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.

Ancestim

Stemgen (Amgen Australia)

vials containing 1.875 mg as powder for reconstitution

Approved indication: stem cell transplant

Australian Medicines Handbook Section 14.2

Some cancer treatments require the patient to have an autologous stem cell transplant after chemotherapy. The cells for transplant are collected before treatment. Granulocyte colony stimulating factor (G-CSF) is often used to increase the number of circulating haemopoietic precursor cells available for collection. Ancestim has been developed for use with G-CSF to further increase the number of cells which can be harvested for transplant. It is a recombinant form of human stem cell factor, the protein which normally stimulates stem cell production.

Ancestim and G-CSF have been compared with G-CSF alone in 205 women with breast cancer. The objective was to collect a target number (5×10^6/kg) of $CD34^+$ cells. Treatment continued until the target was reached or aphoresis had been carried out five times. The proportion of the patients given the combination who reached the target was 63% compared with only 47% of the patients given G-CSF alone. Fewer collections were needed in the combination group; a median of four aphoresis procedures was required.

Everyone prescribed ancestim must be given a bronchodilator and H_1 and H_2 antagonists before each subcutaneous injection. There is a risk that ancestim will stimulate mast cells and cause allergic reactions. Nearly all patients will experience an injection site reaction. Other common adverse effects include respiratory symptoms, paraesthesia and rashes.

The stimulant effect of ancestim may promote the growth of tumour cells. Particular caution is needed if the drug is considered for use in patients with myeloid malignancies, melanomas, or small cell lung cancers.

While ancestim has achieved its targets for efficacy, there is little information on its benefits for the patients. Although the patients may be spared additional aphoresis, it is unknown if adding ancestim to G-CSF will ultimately improve end-points such as survival.

Desirudin

Revasc (Aventis Pharma)

vials containing 15 mg as lyophilised powder

Approved indication: prevention of thromboembolism

Australian Medicines Handbook Section 7.1

The influence of the leech on medical practice seems set to continue into the next century following the approval of desirudin. This is a recombinant product with a structure that is almost identical to hirudin, an anticoagulant found in the saliva of *Hirudo medicinalis*. It has been approved for the prevention of thromboembolism after hip replacement surgery.

Desirudin is reconstituted with mannitol and injected subcutaneously no more than 30 minutes before elective hip replacement. Twice daily injections continue for 9–12 days until the patient is walking. The injections should be rotated through at least four different sites.

The maximum plasma concentrations occur within three hours of injection. Desirudin is partly metabolised before excretion. Approximately half the dose is excreted unchanged in the urine. The APTT should be monitored in patients with impaired hepatic or renal function.

Desirudin acts by specifically inhibiting thrombin. As desirudin can inactivate thrombin bound to fibrin, it has a potential advantage over heparin which also has a less specific action.

A double-blind trial has compared subcutaneous heparin and desirudin in 1119 patients having hip surgery.[1] Patients given the dose of desirudin recommended for use in Australia (15 mg twice daily) were significantly less likely to develop deep vein thrombosis than those given unfractionated heparin (18.4% versus 34.2%). The respective frequencies of proximal thrombosis were 3.1% versus 19.6%. The frequency of bleeding complications was similar in both groups.

Episodes of bleeding occurred in 13% of patients given desirudin in clinical trials. There is no antidote. Other adverse effects include haematoma, injection site masses and secretion from the wound.

While hirudin is more effective than subcutaneous unfractionated heparin, its role in clinical practice is not yet clear. There needs to be a comparison between hirudin and other approaches to preventing thrombosis such as adjusted dose intravenous heparin or subcutaneous low molecular weight heparin.

REFERENCE

1. Eriksson BI, Ekman S, Kalebo P, Zachrisson B, Bach D, Close P. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 1996;347:635-9.

Rofecoxib

Vioxx (Merck Sharp & Dohme)

12.5 mg and 25 mg tablets

Approved indication: osteoarthritis

Australian Medicines Handbook Section 15.1

Rofecoxib is the second inhibitor of cyclo-oxygenase 2 (COX-2) to be marketed in Australia. Unlike celecoxib

(see 'New drugs' Aust Prescr 1999;22:147-8), in Australia its approval is limited to osteoarthritis.

Compared to celecoxib, rofecoxib is more selective for COX-2. It therefore has little effect on the synthesis of prostaglandins in the gut. Rofecoxib has a half-life of 17 hours and can be taken once a day. Each dose is well absorbed resulting in a bioavailability of 93%. The drug is metabolised in the liver and most of the metabolites are excreted in the urine.

In clinical trials rofecoxib has reduced joint pain in osteoarthritis more than placebo. It also improves stiffness and joint function. During a six-week study the efficacy of 12.5 mg or 25 mg rofecoxib daily was similar to that of 800 mg ibuprofen three times a day. In a year-long comparison, rofecoxib was comparable to 50 mg diclofenac three times a day.

Studies which used endoscopy to look for gastroduodenal ulcers, found that rofecoxib 25 mg or 50 mg/day caused significantly fewer ulcers than ibuprofen 2400 mg/day during 24 weeks of treatment. However, gastrointestinal bleeding can still occur. Among the 3357 patients treated with rofecoxib in clinical trials, three experienced a haemorrhage. This incidence is lower than that seen with non-steroidal anti-inflammatory drugs, but a long-term study of comparative safety has not been performed.

In the clinical trials of rofecoxib the most commonly reported adverse effects were headache, diarrhoea and abdominal pain. Some patients will have increased blood pressure or fluid retention so extra caution is required if a patient has heart failure or reduced renal function. Approximately 1% of patients will develop abnormal liver function tests. Rofecoxib interacts with several drugs including warfarin and ACE inhibitors.

For patients with osteoarthritis, who cannot be managed with other analgesics, prescribers now have a choice between celecoxib and rofecoxib. Although rofecoxib is more selective it may not be safer. Until evidence of long-term safety and efficacy is available the choice of treatment will be influenced by the cost of the drugs.

Verteporfin

Visudyne (CIBA Vision)

vials containing 15 mg as powder for reconstitution

Approved indication: macular degeneration

Australian Medicines Handbook Section 11.4

As people grow older they can develop macular degeneration. This is caused by a failure to clear the products of retinal metabolism. In some patients this prompts vessels to grow from the choroid into the retina. If these abnormal vessels leak or bleed, the resulting scar reduces the patient's central vision. The only treatment is laser photocoagulation, but this has several limitations.[1]

Verteporfin is a drug treatment which aims to destroy new blood vessels affecting the retina. As verteporfin is not very soluble it has to be formulated in a liposomal delivery system. This is diluted and given as an infusion over 10 minutes. Verteporfin is transported around the body by lipoproteins.

To activate the drug a non-thermal laser light is shone into the affected eye 15 minutes after the infusion begins. An exposure of 83 seconds generates reactive oxygen radicals which may cause damage to vascular endothelium. This can lead to the occlusion of the abnormal vessels.

In double-blind trials involving 609 patients, 402 eyes were given photodynamic therapy with verteporfin and 207 eyes were treated with a placebo. The treatments were repeated every three months if fluoroscein angiography revealed leaking vessels. After one year the visual acuity and angiographic assessments were significantly better in the eyes exposed to verteporfin. The loss of visual acuity was particularly reduced in a sub-group of patients with classic choroidal revascularisation. Only 33% of this group had a substantial loss of vision compared with 61% of the placebo group.[2] Verteporfin has only been approved for use in patients with predominantly classic subfoveal choroidal neovascularisation.

There were few serious adverse reactions to verteporfin. Compared to placebo, there were more complaints about visual disturbance, injection site reactions and nausea.[2] Although verteporfin has a half-life of 5-6 hours, patients are advised to remain indoors for five days after treatment. This is because they become photosensitive after treatment. Although verteporfin may tend to accumulate in abnormal vessels it can also enter the retina. This could result in retinal damage when the drug is activated.

The long-term effects of verteporfin are currently unknown. Although it can help some patients with macular degeneration, future research is needed to prevent this common cause of blindness.[1]

REFERENCES

1. Fine SL, Berger JW, Maguire MG, Ho AC. Age-related macular degeneration. N Engl J Med 2000;342:483-92.
2. TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. Arch Ophthalmol 1999;117:1329-45.

NEW FORMULATION

Ibuprofen

Nurofen Meltlets (Boots Healthcare)

200 mg tablets

NEW STRENGTHS

Desferrioxamine mesylate

Desferrioxamine for injection BP (Faulding)

2 g vials

Sodium tetradecyl sulfate

Fibro-vein (Australasian Medical and Scientific)

0.2%, 0.5% and 1% injections

Sotalol hydrochloride

Sotacor (Bristol-Myers Squibb)

80 mg tablets

NEW COMBINATIONS

Fosinopril sodium/hydrochlorothiazide

Monoplus (Bristol-Myers Squibb)

10 mg fosinopril sodium/12.5 mg hydrochlorothiazide and 20 mg fosinopril sodium/12.5 mg hydrochlorothiazide tablets

Irbesartan/hydrochlorothiazide

Avapro HCT (Bristol-Myers Squibb)

150 mg irbesartan/12.5 mg hydrochlorothiazide and 300 mg irbesartan/12.5 mg hydrochlorothiazide tablets

Karvezide (Sanofi-Synthelabo)

150 mg irbesartan/12.5 mg hydrochlorothiazide and 300 mg irbesartan/12.5 mg hydrochlorothiazide tablets

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