long-term outcomes and comparative efficacy are unknown, and who understand and accept the local perioperative mortality rate (5–15% is considered acceptable).[12]

Non-invasive ventilation is a major advance for the management of hypercapnic/acidotic exacerbations of COPD. The benefits in stable COPD with respiratory failure are being evaluated in an Australian multicentre trial. Several experimental drugs are being evaluated for their effects on airway inflammation and extracellular matrix destruction in COPD.

Conclusion

COPD is a chronic and disabling condition caused by smoking. Disability can be minimised by a systematic approach to management that emphasises the use of safe, effective medications, withdraws unsafe or ineffective therapy, and attends to the effects of physical deconditioning and psychosocial distress through rehabilitation.

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FURTHER READING

See resources on the following web sites:
http://www.aacvpr.org
http://www.goldcopd.com

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 158)

9. Inhaled corticosteroids produce a sustained improvement in lung function in most patients with chronic obstructive pulmonary disease.
10. Giving a beta agonist by nebuliser is more effective than giving it by metered dose inhaler and spacer.

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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Cetrorelix acetate

Cetrotide (Serono)

vials containing 250 microgram or 3 mg as powder for reconstitution

Approved indication: assisted reproduction

Australian Medicines Handbook Section 10.6.3

Luteinising hormone has an important role in the menstrual cycle. In assisted reproduction programs a premature surge in luteinising hormone can cause ovulation, and therefore disrupt the collection of oocytes. This surge can be prevented by antagonising luteinising hormone releasing hormone (LHRH).

Cetrorelix competes with LHRH for binding sites in the pituitary gland. This reduces the secretion of luteinising hormone and follicle stimulating hormone. A 250 microgram dose is injected every day starting five or six days after ovarian stimulation is begun. These injections continue until the day before ovulation is induced. A single large dose (300 mg) can be used to suppress ovulation for at least four days.

Analogues of gonadotrophin-releasing hormones have also been used to prevent surges of luteinising hormone. (Prolonged administration of an analogue agonist eventually reduces gonadotrophin production.) Cetrorelix has therefore been compared with the LHRH agonists such as triptorelin and buserelin. While cetrorelix was as efficacious as the agonists it has the advantage of a more immediate action.

The most frequent adverse effects of cetrorelix are injection site reactions. Ovarian hyperstimulation can occur, but it is uncertain if this is caused by cetrorelix rather than the hormones used to promote follicular development. Compared to patients given LHRH agonists there are fewer cases of ovarian hyperstimulation.

While cetrorelix has been approved for use by specialists in the management of female infertility, researchers are studying other possible uses of LHRH antagonists.

Ganirelix

Orgalutran (Organon)

250 microgram/0.5 mL in pre-filled syringes

Approved indication: assisted reproduction

Australian Medicines Handbook Section 10.6.3

Ganirelix is the second member of its class to be approved for use in Australia. The first luteinising hormone releasing hormone (LHRH) antagonist to be approved was cetrorelix (see above).

These drugs are given to prevent premature ovulation when controlled ovarian hyperstimulation is used to assist conception. The patients are given follicle stimulating hormone (FSH) starting on the second or third day of their menstrual cycle. When they have their sixth dose of FSH they start daily subcutaneous injections of ganirelix. By binding to pituitary gonadotrophin receptors, ganirelix inhibits a surge in the concentration of luteinising hormone. By preventing this surge, the timing of ovulation can be controlled. This enables an adequate number of follicles to develop to the required size for collection.

Earlier attempts to create gonadotrophin antagonists had problems because they triggered allergic reactions by releasing histamine. Although this does not appear to occur with ganirelix, it can cause reactions at the injection site in up to 15% of patients. Other adverse effects include headache and nausea.

The efficacy of ganirelix is probably similar to that of the gonadotrophin agonists which have also been used to prevent surges of luteinising hormone. Ganirelix has the advantage of acting more quickly. There is, however, a concern that implantation rates may be reduced for follicles exposed to LHRH antagonists.[1]

REFERENCE

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Lercanidipine hydrochloride

Zanidip (Solvay)

10 mg film-coated tablets

Approved indication: hypertension

Australian Medicines Handbook Section 6.4.6

Lercanidipine is a dihydropyridine calcium channel antagonist. Four other dihydropyridines are already available in Australia (see 'Calcium channel antagonists' Aust Prescr 1997;20:5-8).

Like other dihydropyridines, lercanidipine relaxes vascular smooth muscle to lower peripheral resistance. This vasodilatation occurs slowly so patients are less likely to develop acute hypotension and reflex tachycardia.

Although lercanidipine is completely absorbed its bioavailability is reduced to 10% by first-pass metabolism. The tablets should be taken at least 30 minutes before a meal because food increases the bioavailability. As the enzymes involved in the first-pass metabolism can become saturated, doubling the dose causes the plasma concentrations to more than double.

Lercanidipine is eliminated by liver metabolism. It is completely metabolised with approximately half the metabolites being excreted in the urine. This metabolism involves cytochrome P450 3A4 so the plasma concentration of lercanidipine may be increased by drugs, such as erythromycin, fluoxetine and ketoconazole, which inhibit the enzyme. The plasma concentration may be reduced by drugs, such as phenytoin and carbamazepine, which induce CYP 3A4. Lercanidipine is contraindicated in patients with moderate or severe liver disease and in patients with severe renal impairment. Although the half-life of lercanidipine is relatively short, its antihypertensive effect is sustained for 24 hours.

Short-term studies show that lercanidipine reduces diastolic blood pressure by 5-7 mmHg more than a placebo. During comparative studies lasting 12-16 weeks no significant differences emerged between lercanidipine and slow-release nifedipine, atenolol, hydrochlorothiazide or captopril. In a double-blind crossover study of 16 patients, lercanidipine reduced diastolic blood pressure by 13 mmHg while amlodipine produced a 10 mmHg reduction.[1]

Many of the adverse effects of lercanidipine are caused by vasodilatation. Headache, flushing and palpitations are the commonest adverse reactions. As most studies have only lasted a few months, more information is needed on the long-term safety of lercanidipine. Given the concerns about the adverse effects of dihydropyridines[2], it is unlikely that lercanidipine will have a prominent role in the treatment of hypertension.

Although it appears to be effective for mild to moderate hypertension it is not indicated for severe hypertension.

REFERENCES

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2. McNeil JJ. Calcium channel blockers: the continuing controversy. Aust Prescr 1999;22:2-3.

Lopinavir/ritonavir

Kaletra (Abbott Australia)

capsules containing 133.3 mg lopinavir/33.3 mg ritonavir

oral solution containing 400 mg lopinavir/100 mg ritonavir in 5 mL

Approved indication: HIV

Australian Medicines Handbook Section 5.3

Combinations of antiviral drugs which include a protease inhibitor effectively suppress HIV. By inhibiting viral proteases drugs, such as ritonavir, reduce replication of the virus.

Lopinavir is also a protease inhibitor. After absorption it undergoes high first-pass metabolism and is rapidly cleared from the circulation. Lopinavir is extensively metabolised by cytochrome P450 3A. This is one of the enzymes inhibited by ritonavir, so giving ritonavir in combination with lopinavir increases the plasma concentrations of lopinavir.

The combination should not be prescribed with drugs such as triazolam, midazolam, simvastatin, lovastatin, ergot derivatives, cisapride or rifampicin. Other drugs with potentially significant interactions include atorvastatin, cerivastatin, dihydropyridines, oral contraceptives, sildenafil and warfarin. Patients should not take St John's wort as this reduces the plasma concentrations of lopinavir/ritonavir.

A randomised double-blind trial has studied lopinavir/ritonavir in combination with stavudine and lamivudine in patients who have not been previously treated with antiretroviral drugs. After 48 weeks of treatment the concentration of HIV RNA had fallen below 400 copies/mL in most patients.[1]

In a comparison with nelfinavir, another protease inhibitor, lopinavir/ritonavir was given to patients who also took stavudine and lamivudine. After 24 weeks the HIV RNA was below 400 copies/mL in 71% of the patients taking nelfinavir and in 79% of those taking lopinavir/ritonavir. This difference is statistically significant.

Lopinavir/ritonavir has also been studied in patients previously treated with a protease inhibitor. It has been given in a regimen with two nucleoside reverse transcriptase inhibitors and nevirapine (a non-nucleoside reverse transcriptase inhibitor). After 72 weeks, 75% of the patients had less than 400 copies/mL.

Approximately 3% of the patients withdrew from clinical trials of lopinavir/ritonavir because of adverse reactions. Diarrhoea affects 14-22% of patients. Other adverse effects include nausea, abdominal pain and asthenia. The combination alters liver function and can also increase concentrations of total cholesterol and triglycerides. Possibly related to the changes in triglycerides, are reports of pancreatitis in patients taking lopinavir/ritonavir.

Although lopinavir/ritonavir can be used to treat patients who have previously been treated with a protease inhibitor the extent of cross-resistance is uncertain. Some viruses will develop a reduced sensitivity to lopinavir/ritonavir during treatment.

Lopinavir/ritonavir may have a role in treating patients who are infected with HIV that is resistant to other drugs. Its precise role and the most suitable regimen will need further study as there are no data about the clinical outcomes of treatment.

REFERENCE

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Meningococcal group C conjugate vaccine

Meningitec (Wyeth)

vials containing 0.5 mL

Approved indication: immunisation

Australian Medicines Handbook Section 20.1

Neisseria meningitidis is a major cause of meningitis and infants are particularly at risk. Babies are not currently immunised against the meningococcus because the available polysaccharide vaccines are not very effective. Conjugating the meningococcal group C oligosaccharide to diphtheria protein increases the immune response.[1] Immunogenicity data enabled this conjugate vaccine to be approved in the UK, without a trial of the vaccine's efficacy.

A randomised controlled trial compared a conjugate vaccine with a quadrivalent polysaccharide vaccine in 127 infants aged 15-23 months. Each child had two injections two months apart, followed by a booster dose of polysaccharide vaccine a year later. After two doses the IgG response in the children who received conjugate vaccine was 10 times greater than the response to the polysaccharide vaccine. Their titres were still twice as high one year later. One month after the booster their titres were 50 times greater than those of the children who had the polysaccharide vaccine.[2]

Meningococcal group C conjugate vaccine is now part of the routine immunisation schedule in the UK. A study of the first nine months of experience with the vaccine estimated the short-term efficacy of a single dose to be 92% for toddlers and 97% for adolescents. Only two of the 32 toddlers who developed meningitis had been immunised.[3] There are no efficacy data for infants who receive a course of three injections.[3]

The injections are given intramuscularly. Meningococcal vaccine can be given at the same time as routine childhood vaccines, but there is limited information about giving it with inactivated polio vaccine or varicella vaccine.

Injection site reactions are common. Some children will develop a fever in excess of 38°C and there may be signs of irritability. Convulsions have been reported.

While the conjugate vaccine appears to be safe and effective in the short term, it will not protect people against other causes of meningitis, for example *Neisseria meningitidis* group B which is more common in Australia.

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Moxifloxacin hydrochloride

Avelox (Bayer)

400 mg tablets

Approved indication: respiratory infections

Australian Medicines Handbook Section 5.1.12

Moxifloxacin is a fluoroquinolone antibiotic. Like other fluoroquinolones it is active against Gram-negative bacteria such as *Haemophilus influenzae*. Compared to older members of the class, such as ciprofloxacin, moxifloxacin has more activity against Gram-positive bacteria such as *Streptococcus pneumoniae*.

Given its spectrum of antibacterial activity moxifloxacin has been approved for the treatment of community-acquired pneumonia, exacerbations of chronic bronchitis and sinusitis. In studies of patients with community-acquired pneumonia, moxifloxacin has been as effective as other drugs such as clarithromycin.

Moxifloxacin is as effective as cefuroxime in the treatment of acute maxillary sinusitis. Cefuroxime was also equivalent to moxifloxacin in the treatment of exacerbations of chronic bronchitis. For this indication, a five day course of moxifloxacin is as effective as a seven day course of clarithromycin.

Moxifloxacin has a half-life of 12 hours, but can be given once a day. It is eliminated by renal and hepatic clearance. The metabolism of moxifloxacin does not involve the cytochrome P450 system. Although it has not been associated with the severe liver problems associated with trovafloxacin, moxifloxacin should not be given to patients with significant hepatic impairment.

Like other oral antibiotics, nausea, vomiting and diarrhoea are common adverse effects of moxifloxacin. It may cause dizziness and lightheadedness so patients should know how they react to this drug before they drive or operate machinery. Moxifloxacin can also prolong the QT interval so there is a potential for arrhythmias. Similar ECG changes led to the withdrawal of grepafloxacin. Moxifloxacin should therefore not be given to patients with a prolonged QT_c interval, hypokalaemia, or those taking drugs which prolong the QT_c interval. Although the photosensitivity potential of moxifloxacin appears to be low, hypersensitivity reactions can occur after the first dose.

Bacteria are becoming resistant to the fluoroquinolones and there is cross-resistance to drugs within the class. To maintain the usefulness of these drugs, moxifloxacin should probably not be used as a first-line treatment for common infections such as sinusitis.

Thyrotropin alfa-rch

Thyrogen (Genzyme)

0.9 mg/mL in 5 mL vials

Approved indication: thyroid cancer testing

Australian Medicines Handbook Section 10.3

This recombinant form of human thyroid stimulating hormone (TSH) can be used in diagnostic tests of patients with thyroid cancers. One indication, in conjunction with radioactive iodine imaging, is for the detection of remnant thyroid tissue after total thyroidectomy. The radioiodine is given 24 hours after the second of two intramuscular injections of reconstituted thyrotropin (also given 24 hours apart). A similar regimen is used for thyroglobulin testing with a serum sample being taken 72 hours after the second injection. (Thyroglobulin should be undetectable after total thyroidectomy.)

The common adverse effects of thyrotropin are nausea and headache.

NEW FORMULATIONS

Calcipotriol

Diavonex Scalp Solution (CSL)

50 microgram/mL solution

Gliclazide

Diamicron MR (Servier)

30 mg modified-release tablets

NEW STRENGTH

Conjugated oestrogens/ medroxyprogesterone acetate

Premia 10 (Wyeth)

packs of 14 tablets containing 0.625 mg conjugated oestrogens and 14 tablets containing 0.625 mg conjugated oestrogens/ 10 mg medroxyprogesterone acetate

NEW COMBINATION

Abacavir/lamivudine/zidovudine

Trizvir (GlaxoSmithKline)

tablets containing 300 mg abacavir/150 mg lamivudine/ 300 mg zidovudine

NEW PROPRIETARY BRANDS

Cefotaxime sodium

DBL Cefotaxime Sodium for Injection (Faulding)

500 mg, 1 g and 2 g vials

Gliclazide

Nidem (Arrow)

80 mg tablets

Answers to self-test questions

1. False	3. True	5. True
2. True	4. False	6. True
7. True	9. False	
8. True	10. False	