Prescribing for patients on dialysis

**SUMMARY**

The pharmacokinetics of a drug may be altered in patients with renal impairment who require dialysis. Some drugs are contraindicated.

The drug’s clearance and therapeutic index determine if a dose adjustment is needed. A lower dose or less frequent dosing may be required.

Consult a reference source or the patient’s nephrologist before prescribing. Start at a low dose and increase gradually. If possible give once-daily drugs after dialysis.

**Introduction**

The prevalence of kidney disease is rising and there are now over 11 400 Australians receiving dialysis. These patients may rely on their GPs for much of their medical care. Prescribing for patients who are on dialysis can be challenging, however a few basic principles and the use of easily available reference materials (Box) can ensure that these patients are managed safely. A study in the USA found up to one-third of haemodialysis patients are prescribed a drug at a dose that differs from the recommended dose and adverse reactions occur in one-fifth.

Polypharmacy, multiple comorbid illnesses and drug clearance by dialysis all complicate prescribing.

**Dialysis**

Dialysis is the transfer of uraemic solutes from blood to an extracorporeal fluid (dialysate) by diffusion across a semi-permeable membrane. This may be done by pumping blood through a dialyser containing a membrane and dialysate (haemodialysis), or by instilling dialysate into the peritoneal cavity and using the peritoneum itself as a membrane (peritoneal dialysis). Solute removal via haemodialysis is relatively efficient and so can be done intermittently – typically three times per week – whereas peritoneal dialysis is less efficient and so is usually required for 12–24 hours every day.

**Principles of prescribing**

Renal impairment reduces the clearance of some drugs. When prescribing for patients on dialysis, it is essential to consult a reference guide (Box) to determine if the drug is subject to renal clearance and requires a dose adjustment. Given the paucity of large pharmacokinetic studies, dosing recommendations often differ and it may be difficult to favour one source over another. If no ‘dialysis’ dose is available, one should assume that the patient’s glomerular filtration rate is less than 10 mL/min/1.73m². Although many patients have some residual renal function, their serum creatinine may fluctuate markedly and it should not be used to estimate glomerular filtration rate.

Dose adjustments can be made by reducing the dose, increasing the interval between doses or a combination of the two. The approach to take is determined by the relative importance of stable serum drug concentrations (for instance to maintain the antimicrobial effect of penicillins), the adverse effects of peak concentrations after intermittent doses, and patient convenience.

Multiple practitioners often share the care of patients on dialysis (e.g. GPs, specialist physicians, vascular surgeons and dialysis nurses). Information about the adjusted dosing regimen should be included in correspondence and, where appropriate, explain why the dose has been adjusted, to avoid confusion.

**Pharmacokinetics**

The two main considerations that determine if a particular drug requires dose reduction in dialysis patients are renal clearance and therapeutic index. Other factors that may affect dosing include clearance by dialysis, increased availability of highly protein-bound drugs due to hypoalbuminaemia, altered volume of distribution and the presence of comorbid hepatic dysfunction.

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**Box Suggested resources for drug dosing in dialysis**

- Australian Medicines Handbook (https://amhonline.amh.net.au)
- MIMS Australia (http://mims.com.au)
- Bailie and Mason’s 2014 Dialysis of Drugs (http://renalpharmacyconsultants.com/publications)
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Clearance
Consider the magnitude of the renal component of total clearance of the drug and any active metabolites. For drugs subject to significant renal clearance, the marked decrease in glomerular filtration rate seen in patients on dialysis results in an increase in half-life and drug accumulation with repeated dosing in the absence of dose adjustment. These changes also apply to renally cleared drug metabolites which may be active or toxic.

The increased half-life also prolongs the time to achieve a steady-state which, in clinical practice, means a longer period is required before judging that the maximum effect of a particular dose has been achieved. The starting dose should be low and caution is required before increasing drug doses. Given the longer time to steady state, a loading dose can be considered if giving a renally adjusted dose could lead to a delay in reaching a therapeutic serum concentration (for instance, if treating a severe infection). In practice, loading doses are rarely used.

Therapeutic index
A drug with a wide therapeutic index may be safely given without a dose reduction knowing that, although the drug concentration will be higher, this is unlikely to result in harm. However, drugs with narrow therapeutic indices may require substantial dose reductions.

Dialysis and drug clearance
Patients on dialysis are subject to extracorporeal clearance of small molecules, including many drugs. The extent to which dialysis removes a particular drug from plasma is dependent on its water solubility, molecular weight, protein binding and volume of distribution. Many reference sources contain lists of drugs cleared by dialysis (Box).

Haemodialysis can pose a challenge as it is intermittent and has the potential for relatively rapid drug clearance. In practice this is most important when prescribing once-daily drugs, especially antibiotics. It may be best to give them after dialysis. Dose timing is typically left unchanged for drugs dosed more frequently, as complex dosing regimens may reduce adherence to therapy. In peritoneal dialysis, timing is not important as the clearance of small molecules is slower and more even than in haemodialysis.

Commonly prescribed drugs
Many drugs are not renally cleared. Specific examples of commonly used drugs include proton pump inhibitors, statins, corticosteroids and calcium channel blockers. They are unlikely to need a dose adjustment in patients on dialysis.

Analgesics
Patients on dialysis may have comorbid pain, but its treatment is often suboptimal. Paracetamol is the preferred simple analgesic. It is safe and can be used without dose modification.

Although nephrotoxicity might be considered of little importance, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may cause sodium retention, hypertension and gastrointestinal toxicity. Due to the increased risk of myocardial infarction seen in the general population, we do not recommend cyclo-oxygenase-2 inhibitors in dialysis patients as they are already at markedly higher baseline cardiovascular risk. Topical NSAIDs appear to be safe as systemic absorption is minimal.

Many opioids, or their active metabolites, are renally cleared (Table). Codeine and morphine have active, renally excreted metabolites so they are not recommended because of the increased risk of toxicity. Hydromorphone is our preferred oral opioid for treating severe pain. It is five to seven times more potent than morphine so starting doses are correspondingly low (0.5–1 mg orally 6-hourly). Its active metabolite hydromorphone-3-glucuronide can accumulate, but is substantially cleared by haemodialysis and is less likely to cause adverse effects than morphine metabolites. Oxycodone may be used, although the sustained-release formulations should be used only with caution due to the risk of accumulation and toxicity. Fentanyl and buprenorphine both undergo hepatic clearance and can be used when the oral route is not suitable. Whichever opioid is chosen, it is important to use small starting doses and closely monitor up-titration to avoid toxicity. Neuropathic pain is common in patients on dialysis. Amitriptyline is heptatically metabolised and does not accumulate. However, it has numerous adverse effects including anticholinergic effects and postural hypotension which may limit its use in patients with multiple comorbidities. Gabapentin and pregabalin are effective and may also treat uraemic pruritis. However, they are extensively renally cleared and marked dose reductions are necessary to avoid sedation, ataxia and dizziness. Doses should be taken after dialysis.

Opioid-induced constipation
In surveys, over half of the patients on dialysis report constipation. Prevention of opioid-induced constipation is particularly important in patients on peritoneal dialysis as constipation may markedly reduce its effectiveness. Lactulose, docusate, senna and bisacodyl are all suitable treatments. Preparations containing polyethylene glycol (macrogol) are also generally safe as laxatives or bowel preparation. Patients should be advised that the co-administered...
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The antiviral drug aciclovir and its prodrugs, famciclovir and valaciclovir, are extensively renally excreted. These drugs accumulate rapidly in patients on dialysis and may cause severe neurological toxicity. They should only be prescribed after discussion with the treating nephrologist and with appropriate dose reduction and close clinical follow-up.

Contrary to recent support for extending its use in chronic kidney disease, it should be avoided in patients on dialysis. Cephalosporins and penicillins have wider therapeutic indices and vary in the need for dose adjustment. Once-daily doses should be prescribed after haemodialysis.

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Antimicrobials

Many antibiotics require dose adjustment in patients receiving dialysis. Therapeutic Guidelines: Antibiotic provides a comprehensive and user-friendly reference.

Nitrofurantoin is primarily renally excreted, and relies on urinary concentration to achieve its effect. It is rarely associated with neurotoxicity and life-threatening pulmonary toxicity.

### Table: Analgesic use in dialysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clearance</th>
<th>Suggested starting dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>Its major renally excreted metabolite hydromorphone-3-glucuronide is inactive</td>
<td>0.5–1 mg orally 4 times a day</td>
<td>Preferred oral opioid in dialysis patients</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Both oxycodone and its active metabolite oxymorphone are renally excreted</td>
<td>2.5–5 mg orally 3 times a day</td>
<td>Use controlled-release preparations with caution</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Active renally excreted metabolite O-desmethyltramadol</td>
<td>50 mg orally twice a day</td>
<td>Maximum 100 mg twice a day</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Hepatic metabolism with no accumulation of metabolites</td>
<td>5 microgram/hour transdermally</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Hepatic metabolism with no active metabolites</td>
<td>12 microgram/hour transdermally</td>
<td>Not dialysed</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Renal excretion</td>
<td>100 mg orally at night on dialysis days</td>
<td>Large dose reductions required</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Renal excretion</td>
<td>25 mg orally at night on dialysis days</td>
<td>Large dose reductions required</td>
</tr>
<tr>
<td>Morphine</td>
<td>Metabolised to renally excreted glucuronide metabolites (M-6-G and M-3-G)</td>
<td>2.5 mg orally 3 times a day</td>
<td>Avoid if possible</td>
</tr>
<tr>
<td>Codeine</td>
<td>Renally excreted active metabolites</td>
<td>–</td>
<td>Avoid</td>
</tr>
<tr>
<td>Dextro-propoxyphene</td>
<td>Cardiotoxic metabolite nonpropoxyphene accumulates</td>
<td>–</td>
<td>Avoid</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Hepatic clearance</td>
<td>1 g orally 3–4 times a day</td>
<td>Preferred simple analgesic</td>
</tr>
</tbody>
</table>

### Anticoagulants

Despite controversy surrounding its use for stroke prevention in dialysis patients with atrial fibrillation, warfarin remains the anticoagulant of choice for those with venous thromboembolism or other indications for anticoagulation. The dose is adjusted according to the INR in the usual manner. Close monitoring and avoidance of supratherapeutic INRs is particularly
imported as patients on dialysis have increased rates of bleeding with warfarin.\textsuperscript{21} Low-molecular-weight heparins are renally excreted and they are rarely used for anticoagulation as their effect is difficult to predict.\textsuperscript{2} Unfractionated heparin is preferred for acute treatment of venous thromboembolism in patients on dialysis. The newer oral anticoagulants (such as dabigatran and rivaroxaban) are contraindicated. They all undergo a degree of renal clearance which makes them unsuitable for patients on dialysis.\textsuperscript{26}

**Conclusion**

Recognising that patients on dialysis are more prone to drug toxicity is the first step in avoiding harm. There are many easily accessible reference sources to guide dose adjustments in renal failure. Clinical judgement is always required to balance the required treatment intensity against the risk of toxicity in an individual patient. If in doubt, contact the treating nephrologist or renal unit pharmacist for advice. In general, commence with a low dose, observe closely for adverse effects and increase the dose only after a timely interval. Put simply: ‘start low and go slow’.

**Conflict of interest:** none declared

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**REFERENCES**


11. Geerts AF, Eppenga WL, Heerdink R, Derijks HJ, Wensing MJ, Egberts TC, et al. The newer oral anticoagulants (such as dabigatran and rivaroxaban) are contraindicated in dialysis patients as they depend on the glomerular filtration of glucose for their effect.\textsuperscript{28}

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**SELF-TEST QUESTIONS**

**True or false?**

7. Trimethoprim is not recommended in patients who require dialysis.

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**ARTICLE**

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