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.

Orlistat

Xenical (Roche)

120 mg capsules

Approved indication: obesity

Australian Medicines Handbook Section 12.10

Patients with a body mass index (see box) of 30 or more can be difficult to treat. (See 'Obesity and its management' Aust Prescr 1999;22:12–6). These patients may benefit from orlistat in combination with a low calorie diet.

Orlistat inhibits lipase in the gut. This reduces the absorption of fat by approximately 30%. The decreased absorption of calories eventually leads to weight loss.

Two placebo-controlled trials have assessed the effect of orlistat on several hundred patients.[1,2] The patients were given a diet which contained fewer calories than their daily energy needs. They took orlistat or placebo for a year then were re-randomised and switched to a diet designed to maintain their weight. The patients were followed up for a further year. During the first year of the trials the patients in one study lost an average of 10.3 kg with orlistat and 6.1 kg with placebo.[1] In the second study the mean weight losses were 8.7 kg and 5.8 kg.[2] During the second year of the trials patients who had been re-randomised to placebo put weight back on. Those who had continued on orlistat regained less weight. Some of the patients switched from placebo to orlistat lost a small amount of weight (0.9 kg).[1]

The recommended dose is 120 mg with each main meal. Very little of the dose is absorbed. The effect of orlistat on faecal fat can be seen within two days. Some metabolism may take place within the wall of the gut, but most of the drug is excreted unchanged in the faeces.

As orlistat reduces fat absorption most patients develop adverse effects including fatty stools, loose stools, faecal urgency, flatulence and incontinence. Most of the approximately 9% of patients who discontinued treatment because of adverse effects did so because of gastrointestinal problems.

Although orlistat reduces cholesterol concentrations, it also reduces the absorption of fat-soluble vitamins. Reduced vitamin K absorption could alter the control of patients taking warfarin. In the clinical trials no deficiencies developed so vitamin supplements may not be needed.

Orlistat increases the plasma concentration of pravastatin, but does not alter the pharmacokinetics of digoxin, glibenclamide or phenytoin. Acarbose, which acts on intestinal glucosidase enzymes, should not be prescribed with orlistat as the potential for interactions has not been studied.

Pooled data have revealed more cases of breast cancer in women taking orlistat than in those taking a placebo. The clinical relevance of this observation is uncertain, as is the effect of exposing the colonic mucosa to large amounts of fat.

The clinical trials show that orlistat will enable patients to lose approximately 4 kg more than they would by dieting. This difference is reduced when the patient is given a eucaloric (weight-maintaining) diet. Continuing a hypocaloric diet for two years is the subject of more research. The drug is likely to be even less effective if the patient does not change their lifestyle. One approach is to stop orlistat if the patient has not lost 5% of their weight after 12 weeks of treatment.

REFERENCES

1. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HPF, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. Lancet 1998;352: 167–73.
2. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. JAMA 1999;281:235–42.

$$\text{Body mass index} = \frac{\text{weight in kilograms}}{(\text{height in metres})^2}$$

Quetiapine fumarate

Seroquel (AstraZeneca)

25 mg, 100 mg and 200 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook Section 18.2.2

Quetiapine is one of the 'new antipsychotics'.[1] It acts by antagonising neurotransmitters at several receptors. The affinity of quetiapine for dopamine receptors (D_2) is relatively low compared to its affinity for $5HT_2$ receptors. It also has little affinity for cholinergic receptors.

Patients take quetiapine twice a day. For the first four days of treatment the dose is increased each day. It is then adjusted according to the patient's response.

Each dose is rapidly absorbed and widely distributed. Quetiapine is extensively metabolised by the liver and then excreted in the urine and faeces. Cytochrome P450 (CYP 3A4) is probably primarily responsible for the metabolism. Extra caution is needed if quetiapine is given with inhibitors of this enzyme including some antidepressants. The clearance of quetiapine will be increased by drugs such as phenytoin which induce hepatic enzymes. Hepatic or renal impairment will reduce the clearance of quetiapine. Although its half-life is seven hours, quetiapine occupies the $5HT_2$ and D_2 receptors for up to 12 hours.

Quetiapine can cause postural hypotension so it should be used with caution in patients with cardiovascular disease. Other common adverse effects are somnolence, dry mouth, constipation, dizziness and altered liver function. Quetiapine may mildly prolong the QT_c interval so caution is needed if it is prescribed with other drugs which have this effect. In the USA patients are advised to have their eyes checked every six months because cataracts developed in some animal studies. This precaution is not included in the Australian product information.

Short-term studies have found quetiapine to be as effective as chlorpromazine and haloperidol, but it has a lower incidence of dystonia. In a comparison with risperidone, quetiapine was effective for the treatment of exacerbations of schizophrenia. Approximately 33% of the patients taking quetiapine and 38% of those taking risperidone had at least a 40% reduction in their positive and negative symptom scores. The long-term effectiveness of quetiapine requires further study.

A Cochrane review has found that quetiapine causes no more extrapyramidal effects than placebo and may be more effective. However, the review concludes that more studies are needed before quetiapine can be recommended. Many of the studies in the review had high dropout rates (48–61%) which make the results difficult to interpret.[2]

REFERENCES

1. McGrath J, White P. New antipsychotic medications. Aust Prescr 1999;22:81–3.
2. Srisurapanont M, Disayavanish C, Taimkaew K. Quetiapine for schizophrenia (Cochrane Review). In: The Cochrane Library, Issue 3, 1999. Oxford: Update software.

Quinupristin/dalfopristin

Synercid IV (Rhone-Poulenc Rorer)

vials containing 500 mg for reconstitution

Approved indication: specified infections

Australian Medicines Handbook Section 5.1.13

Overuse of antibiotics has contributed to the development of resistant organisms. There is an urgent need for new treatments for the vancomycin-resistant enterococci which have recently emerged. The streptogramin antibiotics may have a role.

Quinupristin and dalfopristin are derived from the pristinamycins. The combination of the two drugs acts synergistically to inhibit bacterial protein synthesis. This makes the combination bactericidal. It is mainly effective against Gram-positive aerobic bacteria.

After infusion over an hour the combination is rapidly metabolised. These metabolites contribute to the antimicrobial actions. Most of the combination and its metabolites are excreted in the faeces.

Although many bacteria are susceptible to quinupristin and dalfopristin, the combination should be reserved for the treatment of vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (MRSA). As the combination often has to be used in an emergency where no other treatment is available, the efficacy of the combination is difficult to evaluate. In one case control study the mortality was lower in the control group, but fewer patients given the combination died as a result of vancomycin-resistant infection.[1] In general, treatment of infections due to MRSA will have a higher success rate.

Approximately 11% of patients have to discontinue treatment because of reactions at the infusion site. They commonly experience pain, inflammation and oedema. To try to reduce these reactions the intravenous line should be flushed with 5% glucose. Flushing with heparin or saline is not recommended as the quinupristin/dalfopristin combination is incompatible with saline.

Systemic adverse reactions caused 6% of patients to stop treatment. These reactions include arthralgia, myalgia, nausea, vomiting and rashes. Liver function may also be affected.

The quinupristin/dalfopristin combination inhibits the enzyme cytochrome CYP 3A4. It can therefore inhibit the metabolism of drugs such as midazolam and nifedipine.

While this new product may help some patients with severe infections, it is important not to overlook the basic principles of management. For example, surgical debridement and the removal of infected devices such as catheters may be essential for successful treatment.[2]

REFERENCES

1. Linden PK, Pasculle AW, McDevitt D, Kramer DJ. Effect of quinupristin/dalfopristin on the outcome of vancomycin-resistant *Enterococcus faecium* bacteraemia: comparison with a control cohort. J Antimicrob Chemother 1997;39 Suppl A:145–51.
2. Lai KK. Treatment of vancomycin-resistant *Enterococcus faecium* infections. Arch Intern Med 1996;156:2579–84.

Tamsulosin hydrochloride

Flomax (CSL)

400 microgram modified-release capsules

Approved indication: benign prostatic hypertrophy

Australian Medicines Handbook Section 13.2.1

$Alpha_1$ adrenoceptor antagonists, such as prazosin and terazosin, can be used to treat the symptoms of benign prostatic hypertrophy.[1] They act by reducing smooth muscle tone in the prostate and bladder neck. Tamsulosin acts in the same way, but is claimed to be more selective for the $alpha_1$ adrenoceptors in the prostate.

The once-daily dose is absorbed slowly. Although food reduces the bioavailability, it is recommended that the dose is taken 30 minutes after breakfast. Most of the drug is metabolised by the liver and the metabolites are excreted in the urine.

In placebo-controlled trials tamsulosin improved the maximum urine flow rates. A comparison of tamsulosin with alfuzosin (a non-selective $alpha_1$ adrenoceptor antagonist), found that both drugs increased maximum flow rate by 1.6 mL/second.[2] Similar results were seen in a comparison with terazosin.[3]

Blocking the $alpha_1$ adrenoceptors reduces the blood pressure, but hypotension is not a frequent problem with tamsulosin. Symptoms, such as dizziness, suggestive of low blood pressure occurred in 9.2% of the tamsulosin group and 10.5% of the

alfuzosin group.[2] In the placebo-controlled studies, the only adverse event which occurred significantly more with tamsulosin was abnormal ejaculation. This affected almost 7% of the men taking tamsulosin.

Overall, tamsulosin is as effective as other drugs in its class, but may have fewer adverse effects. This may be an advantage if tamsulosin does not cost more than its competitors.

REFERENCES

1. Stricker PD. Drug treatment of benign prostatic hypertrophy. Aust Prescr 1995;18:30–2.
2. Buzelin JM, Fonteyne E, Kontturi M, Witjes WPJ, Khan A. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction (symptomatic benign prostatic hyperplasia). Br J Urol 1997;80:597–605.
3. Lee E, Lee C. Clinical comparison of selective and non-selective a_1A-adrenoreceptor antagonists in benign prostatic hyperplasia: studies on tamsulosin in a fixed dose and terazosin in increasing doses. Br J Urol 1997;80:606–11.

NEW FORMULATIONS

Beclomethasone dipropionate

Qvar (3M Pharmaceuticals)

inhaler and autohaler delivering 50 microgram or 100 microgram per inhalation

Approved indication: asthma prophylaxis

Australian Medicines Handbook Section 19.2

This new formulation delivers beclomethasone dipropionate using a propellant which does not contain chlorofluorocarbons. In addition, the beclomethasone is in solution rather than in suspension. As a result, this formulation produces much smaller droplets than the particles produced by conventional inhalers. This results in a bigger dose being deposited in the lungs.

Lower doses of this formulation are needed to produce the same effects as a conventional inhaler. A patient currently inhaling a total daily dose of 400 microgram of beclomethasone will probably need only 200 microgram of the new formulation. As the delivery devices only provide half the dose per inhalation as that delivered by conventional puffers, a patient will take the same number of puffs as they currently do with inhalers delivering 100 microgram per inhalation.

Follitropin beta

Puregon (Organon)

vials containing 50 IU/0.5 mL, 100 IU/0.5 mL, 150 IU/0.5 mL and 200 IU/0.5 mL solution for injection

Haemophilus influenzae type b

Liquid PedvaxHIB (CSL)

7.5 microgram vials

Mycophenolate mofetil

CellCept (Roche)

500 mg powder for infusion

NEW STRENGTHS

Cabergoline

Cabaser (Pharmacia & Upjohn)

1 mg, 2 mg and 4 mg tablets

Interferon beta-1a (rch)

Rebif (Serono)

22 microgram and 44 microgram pre-filled syringes

Epoetin alfa

Eprex (Janssen-Cilag)

vials containing 40 000 IU/mL

Ganciclovir

Cymevene (Roche)

500 mg capsules

NEW COMBINATIONS

Dipyridamole/aspirin

Asantin SR (Boehringer Ingelheim)

sustained-release capsules containing 200 mg dipyridamole and 25 mg aspirin

Haemophilus influenzae type b/hepatitis B

Comvax (CSL)

0.5 mL single dose vials containing 7.5 microgram Haemophilus influenzae type b and 5 microgram hepatitis B surface antigen

NEW PROPRIETARY BRANDS

Amoxycillin trihydrate

DBL Amoxycillin (Faulding)

250 mg and 500 mg capsules

Amoxycillin/clavulanic acid

Ausclav products (Sigma)

tablets, and powder for syrup

Clozapine

SBPA Clozapine (SBPA)

25 mg and 100 mg tablets

Fluoxetine hydrochloride

Lovan Liquid (Alphapharm)

20 mg/5 mL

SBPA Fluoxetine (SBPA)
20 mg capsules

Moclobemide

Arima (Alphapharm)

300 mg tablets

Ranitidine hydrochloride

Ausran (Sigma)

150 mg and 300 mg tablets

The painting on the cover

Australian Prescriber's international readership is growing. To identify the journal as distinctively Australian, the cover features an Australian Aboriginal painting. Jennifer Summerfield, the Aboriginal artist, lives in the centre of Australia, and created the painting in 1998 for National Medicines Week. The central icon is of a gathering of people sitting around a fire, talking. Jennifer's story follows:

I'm Jennifer Summerfield. I am a Pitjantjatjara woman. I live at Umuwa on the Anangu Pitjantjatjara Lands in the north west of South Australia. I work as an Anangu Health Worker for Nganampa Health Council. I am the artist who did the painting for National Medicines Week.

This painting is about using medicine properly, especially for older people. Store your tablets in a cool place or in your bag away from kids and other old people. Take your medication at the right time with the pictures of the sun showing in the morning, at midday and in the evening. Don't throw your medicines on the ground. If you don't take your tablets you may be blind or never walk again. This is what the painting is about.

The older people in the middle of the painting are keeping their medicine safe in a bag. The people in each corner have not taken their medicines and have become blind or crippled. There is the sun to tell them to take their medicine, in the morning, at midday and in the evening. People at the middle top of the painting are taking their medicines. People down the bottom of the painting sometimes take their medicine and sometimes throw it away. Then young kids can find that medicine and take it and become sick. The two black paintings show that when people don't take their medicine properly, they die. Around the outside of the painting are a few bush medicines.

Answers to self-test questions

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

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. 2, 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