Common prescribing errors in renal patients

This article will outline some of the common prescribing errors that occur and how to avoid them when prescribing for renal patients including patients with chronic kidney disease, established renal failure and transplant patients.

Medication errors in renal patients can occur in both primary and secondary care and can happen at any time during the patient journey. They can cause mild side effects or lead to a hospital admission or transfer to the renal ward. An American study by Yap et al (2005) found that 25% of patients who had been identified as having chronic kidney disease were prescribed doses of various medications which were too high for their degree of renal impairment. When prescribing for patients with chronic kidney disease it is important not to prescribe anything which may cause a further reduction in renal function.

Acute kidney injury is defined as a rapid deterioration in renal function and can occur over hours to days. Between 5 and 20% of acute kidney injury is drug related (Ashley, 2004). From 5–7% of hospital inpatients and 5–20% of critically ill patients will develop acute kidney injury (Lewington and Kanagasundaram, 2011). The most common medication-related causes are aminoglycosides and radiocontrast agents. In primary care angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, non-steroidal anti-inflammatory drugs and diuretics are the most common causes (Davidman et al, 1991). Acute kidney injury can be subdivided into pre-renal, renal or post-renal failure depending on where the injury occurs.

This article will cover:

- Calculating renal function – which equation to use
- Aminoglycosides
- Other antibiotics
- Antivirals
- Analgesics and adjunctive therapies
- Misinterpretation of blood results
- Anticoagulation
- Prevention of contrast-induced nephropathy
- Transplant medication.

Calculating renal function

If renal impairment is not recognized it can lead to patients receiving inappropriately high doses of medication leading to increased risk of side effects.

Previously creatinine was used as a measure of renal function but unfortunately this is not a good marker especially in patients with a low body mass, so many patients with chronic kidney disease were not identified. The modification of diet in renal disease (MDRD) equation was introduced in 2002 and was validated in Caucasian and African American patients with chronic kidney disease. It takes into account creatinine level, age, sex and some racial groups and has been normalized for a body surface area of 1.73m^2. Estimated glomerular filtration rate is now reported from all laboratories in the UK at the same time as creatinine and this makes it easier to recognize patients with renal impairment (Devaney et al, 2006; Spruill et al, 2007). Estimated glomerular filtration rate is an accurate indication of renal impairment for most patients, caused by the majority of drugs.

The Cockcroft and Gault equation estimates creatinine clearance and has been used in most pharmaceutical manufacturers' studies. The Cockcroft and Gault equation should be used for high-risk drugs with a narrow therapeutic range and nephrotoxic agents (Levy et al, 2004; Aronof et al, 2007; Spruill et al, 2007; Ashley and Currie, 2009; Joint Formulary Committee, 2011). The Cockcroft–Gault equation is:

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times F}{\text{Serum creatinine (µmol/litre)}}$$

where F=1.23 (males) and 1.04 (females)

Using actual body weight can lead to inaccuracies when prescribing for patients. Ideal body weight should be used for obese patients, as actual body weight would overestimate creatinine clearance leading to an overdose. Use actual body weight for patients with large quantities of muscle to prevent under dosing.

Both equations have limitations so if an accurate glomerular filtration rate is required, e.g. for chemotherapy agents, then an isotope glomerular filtration rate should be used as it gives the most accurate value.

Aminoglycosides

All aminoglycosides can cause nephrotoxicity and ototoxicity if not monitored appropriately or used in at-risk populations. The use of aminoglycosides is increasing with new antibiotic policies being put in place in many

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hospitals to limit the use of broad-spectrum antibiotics which are associated with an increased incidence of *Clostridium difficile* infection. The fear is that this will increase the number of patients referred to the renal service. Sloan et al (2011) showed that at present there has been no increase in the number of patients requiring dialysis, although that does not mean that aminoglycosides are safe to use. Correct dosing and monitoring is essential. Extreme care should be taken in patients in whom it is important to preserve renal function, e.g. those on peritoneal dialysis, and patients with chronic kidney disease or acute kidney injury.

The dose of aminoglycosides needs to be adjusted according to creatinine clearance and therapeutic drug levels. Patients on dialysis should not be dosed using gentamicin nomograms but according to trough levels. Most renal units will have a protocol for this group of patients. Approximately 50% of gentamicin is dialysed out so if a patient is on haemodialysis or haemodiafiltration it is important to know when the trough level was taken in order to determine whether a dose adjustment is required. Aim for pre-dialysis trough levels of <4 mg/dl (<2 mg/dl for post-dialysis or peritoneal dialysis patients). Gentamicin should be used sparingly in patients on peritoneal dialysis as the efficiency of their dialysis relies on them passing urine (Daugirdas et al, 2001; Levy et al, 2004; Ashley and Currie, 2009).

Other antibiotics

When prescribing antibiotics it is important to be aware of the patient's renal function and urine output. Many antibiotics are renally excreted therefore a dose reduction is required. Texts like the *Renal Drug Handbook* by Ashley and Currie (2009) and *Drug prescribing in renal failure: dosing guidelines for adults* by Aronof et al (2007) should be consulted for specific advice.

Timing is also very important in haemodialysis patients, e.g. the frequency of meropenem is reduced to once daily administration and 50% of the drug is dialysed out, but if prescribed in the morning there is the risk either of the drug being totally omitted or being given but dialysed out. In the UK, giving supplementary doses after dialysis is not recommended, as it is much simpler to change the time of administration (Daugirdas et al, 2001; Ashley and Currie, 2009).

- The majority of penicillins and cephalosporins are safe to use in chronic kidney disease. The ones to take care with are benzylpenicillin (Genus Pharmaceuticals, 2008) and ceftazidime (Wockhardt UK Ltd, 2011). Both are neurotoxic in overdose leading to confusion and convulsions (Joint Formulary Committee, 2011). This can be exacerbated if used in combination with other penicillins, e.g. flucloxacillin and benzylpenicillin used together for cellulitis. The dose of both antibiotics should be reduced if there are any signs of neurotoxicity
- Macrolides and quinolones may be given at normal doses for short periods of time but nausea can be problematic with long courses, e.g. for endocarditis, but usually resolves with dose reduction
- If a patient does not pass any urine then some antibiotics are ineffective, e.g. nitrofurantoin. This can also be toxic in overdose, causing neuropathy and blood dyscrasias (Joint Formulary Committee, 2011)
- Care should be taken with vancomycin as the dose is adjusted according to creatinine clearance in chronic kidney disease. In patients having haemodialysis or haemodiafiltration, a single intravenous dose of 1–1.5 g should be given and trough levels monitored. Depending on what type of dialysis is undertaken at the hospital that dose can last for 3–7 days. The normal algorithms for vancomycin should not be used for any dialysis patient as these can lead to toxicity (Daugirdas et al, 2001).

Antivirals

Antivirals can often lead to hospital admissions when given in normal doses to patients with chronic kidney disease. The dose of all antivirals must be significantly reduced. They are extremely neurotoxic and can lead to severe confusion and nausea (Daugirdas et al, 2001). This is the same for all antivirals and is a very common prescribing error, especially in primary care but also within the hospital setting.

Analgesics and adjunctive therapies

According to Levy et al (2004) pain is a common problem in renal patients for numerous reasons, e.g. musculoskeletal pain or neuropathies, and can have a major impact on a patient's quality of life. As with all patients the World Health Organization analgesic ladder should be followed.

Simple analgesia, e.g. paracetamol, is usually not a problem. Opiates can lead to problems if used in normal doses or titrated too quickly in renal patients.

Non-steroidal anti-inflammatory drugs or cyclo-oxygenase-II inhibitors

Non-steroidal anti-inflammatory drugs and to a certain extent cyclo-oxygenase II inhibitors inhibit renal vasodilatory prostaglandins and are contraindicated in chronic kidney disease patients not on dialysis as they reduce glomerular filtration rate (Pham et al, 2009). In dialysis patients non-steroidal anti-inflammatory drugs can be prescribed if the patient is anuric but should be used with caution for as short a period as possible if a patient on haemodialysis or peritoneal dialysis still passes urine (Levy et al, 2004; Watson et al, 2006; Ashley and Currie, 2009). It is important to remember that many patients on dialysis retain some renal function (glomerular filtration rate <5 ml/min) and a useful urine output allows them more freedom in terms of fluid intake and a reduction in the number of hours on dialysis or perito-

neal dialysis exchanges. Loss of residual renal function in patients on peritoneal dialysis may critically reduce weekly clearance of creatinine such that patients need to convert to haemodialysis.

Gastrointestinal bleeding is more common in dialysis patients so they should always receive stomach protection for the duration of the non-steroidal anti-inflammatory drug course.

Cyclo-oxygenase II inhibitors and cyclo-oxygenase II selective non-steroidal anti-inflammatory drugs are associated with an increased risk of thrombotic events (e.g. myocardial infarction and strokes) so if at all possible should be avoided in patients with renal disease who already have an increased risk of cardiovascular disease. With non-steroidal anti-inflammatory drugs the data are less clear with the greatest risk being with diclofenac followed by ibuprofen, and naproxen being the safest (Joint Formulary Committee, 2011).

Weak opioids

These can cause constipation which may be a problem, especially if using codeine in patients on peritoneal dialysis. This can result in flow problems with their dialysis exchanges causing treatment failure.

If tramadol is to be used start with 50 mg every 8–12 hours and increase gradually to minimize side effects. Many renal patients are also on antidepressants; tramadol should be avoided in patients on selective serotonin-reuptake inhibitors because of the risk of serotonin syndrome.

Dihydrocodeine should be avoided if possible because of the risk of accumulation as dihydrocodeine and its metabolites are renally excreted (Levy et al, 2004; Watson et al, 2006).

Opioids

Opiates used, for example, in postoperative pain or palliative care patients can lead to problems if used in normal doses or titrated too quickly. The main points to be aware of are:

- Opiates have considerable tubular metabolism and renal excretion leading to accumulation in renal patients
- Renal patients have increased CNS sensitivity to opiates
- Sustained release preparations, e.g. MST or Zomorph, may take a few days to accumulate, take longer to clear and cause side effects
- It can be very difficult to balance pain control with side effects
- Renal patients are more likely to experience nausea and constipation as a result of dialysis or uraemia and can be difficult to differentiate from side effects of the opiates.

Morphine is metabolized to morphine-6-glucuronide (a renally excreted active metabolite more potent than morphine) and morphine-3-glucuronide resulting in accumulation and an increased effect. The half-life of morphine-6-glucuronide is increased from 3–5 hours in patients with normal renal function to 50 hours in patients with stage 5 chronic kidney disease. A starting dose of 2.5–5 mg 8-hourly is usually sufficient. If increased too quickly or started at too high a dose patients can suffer severe side effects (Levy et al, 2004; Watson et al, 2006; Ashley and Currie, 2009). For example, a haemodiafiltration patient was discharged from a vascular ward on MST for pain resulting from vascular insufficiency. He had previously been opiate naive before admission. The day after the operation he was prescribed MST 10 mg twice daily which 2 days later, on the day of discharge, was increased to 50 mg twice daily. Two days later the patient was admitted to the hospital as the patient's wife thought he had had a stroke as he was so unresponsive. After a few days and a couple of dialysis sessions the patient recovered.

Oxycodone should be treated in a similar way to morphine. Although it is sometimes slightly better tolerated in renal patients compared to morphine the same problems with accumulation are seen as reported by Levy et al (2004), Watson et al (2006), Pham et al (2009) and Ashley and Currie (2009).

Patches of fentanyl and buprenorphine can also be used. Again low doses are recommended, e.g. start with fentanyl 12 μg every 3 days and with the lowest buprenorphine patch. Remember a fentanyl 25 μg patch is equivalent to 90 mg daily of oral morphine.

Pethidine should be avoided because of the risk of accumulation and neurotoxicity.

The Liverpool Care Pathway for the Dying Patient (2008) for end of life care recommends using fentanyl or alfentanil first line with oxycodone and morphine being alternatives if they are unavailable. Fentanyl and alfentanil have the advantage that they are hepatically metabolized so less accumulation should occur. They should still be started at a low dose and gradually increased.

Adjuvant medication

Adjuvant pain medication should also be used with care. Phantom limb pain and neuropathic pain are common problems with renal patients because they often have concurrent vascular disease and diabetes. Again if adjuvant medications are started at too high a dose or titrated too quickly they can lead to nausea, drowsiness, confusion and a fear of using the drug.

Suggested starting doses are: amitriptyline 25 mg at night, gabapentin 100 mg daily and pregabalin 25 mg daily. The dose can then slowly be increased at 1–2-weekly intervals depending on patient tolerability (Ashley and Currie, 2009). The maximum dose the patient tolerates is very patient specific, e.g. a 100 kg young man can sometimes tolerate no more than 100 mg daily of gabapentin while an 80-year-old 50 kg woman may be able to tolerate 300 mg three times a day.

Misinterpretation of blood results

This is a major problem for patients on haemodialysis or haemodiafiltration. To measure dialysis adequacy urea and electrolytes are measured before and after dialysis. The post-dialysis potassium level can sometimes be under 3 mmol/litre (this will rebound slightly within an hour of the end of dialysis) although the pre-dialysis potassium may be over 5 mmol/litre. If this post-dialysis result is acted on and potassium supplements prescribed it can lead to hyperkalaemia. For example, a haemodialysis patient was admitted with sepsis. Her potassium level was 3.2 mmol/litre (her pre-dialysis potassium level had been 4.6 mmol/litre) and so she was started on sando K 2 tablets three times a day. Two days later her potassium level was 6.2 mmol/litre.

Another error with post-dialysis results is with estimated glomerular filtration rate which will always be much higher post-dialysis, giving the impression that the patient's kidney function has improved if the results are looked at in isolation.

Anticoagulation

Patients with renal impairment are at increased risk of bleeding because of their uraemic state and care should be exercised when prescribing anticoagulants in this population.

Most hospitals now use low molecular weight heparins to treat deep vein thrombosis, pulmonary embolism and acute coronary syndrome as well as medical and surgical venous thromboembolism prophylaxis while in hospital. Low molecular weight heparins are renally excreted, so they accumulate in patients with renal impairment and can increase the risk of bleeding complications (Lobo, 2007). The pharmacokinetics and licensed indications of the different low molecular weight heparins are not all the same and the information available in renal impairment varies significantly. Tinzaparin has the best pharmacokinetic profile whereas enoxaparin provides the best information on dosing in renal impairment (1 mg/kg once daily).

Many hospitals will use unfractionated heparin in place of low molecular weight heparins in patients with a glomerular filtration rate <30 ml/min. Unfractionated heparin should also be used with caution as it too is associated with an increased bleeding risk in patients with chronic kidney disease but this is easier to reverse and has a shorter half-life than the low molecular weight heparins. As unfractionated heparin is more difficult to use some hospitals will still use low molecular weight heparins but at lower doses (20–50% lower) and will attempt to measure anti-Xa levels, however, this is not always practical and should only be considered in high-risk patients or patients on extended courses.

Fondaparinux is now also used in a number of hospitals but again a dose reduction is required in patients with chronic kidney disease (the manufacturer advises avoiding use in patients with a glomerular filtration rate <30 ml/min) to prevent accumulation and increased risk of bleeding. Fox et al (2007) found fondaparinux (normal dose) to be as effective as enoxaparin (reduced dose) and associated with less bleeding complications in acute coronary syndrome or non-ST elevation myocardial infarction, although the risk of bleeding increased in both groups as the patients' glomerular filtration rate reduced. A study has shown that fondaparinux 2.5 mg every second day in patients with severe renal impairment has a similar pharmacokinetic profile as 2.5 mg daily in patients with mild renal failure (Lobo, 2007).

Warfarin should also be used with care and started slowly not only because renal patients are at increased risk of bleeding but they are often also on a number of medications which interact with warfarin, e.g. omeprazole, simvastatin, clopidogrel, antibiotics as well as receiving heparin or low molecular weight heparin on haemodialysis or haemodiafiltration. Taking a blood sample from a dialysis line for an international normalized ratio test can result in an elevated international normalized ratio because of contamination with the anticoagulant used for dialysis. Yang et al (2010) showed an increased risk of haemorrhagic and possibly ischaemic stroke in haemodialysis patients treated with warfarin for atrial fibrillation.

The newer anticoagulants may provide another option but the only one licensed at the moment – dabigatran – should not be used in severe renal impairment according to the Medicines and Healthcare Products Regulatory Agency (2011) because it has increased bleeding complications.

Prevention of contrast-induced nephropathy

This is the third most common cause of hospital-acquired acute kidney injury. It is directly related to higher complication rates, longer hospital stays and mortality of approximately 20% (Seeliger et al, 2012). The incidence of acute kidney injury can be as high as 90% in high-risk populations, e.g. diabetics or patients with pre-existing renal impairment (Toprak, 2007).

There are many different hypotheses about how to best treat contrast-induced nephropathy but no definite answer. The most important interventions are to ensure the patient is aggressively hydrated with either sodium chloride 0.9% or sodium bicarbonate, and any nephrotoxic agents, e.g. non-steroidal anti-inflammatory drugs and aminoglycosides, stopped. Care should be taken with metformin, which is renally excreted and can cause lactic acidosis in acute kidney injury. Gleeson and Bulugahapitiya (2004) discuss various other treatment options, e.g. N-acetylcysteine, theophylline, mannitol, calcium-channel blockers, dopamine, bosentan and prostaglandins, but there is no conclusive evidence that they make any significant difference. The agent that has been studied most extensively is N-acetylcysteine. The papers that promote it suggest that, as it is inexpensive and well

tolerated, it can be a useful treatment (Kelly et al, 2008), but there are an equal number of papers which have shown it to be no better than placebo (Gonzales et al, 2007).

Ionic high osmolality radiocontrast dye is also associated with increased risk of nephrotoxicity so should be avoided in high-risk patients (Gleeson and Bulugahapitiya, 2004; Toprak, 2007).

The Renal Association advise hydration with sodium chloride 0.9% or isotonic sodium bicarbonate pre-procedure, stopping any nephrotoxic medication and avoiding high osmolar contrast agents (Lewington and Kanagasundaram, 2011).

Transplant medication

Calcineurin inhibitors are metabolized by the cytochrome P450 3A4 system therefore have numerous drug interactions. The most common drug interactions are with antibiotics (especially macrolides), antivirals, antifungals, anticonvulsants, calcium-channel blockers, warfarin and lipid-lowering medication. If patients are started or discontinued from an interacting medication, ensure levels are checked within a few days. Levels should be taken immediately before the dose is taken (Ashley, 2010).

Calcineurin inhibitors are critical-dose drugs and are dosed according to levels so it is very important that the patient always receives the same brand of medication (Popat, 2010).

Ciclosporin comes as Neoral and various branded generics, all of which may have slightly different bioavailabilities and are not interchangeable without drug level monitoring.

Tacrolimus comes in three oral forms: Prograf (a twice-daily preparation), Modigraf (granules for suspension) and Advagraf which is a once-daily preparation. There are now also branded generics available for immediate release tacrolimus (Prograf). The Medicines and Healthcare Products Regulatory Agency (2010) has advised that all calcineurin inhibitors should be prescribed by brand.

The anti-proliferative agents, e.g. mycophenolate and azathioprine, are not critical-dose drugs and the dose is adjusted according to side effects, e.g. gastrointestinal intolerance and myelosuppression.

Mycophenolate comes in two forms – as the mofetil salt (Cellcept) and as mycophenolate sodium (Myfortic). Again the two cannot be interchanged and have completely different doses. Generic substitution of mycophenolate mofetil is possible as it is not blood-level dependant.

Azathioprine has been used in combination with steroids since the early 1960s and various generic formulations are available and normally used. It should never be used in combination with allopurinol as it can cause life-threatening myelosuppression because of reduced excretion of azathioprine.

Conclusions

Patients with chronic kidney disease are a diverse group who are very sensitive to the effects of medication if prescribed inappropriately. Chronic kidney disease is very common in the elderly population and dosage adjustments should always be considered when prescribing for them. Every patient should be treated as an individual. **BJHM**

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KEY POINTS

- Estimated glomerular filtration rate is an adequate measure of renal function for the majority of drugs but the Cockcroft and Gault equation should be used for nephrotoxic and critical-dose medication.
- Renal units often have their own guidelines for gentamicin and vancomycin.
- Antivirals should always be reduced in chronic kidney disease.
- Always start with a low dose and gradually increase the doses of analgesics in renal patients.
- Always know when a patient's blood test was taken in relation to his/her haemodialysis or haemodiafiltration session.
- Low molecular weight heparins accumulate in chronic kidney disease leading to an increased risk of bleeding complications.
- Before giving patients contrast dye ensure they are adequately hydrated.
- Prescribe calcineurin inhibitors and Myfortic by brand and do not switch between different generic preparations.

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