Drug Prescribing in Renal Impairment

Renal impairment may be **acute** or **chronic** - both of which can result in problems with medications. Renal impairment may be the result of a variety of renal or systemic diseases, such as **diabetic nephropathy** or **systemic lupus erythematosus**. Normal ageing results in a decline in renal function due to loss of nephrons. When prescribing for elderly patients, it should therefore be assumed that some degree of renal impairment exists[1, 2]. If even mild renal impairment is considered likely, renal function should be checked before prescribing any drug which requires dose modification. Reasons for problems with medications in renal impairment include:

- Failure to excrete a drug or its metabolites.
- Many side-effects being poorly tolerated by patients with renal impairment.
- Some drugs ceasing to be effective when renal function is reduced.

Computerised alerts are likely to become more important in reducing errors of prescribing in patients with renal impairment[3, 4].

Assessment of renal function[5]

See separate Assessment of Renal Function article.

- Normal GFR is approximately 100 ml/minute/1.73 m$^2$.
- Since April 2006 in the UK, most local laboratories calculate estimated glomerular filtration rate (eGFR) on all samples sent for creatinine measurement.

Prescribing in renal impairment

- Drugs that are renally excreted may need to have their doses reduced in patients with renal insufficiency or end-stage kidney disease:
  - For prescribing purposes, renal impairment is usually divided into three grades:
    - Mild: GFR 20-50 ml/minute; serum creatinine approximately 150-300 µmol/L.
    - Moderate: GFR 10-20 ml/minute; serum creatinine approximately 300-700 µmol/L.
    - Severe: GFR less than 10 ml/minute; serum creatinine >700 µmol/L.
  - Patients with a GFR above 50 ml/minute do not usually require any dosage adjustment.
  - Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when the renal reserve is already reduced.

- The situation may change if a patient begins dialysis, since some drugs will be removed by the dialysis. Dialysis may lead to the loss of therapeutic effect for some drugs.
- Drugs to which particular attention must be given include many antibiotics, histamine H$_2$-receptor antagonists, digoxin, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs).

- For many drugs with only minor or no dose-related side-effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient. For more toxic drugs with a small safety margin, dose regimens based on GFR should be used.
- The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, if the size of the maintenance dose is reduced it will be important to give a loading dose if an immediate effect is required. The loading dose should usually be the same size as the initial dose for a patient with normal renal function.

Drugs causing biochemical changes

- Prescribing any drug that increases potassium levels is potentially very dangerous - eg, potassium supplements and potassium-sparing diuretics. Other products that contain potassium include ispaghula husk laxatives.
- Products with a high sodium content (eg, some antacids) may cause sodium and water retention in patients with renal impairment.
- Excessive vitamin D replacement therapy can cause hypercalcaemia that may precipitate or exacerbate renal impairment. Many patients with chronic kidney disease (CKD) are prescribed alfalcacidol; therapy should therefore be closely monitored.

Nephrotoxic drugs

Drugs causing prerenal damage

- Drugs that cause excessive gastrointestinal losses, either through diarrhoea or vomiting, also cause volume depletion and may precipitate acute kidney injury (AKI).
- NSAIDs, even in short courses, can cause AKI as a result of renal underperfusion.
- Angiotensin-converting enzyme (ACE) inhibitors can also cause a deterioration in renal function. However, this is a problem only in patients with compromised renal perfusion, particularly those with renal artery stenosis.
Care should be taken when an ACE inhibitor and NSAID are prescribed together, as this combination may precipitate an acute deterioration in renal function.

Drugs causing intrarenal damage
- Intrarenal damage may result in a direct toxic effect on the kidneys or hypersensitivity reactions.
- Most drugs that cause damage within the kidneys do so as a result of hypersensitivity reactions, which involve either glomerular or interstitial damage.
- Drugs that have been reported to cause glomerulonephritis include penicillamine, gold, captopril, phenytoin and some antibiotics, including penicillins, sulfonamides and rifampicin.
- Drugs that may cause interstitial nephritis include penicillins, cephalosporins, sulfonamides, thiazide diuretics, furosemide, NSAIDs and rifampicin.
- There are a number of drugs that cause direct toxicity to the renal tubules (acute tubular necrosis) - eg, aminoglycosides, amphotericin and ciclosporin.

Drugs causing postrenal damage (urinary tract obstruction)
- High-dose sulfonamides, acetazolamide or methotrexate may cause crystalluria and could therefore cause urinary tract obstruction.
- Anticholinergics (eg, tricyclic antidepressants), and alcohol may cause urinary tract obstruction due to retention of urine in the bladder.

Other nephrotoxic drugs
- Cephalosporins: cephaloridine, one of the first cephalosporins introduced, has been associated with direct renal toxicity and is no longer in clinical use. Other cephalosporins are much less likely to produce renal damage but third-generation cephalosporins (eg, cefixime) have (very rarely) been reported to cause nephrotoxicity.
Analgesics:
- NSAIDs may cause AKI due to hypoperfusion and interstitial nephritis, as well as analgesic nephropathy (chronic interstitial nephritis and papillary necrosis).
- Analgesic nephropathy has been most commonly seen with combination analgesic products that contain aspirin and/or paracetamol.
- Analgesic nephropathy is one of the few preventable causes of CKD. Discontinuation of the drugs often results in stabilisation or even improvement in renal function but continued use leads to further renal damage.
- Lithium: serum levels of lithium consistently above the therapeutic range have been associated with development of a nephrogenic diabetes insipidus.

Use of a dosage table
Dose recommendations are based on the severity of renal impairment and creatinine clearance and/or GFR. The serum creatinine concentration is sometimes used instead as a measure of renal function but is only a rough guide, even when corrected for age, weight and sex. Nomograms should be used where accuracy is important.

Further reading & references
- Peritoneal dialysis in chronic kidney disease; Renal Association (2010)
- Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care; NICE Clinical Guidelines (July 2014)
  5. Continuing good CKD management; The Renal Association

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