

Everyday drug therapies affecting the kidneys

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SYNOPSIS

The kidney is exposed to many potential toxins because of its anatomy and physiology. Prerenal factors affecting cardiac output, drugs altering intrarenal haemodynamics and those directly toxic to the renal parenchyma may cause life-threatening renal impairment. Comorbidities and pre-existing renal disease increase the risks. Careful assessment before prescribing commonly used drugs, dosage adjustment when indicated and close follow-up are required to avoid the potential iatrogenic pitfalls.

Index words: nephrotoxicity, analgesic nephropathy, acute tubular necrosis.

(Aust Prescr 2000;23:17–9)

Introduction

The normal kidney receives approximately 25% of resting cardiac output. Glomerular filtration produces approximately 180L of ultrafiltrate daily. While most is reabsorbed, filtration allows the excretion of waste products, minerals, acids and drugs, or their metabolites. Excretion may expose the vasculature, tubules and interstitial tissues to very high concentrations of these substances. The kidneys, therefore, quite commonly suffer adverse effects of drug therapy (see box). Comorbidities and co-administration of other drugs increase the likelihood of adverse drug reactions.

Prerenal factors

An adequate cardiac output is an essential requirement for normal renal function. If renal function is impaired by a decreased cardiac output the increase in the concentration of urea is more marked than the increase in the concentration of creatinine. This characteristic laboratory finding results from avid reabsorption of tubular fluid, accompanied by urea which is freely permeable through cell membranes, but

not creatinine which is impermeable to renal tubular cells. To maintain cardiac output, the requirements are:

- sufficient blood volume
- effective cardiac pump
- appropriate peripheral resistance.

Blood volume

Diuretics, particularly the more potent loop diuretics (frusemide, ethacrynic acid, bumetanide), may cause volume depletion. This decreases cardiac output, particularly in patients who already have decreased 'effective' blood volume, such as those suffering cardiac failure, liver failure or nephrotic syndrome.

Effective cardiac pump

Drugs with negative inotropic effects, such as beta blockers and some calcium channel antagonists, have the potential to impair renal function, especially if cardiac output is already compromised. In clinical practice, the adverse effects on the heart usually predominate so the drug is often stopped before the renal dysfunction becomes clinically relevant.

Peripheral resistance

Vasodilator drugs, such as minoxidil and prazosin, rarely cause deterioration of renal function themselves. However, they may be associated with marked salt and water retention, requiring the addition of loop diuretics. Calcium channel blockers, while causing oedema of the eyes and ankles, are actually natriuretic and do not cause salt and water retention.

Intrarenal circulation

The intrarenal circulation is controlled by many factors including prostaglandins and the 'renin angiotensin' system. These systems are able to vary the relative degrees of vasoconstriction or dilatation of the afferent or efferent arterioles of the glomerulus. This alters intraglomerular pressure and therefore the glomerular filtration rate. These systems are particularly activated in disease states where there is already underlying renal impairment or abnormalities of cardiac output. They are also affected by many drugs. Fortunately, stopping the offending drug usually restores renal function fairly promptly.

Non-steroidal anti-inflammatory drugs (NSAIDs)

All the NSAIDs inhibit prostaglandin synthesis, leading to unopposed, intrarenal vasoconstriction. This decreases the glomerular filtration rate. This results in fluid retention, with the risk of increasing cardiac failure in patients with pre-existing cardiac dysfunction, and resistance to antihypertensive therapy in patients with normal cardiac function.

Commonly-used drugs which can affect renal function

- Diuretics
- Beta blockers
- Vasodilators
- Non-steroidal anti-inflammatory drugs
- ACE inhibitors
- Aminoglycosides
- Radio contrast media
- Compound analgesics
- Antiviral agents
- Lithium

Angiotensin converting enzyme (ACE) inhibitors

By interfering with the production of angiotensin II, the ACE inhibitors decrease efferent arteriolar regulation. Clinically significant alterations in renal function may result, particularly in low perfusion states, such as renal artery stenosis to a solitary kidney, or if there is bilateral renal artery disease. If the ACE inhibitor adversely affects renal function you should consider the presence of functionally significant renovascular disease, however the absence of such an effect does not rule out the presence of a renal artery lesion. Furthermore, a small deterioration in renal function may occur in patients who have no renovascular disease, but have a pre-existing mild elevation of serum creatinine when they start an ACE inhibitor. This deterioration will often reverse in time if the ACE inhibitor is continued.

Parenchymal damage

Many drugs can cause structural damage to the renal parenchyma. This usually presents as acute tubular necrosis.

Aminoglycosides

The aminoglycoside antibiotics remain a relatively common cause of acute deterioration in renal function. They have the potential to cause significant morbidity and even mortality. Even when cautiously administered, therapy for more than seven days has been reported to cause a rise in serum creatinine in up to 30% of patients. Other factors, such as pre-existing impaired renal function, hypovolaemia, concomitant diuretic use, and reduced serum potassium or magnesium, can all increase the nephrotoxicity of aminoglycosides. Clinically, the onset of renal failure may be quite insidious because oliguria is not usually present. A warning sign may be the development of hypokalaemia which precedes the rise in serum creatinine resulting from the aminoglycoside-induced acute tubular necrosis. Although measuring trough concentrations of aminoglycoside may assist in guiding dosage, many studies have failed to show that monitoring decreases the incidence of nephrotoxicity significantly. Once-daily dosing has, in a number of studies, been shown to decrease the incidence of nephrotoxicity without impairing antibiotic efficacy.

Aminoglycosides are eliminated by glomerular filtration. About 5% of the filtered drug is actively reabsorbed by proximal tubular cells and can reach high concentrations in these cells. The drug is then slowly eliminated, unchanged, over a period of days. Toxic damage to the tubular cells is believed to be related to the ability of the aminoglycoside to disrupt plasma membranes, but additional poorly understood factors are also implicated. A decreased dosage or increased intervals between doses must be prescribed for patients with known impairment of renal function.

Lithium

When serum concentrations are high (e.g. above 1.2 mmol/L), urine output increases and glomerular filtration rate decreases mildly. Urinary concentrating ability is decreased.

Acute renal failure has been reported with lithium intoxication,

but the mechanism is uncertain and it may be due to factors such as volume depletion, direct nephrotoxicity or a combination of both.

Whether chronic renal failure results from lithium-induced interstitial nephritis remains controversial. It is an uncommon complication of this drug. For instance, in 1997 in Australia, out of 1468 new patients entered into the End-Stage Renal Failure Programs, only five patients were listed with a diagnosis of lithium-induced disease. Nevertheless, patients should have their serum creatinine checked every 6–12 months in addition to the monitoring of their lithium concentrations every 3–4 months.

Contrast media

In patients with pre-existing impairment of renal function due to diabetic nephropathy, a common cause of acute renal impairment is contrast media-associated nephrotoxicity. The pathogenesis is poorly understood, but alterations in intrarenal haemodynamics and direct tubular epithelial cell toxicity may be primary factors. Clinically significant contrast-induced nephrotoxicity is uncommon in non-diabetics and is rare in patients with normal renal function. Whilst the use of non-ionic contrast media is less likely to cause renal impairment, it is still not risk-free. The amount of the contrast given may be important, with volumes of more than 30 mL being more likely to be associated with toxicity. A prospective multicentre trial studied 1196 patients, of whom 213 had diabetes mellitus and 509 had serum creatinine of more than 141 micromol/L. In the azotaemic non-diabetic patients, 4% showed evidence of nephrotoxicity, but in those with both azotaemia and diabetes, the incidence was 12% even when non-ionic contrast materials were used.

Diabetic patients with pre-existing impaired renal function are more likely to develop toxicity and are also more likely to require dialysis. Some cases may suffer irreversible renal failure.

A variety of prophylactic measures have been tried. Mannitol, frusemide and dopamine can increase the risk of nephrotoxicity. Calcium channel blockers may be beneficial, but intravenous saline loading appears to be the most successful in reducing the risk. Intravenous normal saline, 80 mL/hour for 6–10 hours before and after the procedure, is recommended providing there are no contraindications such as incipient cardiac failure. NSAIDs and diuretics should be withdrawn 24 hours before an elective investigation.

Clinically, if toxicity occurs, the serum creatinine begins to rise within 24–48 hours, peaks within 3–5 days and then returns to baseline within 7–10 days. Oliguria is uncommon and urine examination usually shows tubular epithelial cells, coarsely granular casts and mild proteinuria.

Analgesic nephropathy

Compound analgesics

Chronic interstitial nephritis and papillary necrosis can develop as a consequence of long-term abuse of combination analgesics, particularly those containing phenacetin.⁸ Possibly as a result of decreased compound analgesic abuse, this disease appears to be decreasing in prevalence in Australia. Two decades ago,

it accounted for 12–15% of patients presenting with end-stage renal failure. More recently, the proportion has dropped to less than 5%, occurring predominantly in an older age group, compared with 20 years ago.

Analgesic abuse may be difficult to diagnose because of patient denial and often non-specific symptoms, signs and laboratory findings. High use is generally defined as use of one or more doses of analgesic daily, for at least five years and a minimum total dose of approximately 3000 doses. To establish the diagnosis, CT scanning without contrast is most useful for detecting papillary necrosis.

Following removal of phenacetin from compound analgesics, there has been a clear decline in the prevalence and incidence of analgesic nephropathy. However, it is still uncertain if phenacetin, or a metabolite, e.g. paracetamol, is the main aetiological agent. The decreased availability of compound analgesics as well as altered consumption habits occurred around the same time making the cause difficult to identify. There have been documented cases of analgesic nephropathy occurring in patients who abuse non-phenacetin-containing compound analgesics. On the other hand, reports of analgesic nephropathy, in association with consumption of single analgesics, are quite rare. In particular there is insufficient evidence to indicate that chronic paracetamol ingestion is nephrotoxic. There is little evidence that regular analgesic consumption increases the progression of renal disease due to other causes, such as glomerulonephritis or diabetes mellitus.

NSAIDs

NSAIDs can cause an acute, usually reversible, deterioration in renal function due to inhibition of renal vasodilatory prostaglandins in the kidney. The risk factors include older age, hypertension, pre-existing impaired renal function, diabetes, diuretics and volume depletion. NSAIDs may also exacerbate salt and water retention in patients with congestive heart failure.

More rarely, NSAIDs may cause an acute interstitial nephritis, characterised by acute renal failure and heavy proteinuria. The renal failure may be severe enough to require dialysis. The syndrome may occur sooner or later after commencing NSAIDs, but the patient usually recovers gradually after the drug is stopped.

Although chronic administration of NSAIDs to experimental animals can induce papillary necrosis, there are no convincing data that prolonged consumption of NSAIDs in humans is a significant risk factor for analgesic nephropathy and chronic renal failure.

Conclusion

The kidney is exposed to many medications. Patients with comorbidities, particularly the aged and those with pre-existing renal disease, diabetes and cardiac failure, are especially at risk of renal impairment. With the increasing availability of computer access to the relevant medical literature, it is wise to check the list of precautions and adverse effects before prescribing for these patients.

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Self-test questions

The following statements are either true or false (answers on page 23)

7. Non-steroidal anti-inflammatory drugs reduce the glomerular filtration rate.
8. Renal impairment due to decreased cardiac output causes a more marked increase in plasma urea concentrations than in creatinine concentrations.

The story of the painting

I'm Jennifer Summerfield. I am a Pitjantjatjara woman. I live at Umuwa on the Anangu Pitjantjatjara Lands in the north west of South Australia. I work as an Anangu Health Worker for Nganampa Health Council. I am the artist who did the painting for National Medicines Week.

This painting is about using medicine properly, especially for older people. Store your tablets in a cool place or in your bag away from kids and other old people. Take your medication at the right time with the pictures of the sun showing in the morning, at midday and in the evening. Don't throw your medicines on the ground. If you don't take your tablets you may be blind or never walk again. This is what the painting is about.

The older people in the middle of the painting are keeping their medicine safe in a bag. The people in each corner have not taken their medicines and have become blind or crippled. There is the sun to tell them to take their medicine, in the morning, at midday and in the evening. People at the middle top of the painting are taking their medicines. People down the bottom of the painting sometimes take their medicine and sometimes throw it away. Then young kids can find that medicine and take it and become sick. The two black paintings show that when people don't take their medicine properly, they die. Around the outside of the painting are a few bush medicines.