

# RENAL FAILURE

— *how drugs can damage the kidney*

By CAROLINE ASHLEY, MSc, MRPharmS

*The first issue of Hospital Pharmacist in February 1994 featured renal pharmacy. With the number of patients requiring treatment for renal failure increasing significantly, the 10th anniversary issue returns to this topic. The first article in this month's special feature reviews drugs that can cause kidney failure*

ALFRED PASIEKA / SPL

*Coloured computed tomography (CT) scan of a section through a whole human kidney*

**D**rug-induced renal failure is a well-recognised phenomenon, although the incidence of drug-induced renal disease remains uncertain. However, some reports suggest that between 5 and 20 per cent of cases of acute renal failure can be directly attributed to drugs and chemicals, although minor damage may pass undetected. It is important to be aware of the types of drug that can induce renal impairment because, if suspected and acted on early, the damage to the kidney may be reversible.

The kidneys provide the final common pathway for the excretion of many drugs and their metabolites, and therefore are frequently subjected to high concentrations of potentially toxic substances. Drugs and their metabolites are taken up selectively and concentrated by the renal tubular cells before excretion into the urine, so high intracellular concentrations are attained, particularly in

the renal medulla, which has relatively little vasculature compared with the cortex. As a result, direct toxic damage occurs, generally affecting the renal tubular cells and renal papillae. Nephrotoxicity of this type tends to be dose-dependent. Many groups of drugs can cause renal damage, and these effects are accentuated in patients with pre-existing renal impairment.

There are various ways in which drugs can cause nephrotoxicity, but the main effects of drugs on the kidneys may be generally categorised as follows:

- Pre-renal effects (eg, water and electrolyte loss, increased catabolism, vascular occlusion, altered renal haemodynamics)
- Obstructive uropathy
- Allergic or immunological damage (eg, hypersensitivity reactions resulting in vasculitis, interstitial nephritis, glomerulonephritis)
- Direct nephrotoxicity (giving rise to acute tubular or interstitial damage and renal papillary necrosis)

## PRE-RENAL EFFECTS

**D**rugs which decrease renal perfusion will have an indirect adverse effect on renal function. This is seen as an acute reduction in glomerular filtration rate (GFR) which is usually reversible on restoring blood supply to the kidneys. Any drug which compromises the circulation may induce acute renal failure — this includes drugs which decrease cardiac output and those that increase peripheral vasoconstriction.

**Volume depletion** Volume depletion with water and electrolyte loss can occur with excessive use of laxatives or aggressive diuretic therapy, particularly with the loop diuretics. This can especially pose a problem in the elderly, but severe renal failure seldom occurs, except in patients with pre-existing renal disease. Similar effects are seen with lithium, and there is a synergistic toxicity with the concurrent use of lithium and diuretics. Non-steroidal anti-inflammatory drugs (NSAIDs) can exacerbate pre-renal

*Ms Ashley is principal pharmacist renal services, Royal Free Hampstead NHS Trust, London*

effects by further reducing renal perfusion. Hypokalaemia from laxative-induced diarrhoea, or overuse of diuretics in the elderly, can produce a chronic nephropathy.

**Increased catabolism** Glucocorticoids can raise plasma urea levels by increasing catabolism. However, renal function is not usually affected unless the individual is dehydrated or there is a degree of pre-existing renal damage present.

Tetracyclines inhibit the incorporation of amino acids into protein, causing a rise in plasma urea levels. They also increase urinary sodium excretion, and may induce nausea, vomiting and diarrhoea, thus further compromising renal perfusion. In renal failure, tetracycline excretion is delayed and the toxic effects increased, with the exception of doxycycline, which has minimal anti-anabolic effects and is eliminated rapidly, even in patients with renal failure.

**Vascular occlusion** Arteriolar and venous occlusion may occur with oestrogen therapy, including oral contraceptives, or as a complication of anticoagulant therapy or following drug-induced haemolysis. This effect is usually reversible, but does occasionally result in the development of acute renal failure.

**Altered renal haemodynamics** Some drugs have specific effects on renal perfusion. Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists can alter renal haemodynamics through their vasodilator effects on the efferent glomerular arterioles. Angiotensin II has a number of intra-renal effects, for example, regulation of renal blood flow and GFR, as well as the tubular reabsorption of sodium and the inhibition of renin release. In patients with severe renal impairment or renal artery stenosis, angiotensin II acts within the kidney to constrict the efferent

glomerular arteriole and maintain glomerular filtration. ACE inhibitors block this effect and cause vasodilatation of the efferent arteriole, leading to a sudden deterioration in GFR. Ideally, the patient's renal function should be measured before starting therapy, and again between one and three weeks after commencing treatment with either an ACE inhibitor, or an angiotensin-II receptor antagonist. A sharp rise in the patient's serum creatinine might indicate the presence of bilateral renal artery stenosis, where the use of ACE inhibitors is contraindicated. Any renal damage is usually reversible if the drug is discontinued promptly. Concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or diuretics does increase the risk of renal damage. There is also a greater risk of developing hyperkalaemia if ACE inhibitors and potassium-sparing diuretics are prescribed together.

NSAIDs inhibit prostaglandin E2, D2 and I2 synthesis within the kidney. These are all potent vasodilators which play an important role in maintaining blood flow to the glomerulus and medulla, especially when vasoconstrictor substances such as angiotensin II or anti-diuretic hormone (ADH) are increased in conditions such as heart failure or severe hypertension. Inhibition of prostaglandin synthesis by NSAIDs results in marked vasoconstriction and a significant decrease in renal blood flow, GFR and urine volume, accompanied by oedema and hypertension. Renal function usually recovers if NSAID therapy is withdrawn early enough, although permanent damage can occur.

Some renally toxic drugs affect kidney function by more than one mechanism, including vasoconstriction. High whole blood levels of both ciclosporin and tacrolimus are associated with a deleterious

effect on renal haemodynamics, since they cause intense constriction of the microvasculature within the kidney, resulting in reduced renal perfusion, a fall in GFR, and hypertension. Consequently, doses must be adjusted to maximise therapeutic effect while minimising renal damage. Whole blood ciclosporin levels greater than 400ng/ml are associated with tubular damage, while levels lower than 100ng/ml are associated with increased risk of acute rejection. Many drugs affecting the cytochrome P450 system will interact with ciclosporin to alter blood levels.

#### — OBSTRUCTIVE UROPATHY

Obstruction to urine flow through the kidneys can be caused by a number of factors, including ureteric fibrosis, renal calculi, blood clots, and mechanical tubular blockage, all of which can result from drug therapy.

**Anticoagulants** Anticoagulants or fibrinolytic agents can cause bleeding in patients, which subsequently causes blood clot formation leading to ureteric obstruction. Retroperitoneal haemorrhage following anticoagulation therapy can also cause ureteric obstruction by external compression. This may be more prevalent in patients with severe renal impairment, since uraemia-induced platelet dysfunction renders the patient more susceptible to bleeding.

**Retroperitoneal fibrosis** Retroperitoneal fibrosis is the overgrowth of fibrous tissue in the lumbar region of the peritoneum. The ureters become embedded, resulting in unilateral or bilateral obstruction and renal failure. The condition has been attributed to several drugs, including methysergide, beta-blockers and methyldopa, but it is mainly ergot derivatives that cause this problem. It

has also been reported to occur with the anti-parkinson drugs bromocriptine and pergolide.

**Ureteric fibrosis** Ureteric fibrosis and obstruction due to sloughed papilla are secondary complications of analgesic nephropathy.

**Tubular blockage: crystalluria** During the treatment of myeloproliferative disorders with cytotoxic agents, tumour-lysis syndrome can occur, particularly if there is a large tumour burden. As a result, uric acid crystals may be deposited in the renal tubules to such an extent that the tubules become blocked, leading to the onset of acute renal failure. The use of prophylactic allopurinol or rasburicase plus the maintenance of a high fluid intake may allay this effect. There is a theoretical possibility of xanthine crystals forming as a result of allopurinol therapy as uric acid is replaced by xanthine; however, the risk of xanthine nephropathy is relatively low.

The early sulphonamides such as sulfathiazole and sulfadiazine were relatively water-insoluble and tended to crystallise in acidic urine. Even with modern sulphonamides, a high fluid intake should be maintained. Crystalluria has also been reported to occur after therapy with acetazolamide, high-dose mercaptopurine, methotrexate, cisplatin, probenecid, naftidofuryl, aciclovir, indinavir, codofovir and ganciclovir.

**Tubular blockage: proteins** Radiological contrast media have been noted to cause precipitation of proteins such as Bence-Jones within the renal tubules. With this in mind, great care should be exercised when using these agents in dehydrated patients or those with myeloma, and the maintenance of a high fluid intake is essential.

**Tubular blockage: haemoglobin** Drug-induced intravascular haemolysis can occur in patients with specific conditions, for example, glucose 6-phosphate dehydrogenase deficiency. If patients were to receive drugs such as antimalarials, sulphonamides, co-trimoxazole, aspirin, paracetamol or occasionally rifampicin, they could experience drug-induced haemolysis. The resulting haem fragments can lead to sufficient haemoglobinuria to block the renal tubules, resulting in acute renal failure.

Analogously, drugs that cause rhabdomyolysis can cause renal insufficiency via myoglobinuria. These include the statins, particularly when used in combination with the fibrates. The risk of rhabdomyolysis is also increased when statins are co-prescribed with ciclosporin.

**Tubular blockage: calcium nephropathy** Over-prescribing of vitamin D preparations

can lead to hypercalcaemia with subsequent calcium deposition within the kidney. Renal calculi (kidney stones) have been described following the excessive consumption of preparations containing vitamin D, calcium-containing antacids, silicates and uricosuric agents.

## — ALLERGIC OR IMMUNOLOGICAL

**Acute interstitial nephritis** Acute interstitial nephritis is a hypersensitivity reaction, characterised by an acute fall in GFR within hours or days to months after exposure to a particular drug. Accompanying symptoms include considerable proteinuria and macroscopic or microscopic haematuria, plus fever, rash, arthralgia and abnormal liver function tests. Recovery of renal function usually occurs over a period of between one and 12 months after discontinuation of the drug, but permanent impairment can result. Steroids may be helpful, although there is no conclusive evidence that they enhance the rate or degree of recovery from acute renal failure. It is important to identify the causative agent since kidney damage is potentially reversible. Many drugs have been reported to cause acute interstitial nephritis, including allopurinol, carbamazepine, cimetidine, erythromycin, gentamicin, interferon, minocycline, penicillins, phenytoin, propranolol, sulphonamides, azathioprine, cephalosporins, clofibrate, frusemide, gold, isoniazid, NSAIDs, phenobarbitone, phenindione, rifampicin and thiazides.

**Chronic interstitial nephritis** Chronic interstitial nephritis, also known as analgesic nephropathy, is characterised by severe papillary necrosis. It is often not diagnosed, since patients tend to under-report their use of analgesics, but it is one of the most common forms of drug-induced renal failure, and occurs following excessive analgesic use. It can cause both acute and chronic renal failure, accounting for between 5 and 30 per cent of patients referred for dialysis worldwide. However, it is one of the few preventable causes of chronic renal failure. Acute renal damage may result from allergic reactions, direct toxic effects to the tubules or acute reduction in renal blood flow. Tubular necrosis with oliguric renal failure may occur following paracetamol overdose, resulting from the formation of toxic metabolites mediated via a cytochrome P450-dependent mono-oxygenase. Chronic damage (analgesic nephropathy) is seen after prolonged use of analgesics. Analgesic combinations, particularly those containing salicylates, caffeine or paracetamol, seem to increase the risk of chronic tubular interstitial disease, suggesting a synergistic effect. Paracetamol can cause direct oxidative damage to renal tubular cells, and

aspirin potentiates the damage in two ways: it inhibits the synthesis of renal prostaglandins, thus reducing medullary blood flow and causing ischaemia, and it inhibits the enzyme systems involved in the defence of kidney tissue against oxidative damage. Papillary necrosis can occur following the consumption of between one and two kilograms of analgesics, equivalent to six tablets per day for between three and five years, but many patients have taken more than 10 times this amount by the time the diagnosis is made. Discontinuation of analgesics often results in stabilisation or improvement of renal function. Conversely, continued consumption of analgesics leads to progressive renal damage. NSAID therapy is a common cause of renal failure in elderly or arthritic patients.

## Drug-induced glomerulonephritis

Drug-induced glomerulonephritis is an immune-mediated disease where antigen-antibody complexes accumulate within the glomerulus, with the deposition of immunoglobulins and complement along the glomerular basement membrane and in blood vessels, precipitating an inflammatory response. Infection and numerous drugs are known to act as antigens or allergens in this situation. The result is a reduced GFR, salt and water retention, expansion of the intravascular volume, and hypertension. This is known as nephritic syndrome. If heavy proteinuria also develops, the patient then develops nephrotic syndrome. Drugs known to cause glomerulonephritis include allopurinol, dapsone, halothane, NSAIDs, penicillins, probenecid, sulphonamides, tolbutamide, captopril, gold, hydralazine, penicillamine, phenindione, rifampicin and thiazide diuretics.

**Lupus erythematosus** Three drugs in particular are associated with lupus erythematosus syndrome: hydralazine, procainamide and isoniazid. Others drugs reported to cause it include methyldopa, penicillamine, phenytoin, and ethosuximide. The condition may be genetically determined, since it is more common in slow acetylators, and becomes more prevalent with prolonged treatment. It is characterised by depositions of IgG and C3 in the glomerulus, but the effects are readily reversible, and severe renal impairment seldom occurs.

## — DIRECT NEPHROTOXICITY

**Acute tubular damage** If acute renal failure caused by pre-renal effects is not reversed by restoring kidney perfusion, acute tubular necrosis or, more rarely, acute cortical necrosis occurs. Tubular necrosis can also be a direct toxic effect of drug therapy. Acute tubular damage can occur with normal

doses but more often is dose-dependent, resulting from high-dose treatment or accumulation of a drug in a patient who is typically either dehydrated or has pre-existing impairment of renal function. Potentiation of the renal damage occurs with the co-administration of two or more nephrotoxic agents.

Examples of drugs causing direct tubular damage are aminoglycosides (adjust dose according to renal function, and monitor blood levels), cephalosporins (the second and third generation cephalosporins are not so nephrotoxic), colistin, frusemide (which also potentiates the nephrotoxicity of aminoglycosides, cephalosporins and polymyxins), amphotericin (causes acute proximal and distal tubular damage, renal tubular acidosis and hypokalaemia), gold and mercurial compounds, paracetamol and aspirin in overdosage, and NSAIDs (especially in dehydrated or elderly patients). Interestingly, the transplant anti-rejection drugs ciclosporin and tacrolimus, in addition to their effects on intra-renal haemodynamics, also have a direct tubular toxic effect. Ciclosporin nephrotoxicity is potentiated by aminoglycosides, vancomycin, ciprofloxacin and NSAIDs, which themselves can also cause direct tubular and interstitial damage.

**Radiological contrast media** Acute renal failure may follow contrast radiography,

especially in patients with diabetes, jaundice, myeloma, dehydration or pre-existing renal disease, where there is prolonged excretion of contrast media through the kidneys, resulting in direct tubular damage. In general, the older ionic contrast media are far more nephrotoxic than their newer, non-ionic counterparts. Within the group of non-ionic contrast media, the extremely hyperosmolar agents (1500–1800 mOsm/kg) are associated with a greater toxic effect than the lower hyperosmolar agents (600–850mOsm/kg). However, the newest iso-osmolar agents are showing promising results with regards to their kidney-sparing effects.

**Osmotic nephritis** Osmotic nephritis is the swelling of the proximal tubular cells of the kidney following the renal filtration and excretion of carbohydrate plasma expanders such as dextrose, mannitol and dextran. Low molecular weight dextrans can cause acute renal failure and should not be given to patients with oliguria or incipient renal failure. Any resulting renal damage may be irreversible.

**Distal tubular damage** Fluorinated anaesthetic agents have been reported to cause acute distal tubular damage, especially in obese patients, resulting in polyuria and hypernatraemia.

Lithium salts can cause nephrogenic diabetes insipidus, resulting in the production of a large volume of dilute urine regardless of the body's store of water. This may lead to hypernatraemia, and is unresponsive to vasopressin and aldosterone. The polyuria and dehydration with renal damage leads to increased plasma lithium levels, thus exacerbating the effect. Both acute and chronic renal failure can occur, with scarring of the renal interstitium.

Inappropriate secretion of ADH, the hormone responsible for controlling the rate at which kidneys excrete or retain free water, can result in hyponatraemia and water intoxication. Of the drugs associated with inappropriate ADH secretion, the most important are carbamazepine, vincristine and cyclophosphamide.

## CONCLUSION

There are many factors involved in drug-induced renal failure, and some drugs produce damage by more than one mechanism. One of the most important principles in drug-induced renal disease is that patients with pre-existing renal impairment, which includes the elderly population, can be predisposed to further renal damage which can precipitate acute renal failure. Hence, particular care should be taken to avoid or limit the use of nephrotoxic drugs in such patients.

### Hospital Pharmacist online

*Hospital Pharmacist* is also published online every month. The website allows access to back issues: from January 2000 through to the current issue. Links to *Hospital Pharmacist's* credit for learning series and to *The Pharmaceutical Journal's* continuing professional development articles are also available. Advice to contributors is also provided. This, and other useful information, is found at [www.pjonline.com/hp](http://www.pjonline.com/hp)

### The renal pharmacy group

The UK renal pharmacy group has been established to encourage the provision of high quality pharmaceutical services to renal patients and associated health care professionals. The group is open to all pharmacists and pharmacy technicians with an interest in renal medicine. Corporate membership is also available. Further information is available from the groups' website at [www.renalpharmacy.org.uk](http://www.renalpharmacy.org.uk)

### FURTHER READING

1. Aronson JK. Drugs and renal insufficiency. *Medicine* 2003;31:103–9.
2. Matzke GR, Frye RF. Drug administration in patients with renal insufficiency. Minimising renal and extrarenal toxicity. *Drug Safety* 1997;16:205–31.
3. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. *New England Journal of Medicine* 2003;348:491–9.
4. Davies DM. *Textbook of adverse drug reactions*. 4th ed. Oxford:Oxford Medical Publications;1991.
5. Fillastre J-P, Godin M. Drug induced nephropathies. *Oxford textbook of clinical nephrology*. 2nd ed. Oxford:Oxford Medical Publications;1997. p2645–58.