DRUG & THERAPEUTICS LETTER

A Quarterly Bulletin from
Drug Information Unit (DIU)
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Vol. 23 **No. 4** **October– December 2016**

Prescribing for patients on dialysis

Introduction

Ten percentage of the world population is affected by chronic kidney disease (CKD) and millions die each year because they do not have access to affordable treatment.[1] Over two million people worldwide currently receive treatment with dialysis or a kidney transplant to stay alive, yet this number may represent only 10% of the people who actually need treatment to live.[2]

The number of people suffering from kidney disease in Nepal is also significant. Department of Health Services Annual Report of Nepal in fiscal year 2014/2015 reports a total of 29,109 newly diagnosed cases of kidney related morbidities [acute renal failure (16.8%), CKD (17.4%), nephrotic syndrome (44%) and nephritis (21.8%)].[3] Prescribing for patients who are on dialysis can be challenging, however a few basic principles and the use of reference materials can ensure that these patients are managed safely.[4] 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 'dialysis dose' and adverse reactions occur in one-fifth.[4] Polypharmacy, multiple comorbid illnesses and drug clearance by dialysis all complicate prescribing.[5]

Dialysis

Dialysis is the transfer of uremic solutes from blood to an extracorporeal fluid (dialysate) by diffusion across a semi-permeable membrane. Haemodialysis, which can be performed intermittently typically three times per week, is considered more efficient than peritoneal dialysis which has to be done in every 12-24 hours.

Principles of prescribing

Renal impairment reduces the clearance of some drugs. When prescribing for patients on dialysis, it is essential to determine if the drug is subject to renal clearance and requires a dose adjustment. If 'dialysis dose' is not available, dose should be adjusted assuming that the patient's glomerular filtration (GFR) rate is less than 10 mL/ min/1.73m^2.

Dose adjustments can be made by reducing the dose, increasing the interval between doses or a combination of the two. The approach to be taken is determined by the relative importance of stable serum drug concentrations, the adverse effects of peak concentrations after intermittent doses, and patient convenience.

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 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.

Clearance

For drugs or their metabolites that are subject to significant renal clearance, the marked decrease in GFR seen in patients on dialysis

results in increased half-life[6] and hence leads to accumulation with repeated dosing in the absence of dose adjustment.

With increase in half-life, time to achieve a steady-state will also be prolonged.[7] 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.

Therapeutic index

A drug with a wide therapeutic index may be safely given without adjusting the dose. However, drugs with narrow therapeutic indices may require substantial dose reductions.[7]

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.[8]

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. In peritoneal dialysis, timing is not important as the clearance of small molecules is slower and more even than in haemodialysis.[7]

Commonly prescribed drugs

Many drugs such as proton pump inhibitors, statins, corticosteroids and calcium channel blockers, are not renally cleared and may not need 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.[9]

Although nephrotoxicity is of little importance, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may cause sodium retention, hypertension and gastrointestinal toxicity. Cyclo-oxygenase-2 inhibitors are also not recommended because of further increase in risk of cardiovascular problems.[10] Topical NSAIDs appear to be safe as systemic absorption is minimal.[7]

Many opioids, or their active metabolites, are renally cleared. Codeine and morphine have active, renally excreted metabolites so they are not recommended. Hydromorphone is the preferred oral opioid for treating severe pain. It is 5 to 7 times more potent than morphine so starting doses are correspondingly low (0.5–1 mg orally 6-hourly).[9] 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. Due to the risk of accumulation and toxicity, only the sustained-release formulations of oxycodone should be used with caution. Fentanyl and buprenorphine both undergo hepatic clearance and are 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 hepatically metabolised and does not accumulate. However, it's adverse effects including anticholinergic effects and postural hypotension limits its use.[9] 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.[9]

Opioid-induced constipation

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 are also generally safe as laxatives or bowel preparation. Saline laxatives (containing magnesium or phosphate salts) are contraindicated in patients on dialysis due to the possibility of severe electrolyte disturbances. Sodium phosphate-containing bowel preparations can cause severe hyperphosphataemia and calcium phosphate deposition.[11]

Antimicrobials

Many antibiotics such as quinolones, cotrimoxazole, glycopeptides and aminoglycosides require dose reduction in patients receiving dialysis. Trimethoprim should be avoided due to the risk of hyperkalaemia and bone marrow suppression.[12]

Nitrofurantoin is primarily renally excreted. Despite recent support for extending its use in chronic kidney disease, it should be avoided in patients on dialysis.[13] Cephalosporins and penicillins have wider therapeutic indices and vary in the need for dose adjustment. Once-daily doses should be prescribed after hemodialysis.[7]

The antiviral drug aciclovir and its prodrugs, famciclovir and valaciclovir, are extensively renally excreted. These accumulate rapidly in patients on dialysis and may cause severe neurological toxicity. They should only be prescribed after consultation with the treating nephrologist and with appropriate dose reduction and close clinical follow-up.

Anticoagulants

Warfarin remains the anticoagulant of choice for those with venous thromboembolism or other indications for anticoagulation. The dose is adjusted according to the international normalized ratio (INR) in the usual manner. Close monitoring and avoidance of supratherapeutic INRs is particularly important as patients on dialysis have increased risk of bleeding.[14] Low-molecular-weight heparins are renally excreted and they are rarely used.[7] Unfractionated heparin is preferred for acute treatment of venous thromboembolism in patients on dialysis. The newer oral anticoagulants (such as dabigatran and rivaroxaban) are not recommended.

Drugs for diabetes

Patients with diabetes who need dialysis have reduced insulin clearance, so they may be more liable to hypoglycaemia with both insulin and insulin secretagogues (sulfonylureas). These patients may also be at increased risk of hypoglycaemia unawareness due to comorbid illnesses and co-prescribed drugs.[7]

Gliclazide and glipizide are the preferred sulfonylureas as they have short half-lives and no active metabolites. All sulfonylureas should be started at low doses and up-titrated carefully. The dipeptidyl peptidase-4 inhibitors vary in their suitability for use in dialysis so the product information should be reviewed before prescribing.[15] Metformin is contraindicated due to the risk of lactic acidosis. Although not renally excreted, thiazolidinediones are associated with fluid retention and are not recommended. The sodium-glucose co-transporter inhibitors are also not indicated in dialysis patients as they depend on the glomerular filtration of glucose for their effect.[16]

Conclusion

Recognizing that patients on dialysis are more prone to drug toxicity is the first step in avoiding harm. 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 for advice. In general, commence with a low dose, observe closely

for adverse effects and increase the dose only after a timely interval.

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