows in pathology tests within 3-5 days

8. Marie has one cerebral metastasis that is treated with radiotherapy. She now has significant pain secondary to T7 shingles. Which THREE treatments are most likely to

cause complications if used at standard doses?

- a) Aciclovir
- b) Dexamethasone
- c) Tramadol
- d) Gabapentin

9. Rose, 87, has become increasingly confused and has been losing weight (BMI 17). She is dehydrated and febrile. Pathology shows a raised white cell count, raised random blood glucose level, an eGFR >60mL/min/1.73m² and a UTI. Which TWO actions are you most likely to take?

- a) Start a cephalosporin at the maximum dose
- b) Arrange a 24-hour collection of urine for protein and creatinine clearance
- c) Initiate aggressive intravenous rehydration while monitoring her fluid status and urea and electrolytes
- d) Consider (if indicated) assessing her renal function using a 24-hour collection of urine for protein and creatinine clearance when she has fully recovered from her acute illness

10. Nelly, 78, has newly diagnosed diabetes and chronic kidney disease with a GFR of 40mL/min/1.73m². Which TWO treatments are you least likely to prescribe for her diabetes?

- a) Glibenclamide (Daonil, GlimeI)
- b) Gliclazide (Diamicon, Glyade, Mellihexal, Nidem)
- c) Metformin (Diabex, Diaformin, Glucohexal, Glucomet, Glucophage)
- d) Glipizide (Melizide, Minidiab)

CONTACT DETAILS

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Address: Postcode:

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer. Your CPD activity will be updated on your RACGP records every January, April, July and October.

NEXT WEEK From the recognition of dust as an industrial hazard in metal mines in about AD1000 to the modern curse of asbestos-related illness, much has been learned about occupational respiratory conditions. To find out how much, don't miss next week's How to Treat on this topic. The authors are Dr Bill Musk and Dr Rob Nickels, department of respiratory medicine, Sir Charles Gairdner Hospital, Perth, WA.

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