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 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.

Caspofungin acetate

Cancidas (Merck Sharp and Dohme)

vials containing 50 mg or 70 mg as lyophilised powder

Approved indication: aspergillosis

Australian Medicines Handbook section 5.2

Immunosuppressed patients, including patients treated with large doses of corticosteroids, are at risk of invasive aspergillosis. They are usually treated with amphotericin. If this does not work then caspofungin can be considered.

Caspofungin is from a new class of drugs which inhibit the synthesis of the glucan component of the fungal cell wall. Although caspofungin is active against species of candida it is only approved for aspergillosis as this was the indication that was granted fast-track approval by the Food and Drug Administration in the USA.

The drug is reconstituted in 0.9% saline or water for injection then given by slow intravenous infusion. A loading dose is given on the first day. On the following days a smaller single dose is given by infusion until the patient improves. Caspofungin is slowly metabolised with only small amounts appearing unchanged in the urine. The dose should be reduced in patients with hepatic impairment.

As caspofungin is reserved for patients who are refractory to or intolerant of other antifungal drugs, its approval has been based on only 58 patients with invasive aspergillosis. Most of the patients had a haematological malignancy or had received a transplant. There was a favourable response in 34% of the people who were refractory to other drugs. Responses were lower in patients with extrapulmonary aspergillosis.

Common adverse reactions in the study included nausea, vomiting, fever and flushing. Some patients developed complications such as phlebitis at the site of infusion. Caspofungin can decrease haemoglobin and increase liver enzyme concentrations. It should not be prescribed with cyclosporin because of the risk of altered hepatic function.

Although only a minority of patients will respond, this is a better outcome than could be expected for patients who are refractory to other drugs. It is unknown if resistance to caspofungin will develop.

Drospirenone/ethinyloestradiol

Yasmin (Schering)

3 mg drospirenone/30 microgram ethinyloestradiol 28 tablets (21 active tablets packaged with 7 placebo tablets)

Approved indication: contraception

Australian Medicines Handbook section 17.1.3

Drospirenone is a new progestogen. It has actions which are similar to those of progesterone.

A fixed combination of drospirenone and ethinyloestradiol is contraceptive. It has been studied in several open trials including a comparison with the combination of ethinyloestradiol 30 microgram and desogestrel 150 microgram (Marvelon). A total of 627 women took one of the pills for 26 cycles. There were three pregnancies with each drug. The incidence of breakthrough bleeding and dysmenorrhea was the same for both pills. Approximately 21% of women will have spotting during the first six cycles of treatment with drospirenone/ethinyloestradiol. Adverse events prompted 11% of the women to withdraw from the study.[1]

The contraindications and precautions for the combination resemble those of other combined pills. Common adverse events include headache, breast pain and nausea.

Drospirenone has been claimed to have antiandrogenic and antimineralocorticoid properties, but the clinical significance of these effects is uncertain. In the comparative study women taking the pill containing drospirenone did not put on as much weight. After two years of treatment mean weight gain was 0.4 kg compared to 0.98 kg with the desogestrel-containing pill. There was no significant difference in the incidence of premenstrual symptoms.[1]

REFERENCE

1. Foidart J-M, Wuttke W, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. Eur J Contracept Reprod Health Care 2000;5:124-34.

Drotrecogin alfa

Xigris (Eli Lilly)

5 mg and 20 mg vials

Approved indication: severe sepsis

Australian Medicines Handbook section 7

Protein C is involved in the inactivation of the coagulation cascade. The activated form of protein C has an antithrombotic effect and a deficiency of protein C can lead to thrombosis (see 'Investigations for thrombotic tendencies' Aust Prescr 1999;22:63-6).

In serious infections inflammatory cytokines can trigger coagulation, so activated protein C has an important role in modulating the procoagulant effect of inflammation. Patients with severe infections may be unable to activate protein C and those with low concentrations of protein C have a poor

prognosis. Trials have therefore investigated whether adding an infusion of recombinant activated protein C (drotrecogin) to the treatment of these seriously ill patients will improve their outcomes.

A multinational double-blind trial enrolled 1690 patients with severe sepsis causing dysfunction of at least one organ system. The 850 patients given drotrecogin were compared with 840 patients who received an infusion of saline for 96 hours. One month after the infusion 25% of the patients given drotrecogin were dead. This outcome was significantly better than for the placebo group as 31% of those patients died.[1]

The danger of giving a recombinant anticoagulant is bleeding. One in four patients given drotrecogin had some bleeding and 3.5% had a serious haemorrhage. Two patients died of intracranial haemorrhage during the infusion.[1] Drotrecogin is contraindicated in patients with a recent history of brain or spinal surgery, head trauma or haemorrhagic stroke. Patients with a bleeding tendency or peptic ulceration are particularly at risk of serious haemorrhage.

There is no antidote to drotrecogin, but as the half-life of endogenous activated protein C is relatively short, stopping the infusion will reduce the concentration within a few hours. In most patients the drug is undetectable two hours after the end of the infusion.

The clinical trialists concluded that one life would be saved for every 16 patients treated with drotrecogin. However, the patients have to be carefully selected to achieve this benefit. Many patients with a potential risk of bleeding were excluded, for example, patients who had taken warfarin or more than 650 mg of aspirin. Drotrecogin is likely to be expensive.

REFERENCE

1. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699-709.

Epoprostenol sodium

Flolan (GlaxoSmithKline)

vials containing 500 microgram as freeze-dried powder

Approved indication: primary pulmonary hypertension

Australian Medicines Handbook section 7.1

Primary pulmonary hypertension is a serious, but rare, condition. A rise in pulmonary artery pressure leads to right ventricular failure and death. The median survival time is less than three years, so patients may die while waiting for a transplant.

Treatment regimens include anticoagulants and the use of vasodilators to reduce pulmonary vascular resistance. Epoprostenol (formerly known as prostacyclin or prostaglandin I_2) is a vasodilator which also inhibits platelet aggregation.

In an eight-week randomised trial, 11 patients with primary pulmonary hypertension were given a continuous infusion of epoprostenol. Compared with 12 patients who received conventional therapy, the infusion group had reductions in pulmonary artery pressure and total pulmonary resistance. Both groups were able to walk further after treatment.[1]

All the patients who completed the study were able to continue treatment with epoprostenol in an uncontrolled trial. This found that the survival of patients with severe symptoms (New York Heart Association class III or IV) increased. Their three-year survival rate was 63% compared with 41% in a group of historical controls.[2]

Improved survival was also seen in a prospective study of 81 patients with class III or IV heart failure. All 41 of the patients given epoprostenol survived, but eight of the 40 people in the control group died during the 12-week study.[3]

Epoprostenol is too unstable to be given orally. Its intravenous half-life is less than six minutes so it has to be given by continuous infusion. In the clinical trials each patient used a portable infusion pump connected to a central venous catheter. The infusion should not be stopped suddenly as the patient can deteriorate within minutes. Adjustments to the infusion rate must be done under observation so that heart rate and blood pressure can be monitored for several hours.

As epoprostenol is a vasodilator its acute adverse effects include hypotension, flushing and headache. Other common adverse effects reported in the clinical trials include tachycardia, jaw pain, myalgia, nausea and diarrhoea.

The indwelling catheter is a risk for infection and more than 20% of patients may develop local infections. In the long-term trial the drug delivery system was implicated in half the deaths.[2] Patients must therefore be taught how to prepare the drug and how to care for their catheter to minimise the risk of sepsis.

Epoprostenol may have an effect on coagulation, but as the patients are also usually taking anticoagulants they should already be being routinely monitored for signs of bleeding. The clearance of digoxin is temporarily reduced by epoprostenol.

Although treatment with epoprostenol has risks, it appears to improve survival and quality of life.[3] Its haemodynamic effects may delay the need for transplant surgery and improve the outcomes for people who need to have surgery. Epoprostenol is also being studied in patients with other causes of pulmonary hypertension, such as scleroderma.

REFERENCES

1. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Ann Int Med 1990;112:485-91.
2. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Int Med 1994;121:409-15.
3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296-301.

Gadoteric acid

Dotarem (Aspen Pharmacare Australia)

0.5 mmol/mL in 10 mL vials

Approved indication: magnetic resonance imaging

Gadolinium-containing products can be used to enhance the contrast in magnetic resonance imaging (MRI). Gadoteric

acid is inert, but has paramagnetic properties. It can be used in whole body imaging and for brain imaging if the blood-brain barrier is abnormal.

Most of the gadoteric acid is excreted unchanged in the urine within 24 hours. There are no data on giving the product to patients with renal failure.

After intravenous injection of gadoteric acid the most common adverse reactions are headache, paraesthesia and nausea.

In the absence of studies large enough to detect significant differences, it is unknown if gadoteric acid has any advantages over similar contrast agents.

Olopatadine hydrochloride

Patanol (Alcon Laboratories)

1 mg/mL eye drops in 5 mL dispensers

Approved indication: seasonal allergic conjunctivitis

Australian Medicines Handbook section 11.3.2

Topical antihistamines are useful in the treatment of allergic conjunctivitis, but until recently levocabastine has been the only single drug available in Australia. Prescribers now have the option of using olopatadine, an H_1 receptor antagonist which also inhibits the release of histamine from mast cells.

Patients instil one or two drops of olopatadine twice a day. Very little of the drug enters the circulation and the quantity that is absorbed is largely eliminated unchanged in the urine.

Olopatadine has been compared with other treatments for allergic conjunctivitis, but many of these alternatives are not available as ophthalmic formulations in Australia. In studies lasting a few weeks olopatadine has compared favourably with drops of azelastine, nedocromil, ketotifen and ketorolac. Some studies have found that patients get more relief with loratadine and olopatadine than with loratadine tablets alone. Olopatadine may help patients whose main complaint is itchy eyes.

Adverse reactions to olopatadine drops include dry eyes, blurred vision, burning and stinging. Some patients may complain of altered taste.

To determine the role of olopatadine in Australian practice will require comparative studies with levocabastine, although the drugs may compete on price. If olopatadine is prescribed, treatment should not exceed 14 weeks.

Pegfilgrastim (pegylated filgrastim)

Neulasta (Amgen)

syringes containing 6 mg/0.6 mL

Approved indication: neutropenia

Australian Medicines Handbook section 14.2.1

Granulocyte colony stimulating factor (G-CSF) promotes the production of neutrophils. Recombinant forms of G-CSF (filgrastim, lenograstim) can be used to treat neutropenia and are useful for patients receiving aggressive chemotherapy (see 'Granulocyte colony stimulating factor (G-CSF)' Aust Prescr 1994;17:96-9).

Recombinant G-CSF has to be given as a daily injection or infusion until the patient recovers. The half-life of filgrastim is approximately three hours, however the addition of a polyethylene glycol molecule extends this to 15–80 hours. This enables patients to be treated with only one subcutaneous dose in each cycle of chemotherapy.

The prolonged half-life of pegylated filgrastim (pegfilgrastim) is brought about by reduced renal clearance. As pegfilgrastim clearance also involves it binding to receptors on neutrophils, clearance will increase as the patient recovers from neutropenia.

A single dose of pegfilgrastim has been compared with daily filgrastim in 310 patients receiving chemotherapy for breast cancer. There were no significant differences in the duration and severity of the neutropenia. Febrile neutropenia developed in 9% of the patients given pegfilgrastim and 18% of those given filgrastim.[1]

The adverse effects of pegfilgrastim are similar to those of filgrastim. More than one in four patients will develop bone pain and this can be severe enough for some patients to need opioid analgesia. Serious adverse effects of filgrastim such as splenic rupture, adult respiratory distress syndrome and anaphylaxis have not yet been reported with pegfilgrastim.

Pegfilgrastim will probably not be significantly cheaper than filgrastim, but its less frequent administration makes it more convenient to use.

REFERENCE

1. Holmes FA, O'Shaughnessy JA, Vukelja S, Jones SE, Shogan J, Savin M, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002;20:727-31.

Tenofovir disoproxil fumarate

Viread (Gilead Sciences)

300 mg tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.3

Patients with HIV are now treated with combinations of antiviral drugs (see 'New approaches in the treatment of HIV infection' Aust Prescr 1998;21:44–6). The combination each patient uses may need to be changed when resistance develops. There are no drugs which will eliminate multiresistant HIV, but tenofovir can be added to the patient's usual regimen.

Tenofovir is an analogue of adenosine monophosphate. By competing with the usual substrate of HIV reverse transcriptase it inhibits the enzyme. This stops the conversion of viral RNA into DNA.

Early trials showed that tenofovir could reduce plasma concentrations of viral RNA. It was therefore tried in patients who had evidence of ongoing viral replication despite antiretroviral therapy. In a dose-ranging study tenofovir or a placebo was added to the combination therapy of 186 patients. After 24 weeks, 19% of the patients taking tenofovir had less than 400 viral copies/mL and 11% had less than 50 viral

copies/mL. In the placebo group only 7% of patients achieved less than 400 viral copies/mL.

A larger trial added 300 mg tenofovir to the treatment of 368 patients while another 182 patients had a placebo added. After 24 weeks 40% of the patients taking tenofovir and 11% of the patients taking placebo had less than 400 viral copies/mL. Only 1% of the placebo group had less than 50 copies/mL compared with 19% of the tenofovir group.

As tenofovir is not well absorbed the tablets contain tenofovir disoproxil fumarate. This compound is a prodrug which is rapidly converted in the liver and plasma. It should be taken with food as this increases bioavailability. Most of a dose is excreted in the urine as tenofovir. Unlike some antiretroviral drugs, tenofovir does not inhibit cytochrome P450, but it does compete with other drugs excreted by renal tubular secretion. These competing drugs include ganciclovir, valaciclovir and aciclovir. Tenofovir can increase the concentrations of didanosine by more than 40%, but the mechanism is unknown.

As some renal toxicity (e.g. phosphaturia) occurred in animal studies, kidney function should be monitored. These studies also reported osteomalacia, but the significance of this finding for patients is not yet known. Most of the adverse effects of tenofovir are gastrointestinal (nausea, vomiting, flatulence and diarrhoea).

There are no long-term safety data for tenofovir and its efficacy is based on surrogate end-points. Although there has been little viral resistance to tenofovir so far, the benefits of tenofovir are still uncertain. In the dose-ranging study the effect of tenofovir on CD4 lymphocytes was not significantly different from that of placebo.

Valganciclovir

Valcyte (Roche)

450 mg film-coated tablets

Approved indication: cytomegalovirus retinitis

Australian Medicines Handbook section 5.3.1

Immunosuppressed patients, particularly those with AIDS, are at risk of cytomegalovirus infection. This can cause a retinitis which may result in blindness. Patients can be treated with ganciclovir, but, as its oral bioavailability is low, treatment has to begin with two or three weeks of intravenous therapy. Valganciclovir is a prodrug of ganciclovir which allows induction therapy to be given orally.

The bioavailability of valganciclovir is approximately 60%, but this can be increased by taking the drug with food. As valganciclovir is converted to ganciclovir in the gut wall and liver, very little reaches the systemic circulation. Ganciclovir is mainly excreted in the urine, so the dose of valganciclovir should be reduced in patients with renal impairment.

A randomised trial studied the progression of newly diagnosed cytomegalovirus retinitis after four weeks of treatment. Seventy patients were treated with intravenous then oral ganciclovir and 71 patients took oral valganciclovir. The retinitis progressed in approximately 10% of each group. After four weeks all the patients took valganciclovir for maintenance. The retinitis progressed after a median time of 125 days in the patients induced with ganciclovir and 160 days in the valganciclovir group.[1]

As ganciclovir has many adverse effects it is not surprising that there are frequent adverse reactions in patients given valganciclovir. Diarrhoea, nausea and vomiting are common. As neutropenia occurs in 27% of patients and anaemia in 26%, frequent blood counts are indicated. Taking too much valganciclovir can cause fatal bone marrow suppression. It is therefore vital to remember that valganciclovir tablets should not be substituted, one for one, for oral ganciclovir capsules.

Patients with cytomegalovirus retinitis may prefer to begin their treatment with oral rather than intravenous therapy. As well as the convenience, valganciclovir avoids the morbidity associated with giving intravenous ganciclovir. However, the available information does not say if patients can be induced with valganciclovir then switched to oral ganciclovir for maintenance therapy.

REFERENCE

1. Valganciclovir Study Group. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002;346:1119-26.

NEW FORMULATIONS

Meningococcal C C-CRM197 conjugate vaccine

Menjugate (CSL)

0.5 mL vials

Meningococcal C polysaccharide conjugate vaccine

NeisVac-C (Baxter)

0.5 mL pre-filled syringes

Sirolimus

Rapamune (Wyeth)

1 mg tablets

NEW STRENGTHS

Efavirenz

Stocrin (Merck Sharp & Dohme)

600 mg tablets

Ipratropium bromide

DBL Ipratropium (Mayne Pharma)

500 microgram/mL solution for inhalation

Testosterone

Androderm (Mayne Pharma)

24.3 mg transdermal patch (delivers 5 mg testosterone/day)

NEW COMBINATION

Eprosartan mesylate/hydrochlorothiazide

Teveten Plus (Solvay)

tablets containing 600 mg eprosartan mesylate/12.5 mg hydrochlorothiazide

NEW PROPRIETARY BRANDS

Alprazolam

Alprax (Arrow)

0.25 mg, 0.5 mg, 1 mg and 2 mg tablets

Benztropine mesylate

Benztrop (Pharmalab)

2 mg tablets

Cephalexin

Cephalexin-BC (Biochemie)

125 mg/5 mL powder for oral suspension

Doxycycline

Doxy-50 Acne Pack (Douglas)

50 mg tablets

Epirubicin hydrochloride

Epirubicin hydrochloride injection (Mayne Pharma)

2 mg/mL solution in 5 mL, 10 mL and 25 mL vials

Gabapentin

Pendine (Alphapharm)

100 mg, 300 mg and 400 mg capsules, 800 mg tablets

Methylphenidate

Douglas-Methylphenidate (Douglas)

10 mg tablets

Mirtazapine

Mirtazon (Arrow)

30 mg tablets

Norfloxacin

Roxin (Arrow)

400 mg tablets

Tramadol hydrochloride

Zydol (Arrow)

50 mg capsules

Answers to self-test questions

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

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