are more likely to be a problem, for example first thing in the morning. Top up doses can be provided by a nicotine inhaler, lozenge or gum. Combination therapies should be considered in smokers who have failed despite behavioural intervention and a reasonable trial of a single formulation.

References

1. Zwar N, Richmond R, Borland R, Stillman S, Cunningham M, Litt J. Smoking cessation guidelines for Australian general practice. Canberra: Commonwealth Department of Health and Ageing; 2004. http://www.health.gov.au/internet/wcms/publishing.nsf/Content/health-pubhlth-publicat-document-smoking_cessation-cnt.htm [cited 2005 May 10]
2. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. Br Med J 2004;328:1519.
3. Borland R, Segan CJ, Livingston PM, Owen N. The effectiveness of callback counselling for smoking cessation: a randomized trial. Addiction 2001;96:881-9.
4. Zhu SH, Anderson CM, Tedeschi GJ, Rosbrook B, Johnson CE, Byrd M, et al. Evidence of real-world effectiveness of a telephone quitline for smokers. N Engl J Med 2002;347:1087-93.
5. Rice VH, Stead LF. Nursing interventions for smoking cessation. *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD001188.pub2. DOI:10.1002/14651858.CD001188.pub2.
6. George TP, O'Malley SS. Current pharmacological treatments for nicotine dependence. Trends Pharmacol Sci 2004;25:42-8.
7. Litt J, Ling M-Y, McAvoy B. How to help your patients quit: practice-based strategies for smoking cessation. Asia Pac Fam Med 2003;2:175-9.
8. White V, Hill D, Siahpush M, Bobevski I. How has the prevalence of cigarette smoking changed among Australian adults? Trends in smoking prevalence between 1980 and 2001. Tob Control 2003;12(Suppl 2):ii67-74.
9. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. N Engl J Med 2002;346:506-12.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

7. Telephone follow-up by a quit line service increases the chance of a smoker successfully quitting smoking.
8. Patients should not use two forms of nicotine replacement therapy at the same time.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Bivalirudin

Angiomax (CSL)

vials containing 250 mg lyophilised powder for reconstitution

Approved indication: percutaneous coronary intervention

Australian Medicines Handbook section 7.1

Patients having procedures such as percutaneous transluminal coronary angioplasty need to be anticoagulated. While heparin can be used, some patients still develop ischaemia and there is a risk of major bleeding.

Bivalirudin is a direct inhibitor of thrombin related to the anticoagulant protein produced by leeches. By reversibly binding to thrombin, bivalirudin stops the conversion of fibrinogen to fibrin and inhibits platelet aggregation.

The anticoagulant effect begins within a few minutes of intravenous administration. The clotting time, activated partial thromboplastin time (APTT), prothrombin time and thrombin time are all increased. Bivalirudin is given as a bolus dose followed by an infusion. It has a half-life of approximately 25 minutes, with most of the dose being metabolised into amino acids. As 20% of the dose is excreted unchanged in the urine impaired renal function prolongs the half-life.

An early study of bivalirudin found that it caused less bleeding but had no greater efficacy than high-dose heparin in preventing ischaemic complications in patients having coronary angioplasty.[1] Development of the drug did not proceed, however when the results were reanalysed several years later they showed a statistical advantage for bivalirudin.[2] As the drugs used during the procedure had changed in the intervening years, there was a need to evaluate bivalirudin with the new approaches.

The REPLACE-2 trial randomised 6010 patients to receive bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor. All patients also received aspirin and the use of clopidogrel was

encouraged. Analysis at 30 days revealed that 7.6% of the bivalirudin group had died, had an infarction or needed urgent revascularisation. In the heparin/glycoprotein inhibitor group 7.1% of the patients reached the same end point. While the two approaches had similar efficacy, bivalirudin significantly reduced major bleeding. Major bleeding occurred in 4.1% of the patients given heparin and a glycoprotein inhibitor compared with 2.5% of the bivalirudin group.[3]

The patients in REPLACE-2 were followed up for a year. After six months there were fewer deaths in the bivalirudin group, but more myocardial infarctions and revascularisations. Although the mortality with bivalirudin was lower after 12 months it was not significantly different from the mortality with heparin.[4]

In addition to bleeding, patients may develop back pain. Unlike heparin, bivalirudin does not cause an immune thrombocytopenia, but it has been associated with thrombocytopenia.

Although bivalirudin causes less bleeding than heparin and a glycoprotein inhibitor, its role in therapy probably requires further study. The higher cost of bivalirudin will also need to be considered before it can replace heparin in general use.

References * †

1. Hirulog angioplasty study investigators. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. N Engl J Med 1995;333:764-9.
2. Bivalirudin angioplasty study investigators. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina. Am Heart J 2001;142:952-9.
3. REPLACE-2 investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention. JAMA 2003;289:853-63.
4. REPLACE-2 investigators. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization. JAMA 2004;292:696-703.

Cinacalcet hydrochloride

Sensipar (Amgen)

30 mg, 60 mg and 90 mg tablets

Approved indications: hyperparathyroidism, hypercalcaemia

Australian Medicines Handbook section 10.3

Parathyroid hormone increases calcium concentrations by increasing bone resorption and the reabsorption of calcium by the kidney. Adenomas of the parathyroid glands cause primary hyperparathyroidism and parathyroidectomy may be indicated. Secondary hyperparathyroidism is a reaction to hypocalcaemia which can have a variety of causes such as renal failure or vitamin D deficiency.

The secretion of parathyroid hormone depends on a receptor which senses the serum calcium concentration. By increasing the sensitivity of this receptor to calcium, treatment with cinacalcet reduces the secretion of parathyroid hormone which in turn reduces the calcium concentration.

Cinacalcet tablets have a bioavailability of 20–25%, but this increases if they are taken with food. Peak plasma concentrations are achieved 2–6 hours after a dose and this corresponds with the nadir of parathyroid hormone secretion. This suppression lasts long enough to allow once-daily dosing for secondary hyperparathyroidism. Cinacalcet is cleared by metabolism which includes cytochrome P450 3A4, 2D6 and 1A2. This results in interactions with drugs such as ketoconazole and rifampicin. Smoking increases clearance by inducing P450 1A2.

Several small studies have investigated cinacalcet in patients with primary hyperparathyroidism or parathyroid carcinoma. A short dose-ranging study found that cinacalcet significantly decreased the serum calcium concentration. In one study, a twice-daily dose of 30 mg reduced the concentration by 11% and 50 mg twice daily reduced it by 18.5%. At its nadir the concentration of parathyroid hormone fell by half.[1] Doses should be titrated according to the hormone or calcium concentration.

More data are available on the use of cinacalcet to treat secondary hyperparathyroidism in patients having renal dialysis. In a 26-week study, 741 patients were randomised to receive once-daily cinacalcet or placebo. Mean concentrations of parathyroid hormone were reduced by 43% in the cinacalcet group, but increased by 9% in the placebo group. However, only 43% of the patients taking cinacalcet reached the target concentration of parathyroid hormone.[2]

Nausea and vomiting are the most frequent adverse reactions to cinacalcet. Less common adverse events are hypocalcaemia, convulsions and paraesthesia.

The studies of cinacalcet have focussed on biochemical tests. There is little information on clinically important outcomes, particularly in primary hyperparathyroidism. Although cinacalcet may be useful in treating the hypercalcaemia associated with parathyroid carcinoma, its approval in primary hyperparathyroidism is restricted to patients who cannot have a parathyroidectomy. While cinacalcet is efficacious in reducing parathyroid hormone concentrations in secondary hyperparathyroidism in patients having renal dialysis, longer-term studies will be needed to assess its effect on bone and the vascular system.

References * †

1. Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M. The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. J Clin Endocrinol Metab 2003;88:5644-9.
2. Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350:1516-25.

Everolimus

Certican (Novartis)

0.25 mg, 0.5 mg and 0.75 mg tablets

Approved indication: transplantation

Australian Medicines Handbook section 14.1

Everolimus is a derivative of the immunosuppressant drug sirolimus. It has been approved for use by patients receiving a heart or kidney transplant.

Although patients' survival after transplant has improved, problems may develop in the long term. For example, treatment with cyclosporin can damage the transplanted kidney and vasculopathy may complicate heart transplants. Everolimus may therefore have a role in preventing organ rejection because it inhibits cell proliferation. This inhibition includes vascular smooth muscle cells as well as T-cells.

Treatment begins as soon as possible after transplantation. Peak concentrations occur within two hours of an oral dose, but absorption is reduced by food. Steady state concentrations are reached within four days. Everolimus is metabolised by liver enzymes including cytochrome P450 3A4. Most of the metabolites are excreted in the faeces. The half-life of everolimus is approximately 28 hours.

Everolimus was compared with azathioprine in patients following heart transplantation. These 634 patients were also treated with cyclosporin, corticosteroids and a 'statin'. The end point of the study was a mixture of death or rejection. After 12 months, 52.8% of the azathioprine group had reached this end point. This was significantly more than the 41.6% of the 209 patients given everolimus 1.5 mg, and the 32.2% of the 211 patients given everolimus 3.0 mg.[1]

Studies in renal transplantation used mycofenolate mofetil as a comparator. Rejection had occurred by six months in 23.5% of the mycofenolate group, 21.6% of those taking everolimus 1.5 mg and 18.2% of those taking everolimus 3.0 mg.

Two studies used everolimus to lower the dose of cyclosporin used after renal transplantation. Although there was no comparator arm in the studies, both doses of everolimus were associated with satisfactory renal function after six months.[2]

As rejection occurs more frequently with lower concentrations, the blood concentration of everolimus must be monitored regularly. More frequent monitoring will be needed if the patient is started on a drug which inhibits (ketoconazole) or induces (rifampicin) CYP3A4.

Adverse events occur in almost everyone treated with everolimus. Approximately 10–22% of patients will discontinue treatment because of adverse events. These include anaemia, leucopenia, thrombocytopenia and infections.[1,2] In the heart transplant study significantly more bacterial infections occurred in the everolimus group. Even if the patients are taking 'statins' their triglyceride and cholesterol concentrations are likely to increase.[1]

Managing patients after transplantation requires balancing the risk of organ rejection against the adverse effects of immunosuppression. Further study will be needed to define the place of everolimus. The results of a Cochrane review of the effects of everolimus and sirolimus in renal transplantation are not yet available.[3]

References

1. RAD B253 Study Group. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003;349:847-58.
2. Vitko S, Tedesco H, Eris J, Pascual J, Whelchel J, Magee JC, et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. Am J Transplantation 2004;4:626-35.
3. Webster AC, Higgins G, Chapman JR, Craig JC. Sirolimus and everolimus for kidney transplant recipients. (Protocol) *The Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004290. DOI: 10.1002/14651858.CD004290.

Poractant alfa

Curosurf (Douglas)

vials containing 120 mg/1.5 mL and 240 mg/3 mL

Approved indication: neonatal respiratory distress syndrome

Australian Medicines Handbook section 19.6.2

Surfactant lowers the surface tension of the alveolar membrane. Premature infants lack surfactant so their alveoli can collapse leading to respiratory distress. The respiratory distress syndrome can be managed or prevented by administering a substitute surfactant down an endotracheal tube. The first artificial surfactant was colfosceril palmitate, but this is no longer marketed in Australia. Beractant is still available. It is a surfactant derived from cows' lungs, whereas poractant alfa is derived from pigs' lungs.

Most of the early trials of poractant alfa were in Europe where it has been approved for marketing for more than 10 years. In a study of 146 babies with respiratory distress syndrome the 28-day mortality rate was 31% in the group who received poractant compared with 51% in the group who did not.[1] Two years later there were no differences between the groups in growth, disability and respiratory symptoms.[2]

If the baby does not respond to the first dose, a half dose may be given after 12 and after 24 hours. Babies given repeat doses have a lower mortality rate at 28 days than those given a single dose (13% versus 21%).[3]

Subsequent studies have investigated if giving poractant to babies at risk of respiratory distress is more effective than waiting for the syndrome to appear. A meta-analysis of these studies showed that the neonatal mortality rate was 15% when poractant was used for prophylaxis and 25% when it was used for treatment. However, prophylaxis did not have a significant advantage in the prevention of chronic lung disease of the newborn.[4]

Administering poractant is not without risk. The endotracheal tube can get blocked and the baby may develop oxygen desaturation, hypotension and bradycardia.

Clinicians now have a choice of using beractant or poractant. Comparative trials suggest that poractant improves oxygenation more rapidly.[5,6]

References *

1. Collaborative European Multicenter Study Group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome. Pediatrics 1988;82:683-91.
2. Robertson B, Curstedt T, Tubman R, Strayer D, Berggren P, Kok J, et al. A 2-year follow up of babies enrolled in a European multicentre trial of porcine surfactant replacement for severe neonatal respiratory distress syndrome. Eur J Pediatr 1992;151:372-6.
3. Speer CP, Robertson B, Curstedt T, Halliday HL, Compagnone D, Gefeller O, et al. Randomized European multicenter trial of surfactant replacement therapy for severe neonatal respiratory distress syndrome: single versus multiple doses of Curosurf. Pediatrics 1992;89:13-20.
4. Egberts J, Brand R, Walti H, Bevilacqua G, Breart G, Gardini F. Mortality, severe respiratory distress syndrome, and chronic lung disease of the newborn are reduced more after prophylactic than after therapeutic administration of the surfactant Curosurf. Pediatrics 1997;100:e4.
5. Speer CP, Gefeller O, Groneck P, Laufkotter E, Roll C, Hanssler L, et al. Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. Arch Dis Child 1995;72:F8-13.
6. Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K, et al. A randomized, multicenter masked comparison trial of poractant alfa (Curosurf) versus beractant (Survanta) in the treatment of respiratory distress syndrome in preterm infants. Am J Perinatol 2004;21:109-19.

Pregabalin

Lyrica (Pfizer)

75 mg, 150 mg and 300 mg capsules

Approved indications: epilepsy, neuropathic pain

Australian Medicines Handbook section 16.1

Gamma-aminobutyric acid (GABA) is a neurotransmitter. Although pregabalin is an analogue of GABA, its therapeutic effect may be on other neural pathways. Pregabalin reduces the release of neurotransmitters by interfering with the calcium channels in nerve terminals. It has therefore been studied in neuropathic pain and as an adjunctive treatment for epilepsy.

Common examples of neuropathic pain are diabetic neuropathy and post-herpetic neuralgia. In a double-blind trial involving 146 patients with diabetic neuropathy pregabalin was more efficacious than placebo at reducing pain. After eight weeks of treatment the pain of the patients taking pregabalin had reduced by 2.5 points, on an 11 point scale, compared with a 0.8 decrease in the placebo group.[1] In another eight-week double-blind trial, which included some Australian patients, pregabalin reduced the pain of herpetic neuralgia more than placebo did. Compared to placebo, mean pain scores were 1.2 points lower with pregabalin 150 mg/day and 1.57 points lower with 300 mg/day.[2]

Most patients with epilepsy can be managed with monotherapy, but some will need adjunctive treatment. Pregabalin has been studied as adjunctive treatment for patients with partial seizures, with or without secondary generalised seizures. An international study compared adding pregabalin with adding placebo to the treatment of 287 patients. After 12 weeks there was no decrease in seizure frequency in the placebo group, but a 20.6% reduction in the pregabalin 150 mg/day group and a 47.8% reduction in the 600 mg/day group. Approximately 44% of the patients taking the higher dose of pregabalin had at least a 50% reduction in seizure frequency.[3]

As pregabalin alters neurotransmission it can cause a variety of neurological adverse effects. In the neuropathic pain studies 28–36% of the patients taking 300 mg/day developed dizziness and 20–24% developed somnolence.[1,2] Other common problems include ataxia, co-ordination problems, confusion and altered vision. Patients are therefore advised not to drive, until the effects of pregabalin are known. Other complaints include peripheral oedema, weight gain and dry mouth.

Most of a dose of pregabalin is excreted unchanged in the urine, with an elimination half-life of six hours. Lower doses are required if the patient has a reduced creatinine clearance.

While pregabalin has met the efficacy criteria for pain relief it is important to note that the response varies between patients. Only 32% of the patients with post-herpetic neuralgia will feel much improved, or very much improved with treatment. The response tends to be greater in patients with somnolence.

There is also a variation in the response of patients with epilepsy. Although seizure frequency will be at least halved in approximately 44% of patients given 600 mg/day, the responder rate with 150 mg/day is not significantly different from placebo (14% versus 6.2%). While 150 mg/day is an acceptable starting dose it may need to be gradually increased.[3]

Chronic pain and epilepsy are long-term problems so there need to be long-term studies of pregabalin to see if its benefits are maintained in the people who respond, and to see if any other adverse effects emerge . There is also a need to see how pregabalin compares with drugs, such as gabapentin, which have similar indications.

References †

1. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110:628-38.
2. Sabatowski R, Gálvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, et al. The 1008-045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances

in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004;109:26-35.

3. Arroyo S, Anhut H, Kugler AR, Lee CM, Knapp LE, Garofalo EA, et al. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 2004;45:20-7.

---

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

NEW FORMULATIONS

Hydromorphone hydrochloride

Palladone XL (Mundipharma)

12 mg, 16 mg, 24 mg and 32 mg extended release capsules

Timolol maleate

Nyogel (Novartis)

1.37 mg/g eye gel

NEW BRAND

Irinotecan hydrochloride

Irinotecan (Mayne Pharma)

vials containing 40 mg/2 mL and 100 mg/5 mL for injection

Correction

Ketotifen hydrogen fumarate (Aust Prescr 2005;28:19–23)

The recommended Australian dosage is one drop twice daily.

Answers to self-test questions

1. True	3. True	5. True	7. True
2. True	4. False	6. True	8. False

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Go to **New issue email alert** to be sent an email each time a new issue goes online.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list contact the *Australian Prescriber* Mailing Service.

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ Send me all the available back issues

NAME: .....

REF NO. .....
(above your name on the address sheet)

ADDRESS: .....

.....

.....

PROFESSION: .....
(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 3407

Editorial office

For general correspondence such as Letters to the Editor, please contact the Editor

Telephone: (02) 6282 6755

Fax: (02) 6282 6855

Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA

Email: info@australianprescriber.com

Website: www.australianprescriber.com