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.

Aldesleukin

Proleukin (CSL)

vials containing 18 million IU as powder

Approved indication: renal cell carcinoma

Australian Medicines Handbook Section 14.2

Renal cell carcinoma is increasing in incidence. Many patients present with metastases and have a poor prognosis. Chemotherapy does not improve survival. In some patients the cancer may spontaneously regress suggesting an immune response. This has prompted research into the role immunomodulators, such as interferon, could play in treatment.

Aldesleukin is a recombinant form of the cytokine interleukin 2. This cytokine stimulates the production of killer cells and enhances the cytotoxicity of lymphocytes. It is also involved in the production of interferon and tumour necrosis factor.

A randomised trial compared aldesleukin, interferon alpha-2a or a combination of both treatments in 425 patients with progressive metastatic renal cell carcinoma. The response to treatment was assessed using CT scans to measure the regression of the tumour. After 10 weeks 6.5% (9/138) of patients given aldesleukin had responded. The response rate at 25 weeks was 2.9%. Patients who received the two treatments in combination had significantly higher response rates (18.6% at 10 weeks, 13.6% at 25 weeks).[1]

Aldesleukin given intravenously has many adverse effects, so it has only been approved for subcutaneous injection. This requires daily injections for five days a week for four weeks. After four weeks the patient has one week's rest and then the cycle is repeated.

The subcutaneous injection has a bioavailability of 35–47%. It is metabolised and excreted by the kidneys with a half-life of 5–9 hours.

In studies involving a total of 103 patients, subcutaneous injections produced a complete response in four patients. The overall response rate was 14%.

Most patients will develop adverse reactions to aldesleukin, chills and fever being particularly common. Approximately 12% of patients develop hypotension. This may be part of a 'capillary leak syndrome' which also includes oliguria, pulmonary oedema and weight gain. More than half the patients will become anaemic or have altered liver function. Patients may develop antibodies to aldesleukin and some of the antibodies will have neutralising activity. Autoimmune and inflammatory diseases may flare up during treatment.

Aldesleukin does not increase survival. In the comparative study median survival was only 12 months.[1] However, the studies of subcutaneous aldesleukin showed that the response was prolonged in the few patients who had a complete response. The median response duration was 64 months. Further studies are needed to identify which factors predict a favourable response.

REFERENCE

1. Groupe Francais d'Immunotherapie. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. N Engl J Med 1998;338:1272-8.

Eprosartan mesylate

Teveten (SmithKline Beecham)

300 mg and 400 mg tablets

Approved indication: hypertension

Australian Medicines Handbook Section 6.4.5

Eprosartan is another one of the recently approved angiotensin$_1$ receptor antagonists (see 'Angiotensin receptor antagonists for the treatment of hypertension' Aust Prescr 1998;21:95–7). As this class expands, there is clearly a need for comparative studies. In the meantime, the precise role of the class in the treatment of hypertension remains unclear. While the drugs do have a low short term incidence of adverse effects, there is little knowledge about their long-term effect on outcomes, either adverse or beneficial.

The absorption of eprosartan is reduced by food, but this is considered to be clinically inconsequential. Absolute bioavailability is 13%. Eprosartan is partly metabolised and excreted in the bile and urine. Its pharmacokinetics are affected by severe liver or kidney disease. Lower starting doses are recommended in the elderly and patients with sodium/volume depletion. The half-life is 5–9 hours, but the manufacturer recommends only once daily dosing. If a patient is not responding, consideration can be given to changing to twice daily dosing before increasing the total daily dose.

Clinical trials show that eprosartan reduces diastolic blood pressure by 2–5 mmHg more than placebo. Studies comparing eprosartan and enalapril show that they are equally effective at lowering diastolic blood pressure. In one study, eprosartan had an effect on systolic blood pressure which was statistically greater than the effect of enalapril.

Like other members of this class, eprosartan has a low risk of adverse reactions. In placebo-controlled trials, 4% of patients taking eprosartan dropped out because of adverse events compared with 6.5% of the placebo group. The incidence of cough is lower than with ACE inhibitors.

Hydromorphone

Dilaudid (Knoll)

2 mg, 4 mg and 8 mg tablets

oral solution containing 1 mg/mL

ampoules containing 2 mg/mL, 10 mg/mL and 50 mg/5 mL

vials containing 500 mg/50 mL

Approved indication: moderate to severe pain

Australian Medicines Handbook Section 3.2

Hydromorphone is an opioid analgesic.[1] It has been available overseas for a long time, but has not been marketed in Australia for many years.

Patients with chronic cancer pain, requiring an opioid analgesic, may tolerate one opioid better than another. Hydromorphone may be an alternative analgesic for patients troubled by the adverse effects of morphine.

Oral hydromorphone is rapidly absorbed, but first-pass metabolism reduces the bioavailability to 25%. The drug is rapidly and widely distributed throughout the body. Most of the absorbed dose is metabolised, so hydromorphone is contraindicated in hepatic impairment. As the major metabolite is excreted in the urine, the drug is also contraindicated in renal impairment. As the half-life of hydromorphone is 2–3 hours, the dose can be rapidly titrated.

The recommended starting dose for oral treatment is 2–4 mg every four hours. A daily oral dose of hydromorphone 6.5–7.5 mg is equivalent to 40–60 mg of morphine or 10–20 mg of methadone. An intramuscular or subcutaneous dose of hydromorphone 1.3–2.0 mg is equivalent to 10 mg of morphine or methadone. A high potency formulation is available for use in narcotic-tolerant patients; this should not be confused with the standard parenteral formulation as an overdose may result.

The adverse effects of hydromorphone resemble those of other opioids, e.g. dry mouth, dizziness, nausea and vomiting. Patients become dependent on hydromorphone, if it is taken regularly, within a few weeks. Tolerance can also be expected. Sudden withdrawal of treatment can cause a withdrawal syndrome.

REFERENCE

1. Chahl LA. Opioids – mechanisms of action. Aust Prescr 1996;19:63-5.

Lepirudin

Refludan (Aventis Pharma)

vials containing 50 mg freeze dried powder

Approved indication: heparin-associated thrombocytopenia

Australian Medicines Handbook Section 7.1.1

Heparin can induce two types of thrombocytopenia. Type I occurs early in treatment and the platelet count soon returns to normal. Type II occurs after 5–10 days of treatment and can result in thromboembolism. Clotting occurs because the formation of a heparin-platelet complex induces the production of antibodies. These antibodies not only cause thrombocytopenia, but also activate the platelets. If untreated, heparin-induced thrombocytopenia can be fatal.

While the heparin can easily be stopped the prothrombotic state may persist. Lepirudin is therefore indicated for patients with Type II thrombocytopenia and its thromboembolic complications.

The drug is a recombinant form of hirudin, a substance produced by leeches. Lepirudin acts by inhibiting thrombin. This effect can be monitored by measuring the activated partial thromboplastin time.

Lepirudin has to be reconstituted and then injected intravenously. This bolus dose is followed by an infusion for 2–10 days. The dose is reduced if the patient has impaired renal function, as lepirudin is metabolised and excreted by the kidneys. A lower dose should also be used if the patient requires thrombolytic therapy.

In clinical trials, patients given lepirudin have been compared with historical controls. Approximately 74% of the patients responded to the treatment with an increased platelet count and an effective degree of anticoagulation. The incidence of new thromboembolic complications, death or the need to amputate a limb was reduced in comparison to the control group. After seven days of treatment the cumulative risk of these complications was 17% in the lepirudin patients and 25% in the control group.

The main adverse effect of lepirudin is bleeding. Thrombolytic therapy increases the risks. While bleeding from wounds and puncture sites is obvious, 9% of patients will suffer a fall in haemoglobin for no obvious reason. Other common problems are allergic reactions, bronchospasm and oedema. Approximately 40% of patients will develop antibodies to lepirudin. This may have implications if a patient requires a second course of treatment. Although the risk:benefit ratio is not clear, there are no specific treatments for heparin-associated thrombocytopenia, so there may be a role for lepirudin.

Live cholera vaccine

Orochol (CSL)

Sachets containing 2–10 x 10^8 colony forming units of *Vibrio cholerae*

Approved indication: immunisation

Australian Medicines Handbook Section 20.1.2

Vaccines based on heat-killed suspensions of *Vibrio cholerae* are not very effective. The injectable vaccine is also associated with systemic adverse effects. A live vaccine given by mouth may have advantages.

The new product is a recombinant form of the bacteria with the deletion of the gene coding for part of the cholera toxin. This live strain is known as *Vibrio cholerae* CVD 103-HgR.

Adult volunteers took the vaccine and were then exposed to virulent *Vibrio cholerae* 8–180 days later. There was complete protection against cholera, if the bacteria were of the same serotype as the vaccine. This protection was present as early as eight days after vaccination.

People (including children more than two years old) who are at a high risk of infection when travelling through endemic areas can take the vaccine at least a week before travel. The single dose sachet has two sections. Their contents are mixed together in 100 mL of water then drunk. The traveller should not eat for an hour after taking the vaccine. Common adverse effects include abdominal pain, increased bowel sounds and headache.

Live oral cholera vaccine should be taken at least one week before starting chloroquine as the antimalarial drug can reduce the immune response. Oral typhoid vaccine and oral cholera vaccine should be given at least eight hours apart, as the cholera vaccine may affect the passage of the capsules, containing the typhoid vaccine, through the gut. If possible, vaccinees should avoid contact with immunocompromised people for eight days after taking the vaccine.

Although the vaccine protected the volunteers in the challenge studies, it was much less effective if the virulent bacteria were from a different serotype. There is also little published evidence yet of the vaccine's effectiveness in field trials. While 60–70% of people will seroconvert after vaccination, this may not reflect the intestinal antibody response or clinical effectiveness. Although a booster dose is recommended every six months the duration of immunity after a single dose is unknown. There is a Cochrane review of cholera vaccines but it currently contains no effectiveness data for this new product.[1]

REFERENCE

1. Graves P, Deeks J, Demicheli V, Pratt M, Jefferson T. Vaccines for preventing cholera (Cochrane Review). In: The Cochrane Library, Issue 3. Oxford: Update Software. 1999.

Repaglinide

NovoNorm (Novo Nordisk)

0.5 mg tablets

Approved indication: type 2 diabetes

Australian Medicines Handbook Section 10.1

Patients with non-insulin dependent diabetes have impaired insulin secretion and a resistance to the effects of insulin. If non-drug treatment fails, patients can be given a sulfonylurea, to stimulate insulin secretion, or metformin, to improve insulin sensitivity.[1] When these drugs fail to control the blood glucose concentrations, repaglinide can be considered.

Repaglinide is not a sulfonylurea, but it stimulates the release of insulin from the pancreas. A dose is taken before meals. It is quickly and completely absorbed, but has a bioavailability of 63%. The peak plasma concentration is reached within an hour of the dose, and a response begins within 30 minutes. Repaglinide is almost completely metabolised by the liver and is cleared from the circulation within six hours.

In clinical trials, repaglinide was more effective than a placebo at reducing blood glucose concentrations. Its efficacy, in trials lasting up to 14 months, seemed to be similar to that of glibenclamide. In a trial lasting several months, the combination of metformin and repaglinide decreased HbA_{1c} and fasting glucose more than either drug alone.

The most common adverse event in the clinical trials of repaglinide was hypoglycaemia. The incidence of hypoglycaemia was similar to that seen with other oral hypoglycaemic drugs. It is important that the dose is titrated for each patient. Patients begin with 0.5 mg and then increase the dose at 1–2 week intervals. The maximum daily dose is 16 mg. Other adverse events resemble those of the sulfonylureas.

Metformin is usually the first drug prescribed for obese patients with diabetes.[1] Repaglinide may be a useful addition, if treatment with metformin alone is inadequate. While repaglinide's quick action is beneficial, it is not clear if it has any advantage over short-acting sulfonylureas. If overseas prices are reflected in Australia, any advantages are likely to be outweighed by the cost of repaglinide.

REFERENCE

1. Proietto J. The management of type 2 diabetes. Aust Prescr 1997;20: 65-7.

Tibolone

Livial (Organon Australia)

5 mg tablets

Approved indication: postmenopausal symptoms and bone loss

Australian Medicines Handbook Section 17.2.3

Tibolone is a synthetic steroid with oestrogenic and progestogenic activity. It can therefore be used to treat menopausal symptoms such as hot flushes.

The activity of the drug involves several metabolites. These are rapidly formed after absorption so plasma concentrations of tibolone are very low. Only small amounts are excreted in the urine.

Several studies have assessed the effect of tibolone on bone density. One study followed healthy postmenopausal women for two years. Women who took 2.5 mg tibolone daily had increases in bone density, while bone density fell in the control group. By the end of the study, there were significant differences in bone density between the groups in the upper femur and lumbar spine.[1]

Another study compared tibolone with oral or transdermal hormone replacement therapy. After two years, bone density was preserved in women who were treated, compared with untreated controls. There were no significant differences in efficacy between tibolone and hormone replacement therapy.[2]

As tibolone has some progestogenic effects it may have an advantage over oestrogen alone, e.g. the risk of breast cancer may be reduced. However, endometrial proliferation can still occur and lead to vaginal bleeding. Any abnormal bleeding occurring after three months of treatment should be investigated. Compared with placebo, more patients taking tibolone experience leukorrhoea, vaginitis, breast pain and weight gain.

Tibolone reduces triglyceride concentrations, but can also reduce HDL cholesterol. As it may increase fibrinolytic activity there is a potential for interaction with anticoagulants. Drugs

which induce liver enzymes, such as carbamazepine and rifampicin, may decrease the effect of tibolone.

Although tibolone has been available overseas for several years its place in therapy is not clear. While it can prevent reductions in bone mineral density its effectiveness in preventing fractures is unknown.

REFERENCES

1. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomised controlled trial. Br J Obstet Gynaecol 1999;106:678-83.
2. Lippuner K, Haenggi W, Birkhaeuser MH, Casez JP, Jaeger P. Prevention of postmenopausal bone loss using tibolone or conventional peroral or transdermal hormone replacement therapy with 17 beta-estradiol and dydrogesterone. J Bone Miner Res 1997;12:806-12.

NEW FORMULATIONS

Pantoprazole

Somac (Pharmacia & Upjohn)

40 mg powder for injection

Ropivacaine hydrochloride/fentanyl citrate

Naropin with fentanyl (AstraZeneca)

2 mg/mL ropivacaine hydrochloride/fentanyl citrate 2 microgram/mL and 2 mg/mL ropivacaine hydrochloride/fentanyl citrate 4 microgram/mL

NEW STRENGTHS

Alendronate sodium

Fosamax (Merck Sharp & Dohme)

5 mg tablets

Pantoprazole

Somac (Pharmacia & Upjohn)

20 mg tablets

NEW COMBINATION

Salmeterol/fluticasone propionate

Seretide Accuhaler (Glaxo Wellcome)

50 microgram salmeterol/100 microgram fluticasone propionate, 50 microgram salmeterol/250 microgram fluticasone propionate and 50 microgram salmeterol/500 microgram fluticasone propionate

Answers to self-test questions

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

Distribution and back issues

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.

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

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

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

The full text of *Australian Prescriber* is available on the internet, free of charge, at www.australianprescriber.com

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* web site on the internet. ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

My reference number is .....

☐ Change my address

My reference number is .....

☐ Send me all the available back issues (from Vol. 21 No. 4, 1998)

☐ Send me the following back issue/s

.....

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6289 7038

Facsimile: (02) 6289 8641

Postal: The Editor
Australian Prescriber
PO Box 100
WODEN ACT 2606
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: http://www.australianprescriber.com