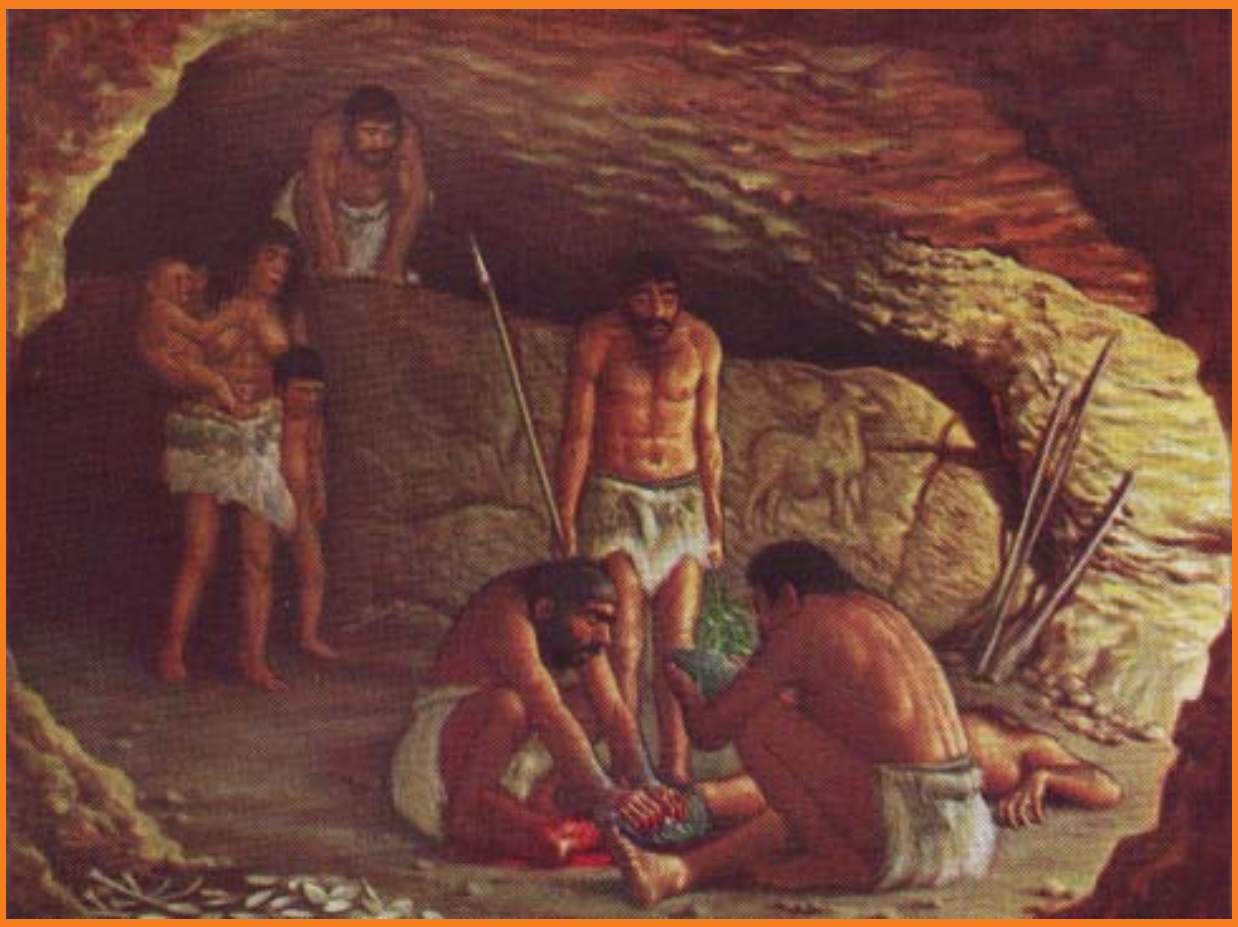
ISSN 1391-0736

The Sri Lanka Prescriber

December 2015; Volume 23, No. 4



CONTENTS

The Sri Lanka Prescriber *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

The Sri Lanka
Prescriber

Copies of the *Sri Lanka Prescriber* and inquiries from M. P. Kuruppu, Deputy General Manager, Marketing, and Ms Anusha Gunatilleke, Manager Promotions and Publicity (Telephone 2338102), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by

Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
E-mail: phrm_cmb@hotmail.com
and
State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2435975
E-mail: anpress@sltnet.lk

Cover picture

BEFORE THE DAWN OF HISTORY

Knowledge of the preparation and application of natural products for healing is as old as man himself. From beginnings as remote and as simple as these came the proud profession of Pharmacy.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Pharmacological management of depression

Three hundred and fifty million people live with depression worldwide. However, it remains undetected, hidden and rarely talked about. The mean age of onset of a depressive episode is about 27 years, with rates twice as much in women as in men. Rates are higher in the unemployed and divorced. Depression is the most important risk factor for completed suicide.

Diagnosing depressive disorder

The two major classification systems – the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; American Psychiatric Association, 2013) and the 10th Revision of the International Classification of Diseases (ICD-10; World Health Organization, 1992) have similar diagnostic criteria.

The ICD-10, which is commonly used in Sri Lanka, differentiates between mild, moderate and severe episodes, based on the number, type, and severity of symptoms. Mild to moderate depressive states are common in general medical practice and in outpatients' departments.

Table 1. The ICD-10 diagnostic criteria for a depressive episode

Typical symptoms

Depressed mood, loss of interest and enjoyment, and reduced energy

Other symptoms

(a) Reduced concentration and attention
(b) Reduced self-esteem and self-confidence
(c) Ideas of guilt and unworthiness
(d) Bleak and pessimistic view of the future
(e) Ideas or acts of self-harm or suicide
(f) Disturbed sleep
(g) Diminished appetite

For depressive episodes of all three grades of severity (mild, moderate and severe) a duration of at least 2 weeks is usually required for diagnosis.

The ICD 10 criteria require duration of symptoms of two weeks or more, but shorter durations may be considered if symptoms are unusually severe or rapid in onset.

At least two typical symptoms and a minimum of two other symptoms are required for diagnosis of mild depression. Moderate depressive episode requires the presence of 2 typical symptoms and 3-4 other symptoms. Diagnosis of severe depressive episode requires the presence of all 3 typical symptoms and at least 4 other symptoms some of which should be of severe intensity.

The clinical presentation may show marked individual variations and atypical features are quite common in adolescents and the elderly.

Managing depressive disorder

Mild to moderate depression can be managed in an outpatient setting. Mild depression can be managed using psychological interventions such as cognitive behaviour therapy, self-help programmes and physical activity (exercise).

Moderate to severe depression requires a higher level of care. Indicators of high risk are presence of suicidal ideas, psychotic symptoms, poor physical health, reduced food and fluid intake and neglect of dependent children. If the risks are high and social support is unsatisfactory the patient should be offered in-ward treatment.

Pharmacological management

Antidepressants are effective in the acute treatment of depressive disorder. The choice of medication depends on the efficacy, cost, availability, side-effects and toxic effects.

Specific serotonin reuptake inhibitors (SSRI) are recommended as first-line treatment for their efficacy, side-effect profile and safety in overdose. There is evidence that escitalopram and sertraline are more effective than the other SSRIs. Serotonin noradrenaline reuptake inhibitors (SNRI) such as

venlafaxine are also effective in the treatment of moderate to severe depressive episodes. Because of the side-effects and high lethality in overdose the older tricyclic antidepressants (TCA) are best avoided especially in patients with cardiac disease, and those on hypotensive drugs because of the risk of falls, or when there is risk of suicide.

Antidepressant treatment should be started at the lowest recommended dose. Depending on the response the dose can be increased in 7-10 days up to the maximum recommended dose. Recommended dose ranges of commonly used antidepressants are given in Table 2. Lower doses are used in the elderly and in physically ill patients. SSRIs and extended release venlafaxine are given once daily. Patients should be educated that symptom relief is seen usually after10-14 days of treatment. A hypnotic can be given for a few days if poor sleep is a problem.

Antidepressant treatment must be continued for at least six months. Patients should be told that the medication should not be stopped as soon as symptoms subside as this can lead to a relapse. Patients with recurrent depressive disorder may need treatment for longer periods.

If a patient does not respond to treatment with the maximum tolerable dose for 4-6 weeks, the antidepressant should be changed. The second-line antidepressant can be one with a different mode of action such as venlafaxine (SNRI), mirtazapine or a high efficacy SSRI such as sertraline or escitalopram. The first medication should be gradually tailed off over a few days as abrupt stoppage can lead to unpleasant withdrawal symptoms such as anxiety.

Table 2. Common antidepressant drugs and their licensed doses

Drug	*Licensed doses*
Citalopram	20-40 mg/day
Escitalopram	10-20 mg/day
Fluoxetine	20-60 mg/day
Fluvoxamine	100-300 mg/day
Paroxetine	20-50 mg/day
Sertraline	50-200 mg/day
Venlafaxine	75-375 mg/day
Mirtazapine	15-45 mg/day

Side-effects

The common side-effects of SSRI are nausea, vomiting, gastritis, diarrhoea, rash, sweating, agitation, anxiety, headache, insomnia, tremor, and sexual dysfunction. The elderly are more at risk of developing hyponatraemia, a dangerous side-effect. SSRI are known to increase bleeding tendencies and should be used cautiously in patients on warfarin. Venlafaxine can increase blood pressure.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is indicated in patients who require rapid improvement such as those who refuse to drink enough to maintain an adequate urine output (depressive stupor), patients with a high suicide risk and mothers with post-partum depression or psychosis. ECT is also indicated in patients who show poor response to antidepressants, in psychotic depression and in the elderly who cannot tolerate an adequate dose of antidepressants.

Special considerations

Psychotic depression

Psychotic depression is a severe form of depression in which the patient experiences delusions (nihilism, poverty, guilt, hypochondriasis) and hallucinations (derogatory voices, unpleasant olfactory sensations etc.) in addition to features of depression. Patients with psychotic depression are best managed by a psychiatrist. Combination of antidepressant and antipsychotic or ECT is effective in its treatment.

Bipolar depression

Bipolar depression is a suicidal ideation disorder that differs from unipolar disorder in severity, time course, degree of suicidal ideation and treatment response. It affords a greater symptom burden than mania or unipolar depression. Bipolar depression can be mistaken for unipolar depression unless a careful history is obtained. Hypomanic episodes can be difficult to detect and a collateral history should be obtained if bipolar depression is suspected.

Bipolar depression is best managed by a psychiatrist. Antidepressant monotherapy is not recommended as it can cause a manic switch. Atypical antipsychotics, mood stabilisers alone or in combination with an antidepressant are recommended in treatment of bipolar depression.

Other treatments

The current therapeutic modalities of depression are many, among which psychotherapy, deep brain stimulation, repetitive transcranial magnetic stimulation, vagal nerve stimulation, sleep deprivation and bright light therapy have evidence for efficacy. Cognitive behaviour therapy, inter-personal therapy and problem solving are effective alone or in combination with antidepressants. However pharmacological management retains its pride of place.

References

1. Taylor D, Paton C, Kapur S. *Maudsley Prescribing Guidelines* 12th ed. Wiley Blackwell. 2015.
2. Gelder M, Andreasen N, Lopez-Ibor J, Jr., Geddes JR eds. *New Oxford Textbook of Psychiatry* 2nded; Oxford; Oxford University Press, 2009.
3. Cipriani AI, Furukawa TA, Salanti G, *et al*. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple treatments meta-analysis. *Lancet* 2009; **373**: 746-58.
4. Rush AJ, Trivedi MH, Wisniewski SR, *et al*. Acute and longer term outcomes in depressed outpatients requiring one or several treatment steps: A STAR* D report. *Am J Psychiatry* 2006; **163**: 1905-17.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, D.C: American Psychiatric Association 2013.
6. World Health Organization *The ICD-10 Classification of Mental and Behavioural Disorders*. Geneva; World Health Organization, 1992.

Professor Raveen Hanwella, MBBS(Col), MD(Psy), FRCPsych, FSLCOP, FCCP, *Professor in Psychiatry, Department of Psychiatry, Faculty of Medicine Colombo.*

Email: <raveenhanwella@yahoo.co.uk>

Dr. Suhashini Ratnatunga, MBBS, MD(Psy), *Senior Registrar in Psychiatry, University Psychiatry Unit, National Hospital of Sri Lanka.*

Email: suhashini_sri@yahoo.com

Conflicts of interest

Prof. Raveen Hanwella has received educational grants from Sun Pharma and Torrent Pharmaceuticals.

Dr. Suhashini Ratnatunga has no conflicts of interest.

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.

Key words: haemodialysis, kidney, pharmacokinetics, renal disease

*(Aust Prescr 2016; **39**: 21-4)*

Introduction

The prevalence of kidney disease is rising and there are now over 11 400 Australians receiving dialysis.[1] 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.[2]

Polypharmacy, multiple comorbid illnesses and drug clearance by dialysis all complicate prescribing.[3]

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.

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

Australian Medicines Handbook (https://amhonline.amh.net.au)

Therapeutic Guidelines: Antibiotic. Version 15 (www.tg.org.au)

MIMS Australia (http://mims.com.au)

Bailie and Mason's 2014 Dialysis of Drugs (http://renalpharmacyconsultants.com/publications)

Oxford Handbook of Dialysis. 3rd ed. Oxford: Oxford University Press; 2009.

The Renal Drug Handbook. 4th ed. London: Radcliffe Publishing; 2014.

Principles of prescribing

Renal impairment reduces the clearance of some drugs.[4] 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/1.73m^2. 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,[5] altered volume of distribution and the presence of comorbid hepatic dysfunction.

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[6] 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.[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 (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.[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.[3] 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.[7]

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.[8,9] Paracetamol is the preferred simple analgesic. It is safe and can be used without dose modification.[10]

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.[11,12] Topical NSAIDs appear to be safe as systemic absorption is minimal.[7]

Many opioids, or their active metabolites, are renally cleared (Table).[7,10,13,14] 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).[10] 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.[15] Oxycodone may be used, although the sustained-release formulations should be used only with caution due to the risk of

Table. Analgesic use in dialysis[6,9-11]

Drug	*Clearance*	*Suggested starting dose*	*Comments*
Hydromorphone	Its major renally excreted metabolite hydromorphone-3-glucuronide is inactive	0.5 – 1 mg orally 4 times a day	Preferred oral opioid in dialysis patients
Oxycodone	Both oxycodone and its active metabolite oxymorphone are renally excreted	2.5 – 5 mg orally 3 times a day	Use controlled-release preparations with caution
Tramadol	Active renally excreted metabolite O-desmethyltramadol	50 mg orally twice a day	Maximum 100 mg twice a day Avoid controlled-release preparations
Buprenorphine	Hepatic metabolism with no accumulation of metabolites	5 microgram/hour transdermally	Not dialysed
Fentanyl	Hepatic metabolism with no active metabolites	12 microgram/hour transdermally	Not dialysed Use with caution in opioid-naïve patients
Gabapentin	Renal excretion	100 mg orally at night on dialysis days	Large dose reductions required. Can treat uraemic pruritis and restless legs syndrome
Pregabalin	Renal excretion	25 mg orally at night on dialysis days	Large dose reductions required Can treat uraemic pruritis and restless legs syndrome
Morphine	Metabolised to renally excreted glucuronide metabolites (M-6-G and M-3-G) M-6-G is active and accumulates within the central nervous system, M-3-G lacks analgesic activity but may cause hyperalgesia and allodyni	2.5 mg orally 3 times a day	Avoid if possible Could be used for emergency analgesia if hydromorphone or fentanyl not immediately available
Codeine	Renally excreted active metabolites	-	Avoid
Dextro-propoxyphene	Cardiotoxic metabolite norpropoxyphene accumulates	-	Avoid
Paracetamol	Hepatic clearance	1 g orally 3 – 4 times day	Preferred simple a analgesic

accumulation and toxicity. Fentanyl and buprenorphine both undergo hepatic clearance and can be used when the oral route is not suitable.[13] 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.[16] Amitriptyline is hepatically 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.[10] Gabapentin and pregabalin are effective and may also treat uraemic pruritus. However, they are extensively renally cleared and marked dose reductions are necessary to avoid sedation, ataxia and dizziness. Doses should be taken after dialysis.[10,17]

Opioid-induced constipation

In surveys, over half of the patients on dialysis report constipation.[9] 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 fluid is not significantly absorbed and so does not count towards a fluid restriction. Saline laxatives (containing magnesium or phosphate salts) are contraindicated in patients on dialysis due to the possibility of severe electrolyte disturbances.[18] In particular, sodium phosphate-containing bowel preparations (Fleet) can cause severe hyperphosphataemia and calcium phosphate deposition.[19]

Antimicrobials

Many antibiotics require dose adjustment in patients receiving dialysis. Therapeutic Guidelines: Antibiotic provides a comprehensive and user-friendly reference.[20] Quinolones, sulfamethoxazole with trimethoprim, glycopeptides and aminoglycosides all require significant dose reductions. Trimethoprim should be avoided in patients due to the risk of hyperkalaemia and bone marrow suppression.[20,21] 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.[22] Despite recent support for extending its use in chronic kidney disease, it should be avoided in patients on dialysis.[23] Cephalosporins and penicillins have wider therapeutic indices and vary in the need for dose adjustment.[7] Once-daily doses should be prescribed after haemodialysis.

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.[24] They should only be prescribed after discussion with the treating nephrologist and with appropriate dose reduction and close clinical follow-up.

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 important as patients on dialysis have increased rates of bleeding with warfarin.[25] Low-molecular-weight heparins are renally excreted and they are rarely used for anticoagulation as their effect is difficult to predict.[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 contraindicated. They all undergo a degree of renal clearance which makes them unsuitable for patients on dialysis.[26]

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.[27] Metformin is contraindicated due to the risk of lactic acidosis. Although not renally excreted, thiazolidinediones are associated with fluid retention and are not recommended.[7] The sodium-glucose co-transporter inhibitors are contraindicated in dialysis patients as they depend on the glomerular filtration of glucose for their effect.[28]

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

References

1. Clayton P, McDonald S, Hurst K, editors. ANZDATA Registry Annual Report 2013. Adelaide: Australia and New Zealand Dialysis and Transplant Registry; 2013. www.anzdata.org.au/anzdata/AnzdataReport/36thReport/ANZDATA_36th_Annual%20_Report.pdf [cited 2016 Jan 4]
2. Manley HJ, Drayer DK, Muther RS. Medication-related problem type and appearance rate in ambulatory hemodialysis patients. BMC Nephrol 2003;4:10. http://dx.doi.org/10.1186/1471-2369-4-10
3. Weir MR, Fink JC. Safety of medical therapy in patients with chronic kidney disease end end-stage renal disease. Curr Opin Nephrol Hypertens 2014;23:306-13. http://dx.doi.org/10.1097/01.mnh.0000444912.40418.45
4. Faull R, Lee L. Prescribing in renal disease. Aust Prescr 2007;30:17-20.
5. Meijers BK, Bammens B, Verbeke K, Evenepoel P. A review of albumin binding in CKD. Am J Kidney Dis 2008;51:839-50. http://dx.doi.org/10.1053/j.ajkd.2007.12.035
6. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. LANGE Basic Science. 12th ed. McGraw-Hill Education; 2012.
7. Floege J, Johnson RJ, Feehally J. Comprehensive clinical nephrology. 4th ed. St Louis (MI): Elsevier; 2010.
8. Bailie GR, Mason NA, Bragg-Gresham JL, Gillespie BW, Young EW. Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for underprescription. Kidney Int 2004;65:2419-25. http://dx.doi.org/10.1111/j.1523-1755.2004.00658.x
9. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis 2007;14:82-99. http://dx.doi.org/10.1053/j.ackd.2006.10.001
10. Davison SN, Ferro CJ. Management of pain in chronic kidney disease. Prog Palliat Care 2009;17:186-95. http://dx.doi.org/10.1179/096992609X12455871937189
11. Andersohn F, Suissa S, Garbe E. Use of first- and second-generation cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs and risk of acute myocardial nfarction. Circulation 2006;113:1950-7. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.602425
12. Cass A, Chadban S, Gallagher M, Howard K, Jones A, McDonald S, et al. Economic impact of end-stage kidney disease in Australia: Projections to 2020. Melbourne: Kidney Health Australia; 2010.
13. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage 2004;28:497-504. http://dx.doi.org/10.1016/j.jpainsymman.2004.02.021
14. Filitz J, Griessinger N, Sittl R, Likar R, Schüttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in hronic pain patients treated with transdermal buprenorphine. Eur J Pain 2006;10:743-8. http://dx.doi.org/10.1016/j.ejpain.2005.12.001
15. Davison SN, Mayo PR. Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients. J Opioid Manag 2008;4:335-6.
16. Mambelli E, Barrella M, Facchini MG, Mancini E, Sicuso C, Bainotti S, et al. The prevalence of peripheral neuropathy in hemodialysis patients. Clin Nephrol 2012;77:468-75. http://dx.doi.org/10.5414/CN107188
17. Solak Y, Biyik Z, Atalay H, Gaipov A, Guney F, Turk S, et al. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. Nephrology (Carlton) 2012;17:710-7. http://dx.doi.org/10.1111/j.1440-1797.2012.01655.x
18. Murtagh FE, Weisbord S. Symptoms in renal disease; their epidemiology, assessment and management. In: Chambers EJ, Brown EA, Germain M, editors. Supportive care for the renal patient. 2nd ed. Oxford: Oxford University Press; 2010.

19. Heher EC, Thier SO, Rennke H, Humphreys BD. Adverse renal and metabolic effects associated with oral sodium phosphate bowel preparation. Clin J Am Soc Nephrol 008;3:1494-503. http://dx.doi.org/10.2215/CJN.02040408

20. Antibiotic. Version 15. In: eTG complete [Internet]. Melbourne: Therapeutic Guidelines Limited; 2014. http://www.tg.org.au/index.php?sectionid=71 [cited 2016 Jan 4]

21. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2015.

22. Geerts AF, Eppenga WL, Heerdink R, Derijks HJ, Wensing MJ, Egberts TC, et al. Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care. Eur J Clin Pharmacol 2013;69:1701-7. http://dx.doi.org/10.1007/s00228-013-1520-x

23. Singh N, Gandhi S, McArthur E, Moist L, Jain AK, Liu AR, et al. Kidney function and the use of nitrofurantoin to treat urinary tract infections in older women. CMAJ 2015;187:648-56. http://dx.doi.org/10.1503/cmaj.150067

24. Strumia S, De Mitri P, Bionda E. Neurotoxicity of acyclovir and valacyclovir in a hemodialyzed patient. Eur J Neurol 2004;11:68-9. http://dx.doi.org/10.1046/j.1351-5101.2003.00719.x

25. Genovesi S, Rossi E, Gallieni M, Stella A, Badiali F, Conte F, et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. Nephrol Dial Transplant 2015;30:491-8. http://dx.doi.org/10.1093/ndt/gfu334

26. Tran H, Joseph J, Young L, McRae S, Curnow J, Nandurkar H, et al.; Australasian Society of Thrombosis and Haemostasis. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J 2014;44:525-36. gttp://dx.doi.org/10.1111/imj.12448

27. Flynn C, Bakris GL. Noninsulin glucose-lowering agents for the treatment of patients on dialysis. Nat Rev Nephrol 2013;9:147-53. http://dx.doi.org/10.1038/nrneph.2013.12

28. Moses RG, Colagiuri S, Pollock C. SGLT2 inhibitors: New medicines for addressing unmet needs in type 2 diabetes. Australas Med J 2014;7:405-15. http://dx.doi.org/10.4066/AMJ.2014.2181

Brendan Smyth, *Renal Registrar,* **Ceridwen Jones,** *Senior Clinical Pharmacist* and **John Saunders,** *Consultant Nephrologist*, *Royal Prince Alfred Hospital, Sydney.*

This article is reproduced from the *Australian Prescriber* 2016;**39**:21-4 by prior arrangement, courtesy of *Australian Prescriber.*

Oral ulcers and their management

Oral ulcers are one of the most common complaints regarding the oral cavity. Usually there are no serious underlying causes, although they could be associated with underlying diseases that should be excluded. A proper clinical history is important in the diagnosis but when required blood investigations and a biopsy should be considered. Ulcers could be single or multiple. The two most common causes of oral ulcerations are local trauma and recurrent aphthous stomatitis. Local trauma is also an aetiological factor in aphthous stomatitis. These ulcers often cause much pain and discomfort and interfere with dietary habits, swallowing and speech. Healing is usually spontaneous, but when it is delayed, a biopsy is carried out to exclude malignancy, as squamous cell carcinomas and lymphomas appear as non-healing ulcers. Necrotising sialometaplasia is a benign ulcerative lesion usually located in the posterior part of the hard palate, often painless, self-limiting and heals in 6-10 weeks. Although entirely benign and requires no treatment, due to its similarity to squamous cell carcinoma histologically and delayed healing, it is sometimes misdiagnosed as being malignant.

The mucous membrane of the oral cavity is comparatively thin and easily damaged by local causes such as mechanical, chemical, and thermal trauma, and irradiation. The sharp edges of teeth, fillings, broken dentures and orthodontic appliances are the common mechanical causes. Self-inflicted wounds should also be considered under this category. Recurrent tearing of upper labial frenulum in a child could be a sign of child abuse. Applying papaw juice or placing a tablet of aspirin on gingiva adjacent to a painful tooth may lead to chemical ulceration. The chemicals used during endodontic procedures also can cause chemical burns. Following radiotherapy the mucous membrane becomes atrophied, and with reduced salivary secretions, oral mucosa becomes vulnerable to trauma and formation of traumatic ulcers.

The management includes removal of the causative factor and if required an antiseptic mouthwash such as 1% povidone iodine or 0.2% chlorhexidine to control secondary infection. Following radiotherapy salivary substitutes are used to improve lubricating effect on the oral mucosa.

Recurrent aphthous stomatitis (RAS) is common, and affects up to 20-25% of the population at some time in their life. Aphthae typically start in childhood or adolescence, and after a variable number of years the ulcers appear less frequently or cease altogether. The disease usually appears to be self-limiting. According to the size of the ulcer there are three types of aphthous ulcers; namely minor, major and herpetiform ulcerations. Minor type is the most common, 2-4 mm in diameter, round or oval with a yellow grey coloured base and an erythematous periphery. They heal without any permanent scars in about 5-7 days. Major aphthous ulcers are more than 1cm in diameter with more symptoms. They may take about 2-3weeks to heal and cause scarring. The least common type is herpetiform ulceration, appearing in crops, which can coalesce to form larger areas of ulceration.

In most cases the aetiology of RAS is unknown. There could be a genetic factor. Other causes include local trauma, nutritional deficiencies such as iron, vitamin B_{12} folate, stress, hormonal changes in females, food allergy and immune deficiency. RAS ulcers are very painful and interfere with meals, speech and swallowing. There is no specific or effective treatment for RAS. Response to various treatments vary widely, and the situation is complicated by spontaneous remissions.

Antiseptic mouthwashes, local anaesthetic creams, protective pastes to cover the ulcerated areas till they heal, and topical or systemic steroids are used during management, and if there are any secondary causes they should be treated. Some respond to tetracycline or doxycycline mouthwashes. For HIV patients, with major aphthae, thalidomide may be prescribed. In Behcet's syndrome, in addition to RAS, the patient will have genital lesions and uveitis. Early ophthalmological referral is important, because eye lesions often culminate in impaired sight.

Oral ulceration following viral, bacterial and fungal infections are also seen quite frequently in clinics. The common viral infections with oral ulceration are caused by herpes simplex and herpes zoster viruses. In herpes simplex in addition to oral ulcers they also cause an acute gingivitis and cervical lymphadenopathy. The herpes zoster ulcers are usually unilateral and will be restricted to the dermatome supplied by a branch of the trigeminal nerve involving both the oral mucosa and adjacent skin. Again an antiseptic mouthwash will be used to control secondary infection. Acyclovir could be used on immunosuppressed patients and also in herpes zoster to minimise the effects of post-herpetic neuralgia and to reduce ophthalmic complications.

The bacterial oral ulcers are caused by Fusobacterium and Spirochetes. [Acute necrotising ulcerative gingivitis (ANUG)], by *Mycobacterium tuberculosis*, and *Treponema pallidum*. For ANUG a penicillin or metronidazole could be used with improvement of oral hygiene. Tuberculosis and syphilis require specialised management.

The other comparatively common causes are dermatological disorders such as lichen planus, erythema multiforme, systemic lupus erythematosis, pemphigus vulgaris, mucous membrane pemphigoid, epidermolysis bullosa and dermatitis herpetiformis. Some commonly used drugs such as antihypertensives, antidiabetics, and non-steroidal anti-inflammatory drugs can produce lichen planus like reactions with ulceration. The cytotoxic drugs such as methotrexate produce nonspecific ulcers, and sulphonamide, barbiturates can cause erythema multiforme with severe ulceration of oral mucosa. The blood dyscrasias such as cyclic neutropenia, leukemias and gastrointestinal disorders such as coeliac disease, Crohn's disease and ulcerative colitis also produce oral ulcers with specific oral mucosal changes.

In case of difficulty in diagnosis and management it is advisable to refer the patient to specialists in this field.

References

1. Nair RG, Salajegheh A, Itthagarum A, *et al*. Orofacial viral infections – an update for clinicians. *Dental Update* 2014; **41**: 518-22.
2. Scully C, Cawson RA. Medical Problems in Dentistry. 4th Edition, Wright; An imprint of Butterworth-Heinemann. A division of Reed Educational and Professional Publishing Ltd; 2001: 175-77.
3. Scully C CBE. Oral and Maxillofacial Medicine. The Basis of Diagnosis and Treatment-Wright; An imprint of Elsevier Limited; 2004: 170-81.

Dr. A M O Peiris, BDS, FDSRCPS, FFDRCS

I have no conflicts of interest regarding this article.

Self-assessment questions

Question 1

A 42-year old man with a history of epilepsy for over 10 years was seen at the epilepsy clinic after a 5-year lapse, complaining of body aches and pains, difficulty in climbing stairs and recent poor control of epileptic convulsions. He was on carbamazepine 400 mg b.d. for 9 years and sodium valproate 200 mg bd for 4 years. He denied non-compliance, but admitted that he took arrack daily before dinner, an intake of ethanol estimated by the SHO as 60 ml/day. Clinical examination was unremarkable, except for failure to stand from a squatting position. The initial investigation results were:

Hb 12.0 g/dl	(13.5 – 16.5)	Bilirubin 18µml/l	(3 – 17)
MCV 80 fl	(80 – 96)	* Calcium 1.9 mmol/l	(2.20 – 2.65)
MCHC 32.5 g/dl	(32 – 36)	Phosphate 0.7 mmol/l	(0.8 – 1.4)
AST 25 U/l	(10 – 40)	Creatinine 90 mmol/l	(60 – 120)
ALT 35 U/l	(10 – 40)	Proteins Albumin 32 g/dl	(35 – 50)
ALP 560 U/l	(40 – 120)	Globulin 28 g/dl	(20 – 25)
C. kinase 260 U/l	(30 – 210)	* Corrected	
Fasting glucose 5.9 mol/l	(4.5 – 5.6)		

What are your observations on this man's problem?

Question 2

A 72-year old woman with a history of failing memory for 3 years and occasional inappropriate emotional outbursts, had a fall and struck her head against a pillar. After the fall she became incontinent of urine, and started wandering aimlessly in the house, so that her husband took over all household duties. She was admitted to hospital on the second day after the fall. Her pulse, BP, rectal temperature, ECG and clinical examination were unremarkable. Funduscopy was normal. She was aggressive and abusive and had to be sedated with diazepam. Urgent biochemical results and imaging reports were:

Na 138 mmol/l	(135 – 145)	Bilirubin 16 µmol/l	(3 – 17)
K 3.8 mmol/l	(3.5 – 5.0)	Albumin 42 g/l	(35 – 50)
Creatinine 85 µmol/l	(60 – 120)	Globulin 32 g/l	(28 – 45)
Urea 4.5 mmol/l	(2.5 – 6.5)	ALP 120 U/l	(40 – 120)
Hb 13.0 g/dl	(11.5 – 15.5)	Corrected calcium 2.25mmol/l	(2.2 – 2.6)
WCC 9.3 × 10^9/l	(4 – 11)	CXR – no abnormalities detected	
Platelets 340 × 10^9/l	(150 – 400)	CT brain scan: 1 cm pituitary tumour;	
MCV 94 fl	(80 – 96)	cerebral atrophy: no midline shift	
TSH 1.81 mU/l	(0.2 – 4.5)	Blood gases. Normal on air	
FT4 18.5 pmol/l	(9 – 21)		
LH 41.3 U/l	(>16)		
FSH 48.0 U/l	(>25)		

1. Give 3 probable diagnoses
2. What other investigations do you recommend?

Answers for self-assessment questions

Question 1 Failure to stand from a squatting position (suggestive of proximal muscle weakness) in an individual taking anti-epileptic medications over a long period, considered along with the raised ALP, hypocalcaemia and hypophosphataemia indicate a probable diagnosis of osteomalacia. The low haemoglobin and plasma albumin are suggestive of poor diet as an additional contributory factor. The raised ALP was shown to be of bony origin. Liver and kidney function appear to be normal. Failure to stand from a squatting position is a feature of proximal muscle weakness in osteomalacia. He needs also a review of epilepsy medication.

Question 2 Three probable diagnoses based on the available data are (i) Dementia, possibly Alzheimer's (ii) Acute brain failure (Syn: Acute confusional state) (iii) Pituitary incidentaloma.

From the medical history, it seems probable that the patient has had a dementing process, and that the head trauma precipitated an acute brain failure (also referred to as acute confessional state or delirium). The pituitary tumour is likely to be an incidental finding.

However, while managing the acute brain failure according to standard conservative guidelines, further investigations are essential to exclude, for example, intracranial infection (eg meningitis, encephalitis), extracranial infection (eg chest, urinary tract), metabolic perturbations (eg hypo- and hyperglycaemia, imbalance of sodium potassium and water), hormonal disturbances of a pituitary tumour, visual fields and pituitary fossa distortion.

Professor Colvin Goonaratna MBBS, FRCP, FCCP, PhD, DSc.
I have no conflicts of interest regarding the self-assessment questions and answers.

ISSN 1391-0736

Printed by Ananda Press, Colombo.