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Further reading

ACC/AHA/ASE 2003 Guideline update for the clinical application of echocardiography. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. http://guideline.gov/summary/summary.aspx?doc_id=4020 [cited 2006 Sep 12]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 143)

3. Arrhythmias limit the usefulness of echocardiography in the diagnosis of diastolic heart failure.
4. Echocardiography is useful for detecting small pulmonary emboli.

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 Executive 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.

Butoconazole nitrate 2%

Gynazole-1 (Arrow Pharmaceuticals)

single dose applicator containing 5 g of cream

Approved indication: local treatment of candidal vulvovaginitis

Australian Medicines Handbook section 17.11.1

Candida albicans is a common cause of vulvovaginitis.[1,2] These infections are usually treated with imidazole antifungal drugs. Butoconazole nitrate is the fifth imidazole agent to be registered in Australia, after clotrimazole, ketoconazole, miconazole and econazole. These drugs come in a number of different formulations (including cream, pessaries and oral tablets) and dosing regimens. Although butoconazole nitrate 2% cream is a new product in Australia, it was first introduced in the USA as a prescription drug in 1986 and is currently marketed there as an over-the-counter product.

Depending on the formulation, up to 6% of an intravaginal dose is absorbed, with peak plasma levels being reached 12–24 hours after administration. The drug is excreted mainly as metabolites in the urine and faeces.

The Australian butoconazole cream has been formulated to adhere to the vaginal wall for longer than the standard butoconazole cream.[3] The prolonged retention time means that this formulation can be given as a single-dose application rather than a three-day course.

In a randomised open-label trial of 181 American women with vulvovaginal candidiasis, a single application of butoconazole cream was compared to a single 150 mg oral tablet of fluconazole. Twelve hours after treatment, 44.4% of women given topical butoconazole experienced first relief of symptoms compared with 29% of women given oral fluconazole. The time to complete relief of symptoms was similar in both treatment groups. Yeast cultures to confirm the presence or absence of candida were not performed in this study so the true microbiological cure rates could not be assessed. The most common butoconazole-related adverse events were vulvovaginal pruritis (3 events) and vulvovaginal burning (3 events). In the fluconazole group, headache (6 events), diarrhoea, nausea, skin sensitivity and upset stomach were the most common drug-related adverse events.[4]

In another trial, a single-dose butoconazole cream was compared to a seven-day miconazole cream. Similar levels of drug efficacy in both treatment groups were observed with regard to clinical symptoms and microbiological cultures.[5]

Two unpublished studies compared butoconazole nitrate 2% cream with a clotrimazole pessary (500 mg) in women with confirmed vulvovaginal *Candida albicans* infection. Microbiological and symptomatic signs of candidiasis were resolved 30 days after treatment in 79 of 118 (67%) women treated with butoconazole compared with 71 of 116 (61%) given clotrimazole.

In trials comparing butoconazole and clotrimazole vaginal treatments, irritation of the vulva, vagina or urethra were the most common drug-related adverse event. These were reported by approximately 1% of patients receiving either treatment.

The use of latex or rubber products such as condoms or contraceptive diaphragms is not recommended within 72 hours of butoconazole application. Additional topical antifungal cream may be required for the treatment of external vulval or perianal areas.

In Australia, 10% clotrimazole is the only single-dose cream

already available for the treatment of candidal vulvovaginitis. It is not known whether the single-dose butoconazole formulation will be more effective.

[T] [T] manufacturer provided some data

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Darifenacin hydrobromide

Enablex (Novartis)

7.5 mg and 15 mg prolonged-release tablets

Approved indication: overactive bladder

Australian Medicines Handbook section 13.1.1

The contraction of detrusor smooth muscle involves stimulation of muscarinic receptors by acetylcholine. Anticholinergic drugs have therefore been used to relax the bladder in patients with urge incontinence. These drugs have unwanted systemic effects so there is a need for a drug with an action that is more specific to the bladder. The M_3 muscarinic receptor has been a target for drug development as it is thought to be the subtype responsible for bladder contraction.

Darifenacin is an anticholinergic drug which has a greater affinity for the M_3 receptor than for other subtypes. Its action diminishes the frequency of detrusor contractions and increases bladder capacity.

Once-daily dosing is possible with the prolonged-release formulation. Peak plasma concentrations are reached seven hours after an oral dose, with a steady state reached in six days. Bioavailability depends on the patient's metabolism. Darifenacin is extensively metabolised in the liver and its pharmacokinetics are affected by moderate hepatic impairment. As the metabolism involves cytochrome P450 2D6 and 3A4, there are several potential drug interactions. The risk of adverse events may be increased by CYP2D6 inhibitors such as cimetidine, fluoxetine and paroxetine. Daily doses of darifenacin should not exceed 7.5 mg if the patient is taking an inhibitor of CYP3A4 such as itraconazole. The anticholinergic adverse effects of tricyclic antidepressants and drugs for Parkinson's disease may be increased by darifenacin.

In one trial 561 patients were randomised to take darifenacin 3.75 mg, 7.5 mg, 15 mg or a placebo for 12 weeks. The respective median reductions in weekly incontinence episodes were 8.6, 9.0, 10.4 and 7.6. The reduction in weekly incontinence episodes was 68% with 7.5 mg and 73% with 15 mg. This was significantly greater than the 56% reduction with placebo.[1] Other placebo-controlled studies had similar results so the recommended starting dose is 7.5 mg daily, increasing if necessary after two weeks to 15 mg daily. In a dose titration trial, 59% of patients needed to increase to 15 mg daily.

Compared with placebo, patients taking darifenacin complain more frequently of dry mouth and constipation. These adverse effects appear to increase with the dose. Other adverse effects include altered vision, dyspepsia and abdominal pain. Caution is needed if darifenacin is considered for patients with decreased gastrointestinal motility or at risk of urinary retention.

Darifenacin has been studied in people with overactive bladder. These people have urinary urgency, but not all of them have urge incontinence. The benefits of darifenacin may be less certain in these patients. Although it achieved statistical advantages over placebo, the absolute changes may be small. For example, a patient given darifenacin 15 mg will have one less micturition per day than a patient given a placebo. They may also have one less episode of urgency per day. Darifenacin does not decrease the number of times a patient is awoken by their overactive bladder significantly more than placebo.[1]

Comparative studies are limited, but tolterodine has been included in a placebo-controlled trial of darifenacin. Unfortunately, a comparative analysis of the 15 mg dose of darifenacin was not done for all the outcomes. Darifenacin only achieved a statistical advantage, over tolterodine, for some outcomes if it was given at a daily dose of 30 mg. It appears that darifenacin's selective action does not give it a large clinical advantage.

[X] manufacturer did not respond to request for data

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Entecavir

Baraclude (Bristol-Myers Squibb)

0.5 mg and 1 mg tablets

Approved indication: chronic hepatitis B

Australian Medicines Handbook section 5.3.1

Hepatitis B can become chronic particularly if the infection occurs in childhood. While some carriers of the virus have

no liver damage, others develop chronic inflammation and cirrhosis. Antiviral drugs, such as lamivudine, adefovir or interferon alfa, can be considered for patients with active inflammation of the liver.

Entecavir is an antiviral drug with activity against hepatitis B viral polymerase. As entecavir is an analogue of the nucleoside guanosine, it competes with the enzyme's usual substrate. This reduces the synthesis of viral DNA. Entecavir is therefore indicated when there is evidence of viral replication. At present it is only approved for adults who have active liver inflammation.

Patients take entecavir once daily. A higher dose is needed if there is resistance to lamivudine because these viral strains are also less susceptible to entecavir. As food reduces absorption, entecavir is taken on an empty stomach. Most of the dose is excreted unchanged in the urine so it should be reduced in people with renal impairment.

Entecavir was compared with placebo in a dose-ranging study of 42 patients with chronic hepatitis B. They took the drug for 28 days and were followed up for a further 24 weeks. All doses of entecavir significantly reduced the concentration of viral DNA.[1]

Another phase II study randomised 185 patients to take entecavir or lamivudine for 24 weeks. Entecavir had a greater effect on viral load with 26% of the patients taking 0.5 mg having undetectable concentrations of viral DNA compared with 18% of the patients taking 100 mg lamivudine. Concentrations of alanine transaminase (ALT) returned to normal in 69% of those taking entecavir and 59% of those taking lamivudine.[2]

The phase III studies of entecavir looked at the effect of treatment on liver histology as well as on laboratory tests. Approximately 1600 patients participated with the majority having two liver biopsies. In patients who were positive for hepatitis B e antigen, inflammation improved in 72% with entecavir and in 62% with lamivudine.[3] The corresponding figures were 70% and 61% in patients without the e antigen.[4] These differences show a statistical advantage for entecavir. Both treatments resulted in an improvement of liver fibrosis in 35–39% of patients. ALT concentrations were more likely to become normal with entecavir. In a study of 286 patients with lamivudine-refractory infections, switching to entecavir was associated with improved liver histology. After a year of treatment improvements were seen in 55% of the patients given entecavir compared with 28% of those who continued lamivudine.[5]

During the clinical trials the most common adverse events were headache and fatigue. After treatment stopped in the dose-ranging study the viral load soon increased.[1] There is a risk that the hepatitis will flare up when the patient stops taking treatment. Safety and efficacy have not been confirmed for more than 48 weeks of treatment and the optimum duration of treatment is unknown. Hepatocellular carcinoma and other cancers have appeared during studies of animals, but the risk in humans is unknown. Like other nucleoside analogues there may be a risk of lactic acidosis.

Resistance to entecavir has been reported. Although there is some cross-resistance with lamivudine, there does not appear to be cross-resistance with adefovir. Currently, there appear to be no published clinical trials comparing lamivudine and adefovir.

Entecavir has efficacy against hepatitis B, but assessing its safety and effectiveness on long-term outcomes will require more study. There is greater certainty that immunisation will prevent more people becoming chronically infected.

T T manufacturer provided some data

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Human papillomavirus vaccine

Gardasil (Merck Sharp & Dohme)

vials containing 0.5 mL liquid

Approved indication: prevention of human papillomavirus infection and associated genital disease

Australian Medicines Handbook section 20.1

Human papillomavirus is one of the most common sexually transmitted viral infections. While most of these infections are transient, some can persist and lead to the development of cervical cancer. In Australia there are approximately 800 new cases of cervical cancer each year. Cervical screening, which is regularly undertaken by 63% of Australian women, has reduced the mortality associated with cervical cancer due to the early identification and management of precancerous lesions.[1]

Over 40 different types of human papillomavirus have been identified that infect the genital mucosa. Human papillomavirus types 6 and 11 cause 90% of genital warts. In Australia, the most prevalent types found in invasive cervical cancer are types 16 and 18.[1]

A quadrivalent human papillomavirus vaccine has been approved in Australia for intramuscular injection in males and females aged 9–15 and in females aged 16–26. This is not a live virus, but contains virus-like particles derived from the major

capsid (L1) protein of human papillomavirus types 6, 11, 16 and 18. The vaccine is indicated for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by these viral types.

The safety and efficacy of the quadrivalent vaccine has been compared to placebo in one phase II trial and two phase III trials. These trials involved a total of approximately 18 000 women aged 16–26 with a history of normal cervical smears. Participants received three doses of either vaccine or placebo at 0, 2 and 6 months. Human papillomavirus infection and associated genital disease were monitored for up to 36 months after the initial vaccination.

The phase II trial enrolled 552 women from the USA, Europe and Brazil. The efficacy analysis was done on the per-protocol population, which was defined as women who did not have antibodies to vaccine-type human papillomavirus at the beginning of the trial and remained free of infection from vaccine-type human papillomavirus through to completion of the vaccination regimen. At 36 months after the initial dose, 94%, 96%, 100% and 76% of women given the vaccine were seropositive for human papillomavirus vaccine types 6, 11, 16 and 18 respectively. There were 4 cases of persistent vaccine-type human papillomavirus infection or associated genital disease in 235 vaccinated women compared with 36 cases in 233 women in the placebo group, representing a vaccine efficacy of 89%.[2]

The efficacy of the vaccine appears to be similar in the phase III trials, but as yet the results have not been published in full. In the per-protocol populations, the number of cases of cervical intraepithelial neoplasia or cervical adenocarcinoma *in situ* was reduced from 80 in 7628 women given the placebo to 4 in 7623 women given the vaccine. Likewise, there was only one case of genital warts, vulval intraepithelial neoplasia or vaginal intraepithelial neoplasia in the vaccine groups compared with 110 cases in the placebo groups. The vaccine did not prevent disease caused by other viral types that were not present in the vaccine.

Although this vaccine is indicated for boys aged 9–15, published evidence of its efficacy in males is lacking.

There were no vaccine-related serious adverse effects reported in the trials. However, there were more injection-site reactions (pain, redness and swelling) and fever in women given the vaccine compared to those given the placebo.

It is likely that this vaccine will reduce human papillomavirus infections, which will in turn reduce cervical cancer and other human papillomavirus-related genital conditions. Men and women are at risk from human papillomavirus infection for as long as they are sexually active. Longer follow-up studies will therefore be needed to assess the duration of efficacy for this quadrivalent vaccine, and to determine whether booster doses will be needed.

T T manufacturer provided some data

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Solifenacin succinate

Vesicare (Arrow Pharmaceuticals)

5 mg and 10 mg tablets

Approved indication: overactive bladder

Australian Medicines Handbook section 13.1.1

Patients with overactive bladders may have urgency and frequency. Some may develop urge incontinence. If these symptoms are troublesome and do not respond to non-drug treatment an anticholinergic drug may help (see 'Anticholinergic drugs for overactive bladder', Aust Prescr 2006;29:22–4).

Solifenacin is an anticholinergic drug with a high affinity for the M_3 muscarinic receptors in smooth muscle. It is well absorbed and can be taken once a day. Solifenacin is metabolised in the liver by cytochrome P450 3A4 so it may interact with other drugs which inhibit or induce this enzyme. Most of the metabolites are excreted in the urine. The half-life is 45–68 hours, but this is prolonged by renal or hepatic impairment.

In a randomised double-blind trial, once-daily solifenacin was compared with placebo in 907 patients with overactive bladder. After 12 weeks the mean number of daily micturitions had reduced, from a baseline rate of about 12 in 24 hours, by 2.4 with solifenacin 5 mg and by 2.8 with solifenacin 10 mg. This was a statistical advantage over the placebo group who had 1.6 fewer micturitions per day. The reduction in incontinence showed a similar pattern with 1.3 fewer episodes in the placebo group and 1.6 fewer episodes with solifenacin 5 mg or 10 mg.[1]

A pooled analysis of trials in patients over 65 years old showed some statistical advantages over placebo, but the absolute differences were small. Solifenacin 5 mg reduced incontinence by a median of 1 episode per day compared with 0.7 episodes with placebo and 1.5 episodes with solifenacin 10 mg. Patients taking placebo had one less micturition per day while those taking solifenacin 5 mg had two less micturitions. The median change with solifenacin 10 mg was 2.3 fewer micturitions per day.[2]

Despite its affinity for the M_3 receptor, solifenacin is not free of anticholinergic adverse effects. In the placebo-controlled trial, 23% of the patients taking solifenacin 10 mg developed a dry mouth compared with 7.7% of the solifenacin 5 mg group and

2.3% of the placebo group. Constipation and blurred vision were also more likely with solifenacin.[1] In the pooled analysis, dry mouth affected 29.7% of the elderly people taking solifenacin 10 mg, 13.5% of those taking solifenacin 5 mg and 4.5% of the placebo group. Constipation affected 17.2%, 8.9% and 4.3% respectively.[2]

Solifenacin can prolong the QT_c interval on the ECG. An ECG should be considered before starting treatment if there is a risk of QT_c prolongation.

Tolterodine is another recently approved drug for overactive bladder. It has been compared with solifenacin in 1200 patients over 12 weeks. The results were not analysed by the dose of solifenacin (5 mg or 10 mg), but overall there was no difference in the frequency of micturition. Solifenacin reduced daily micturitions by 2.45 compared to a reduction of 2.24 with tolterodine. Incontinence episodes per 24 hours reduced by a mean of 1.6 with solifenacin and 1.1 with tolterodine. Adverse events were slightly more frequent with solifenacin.[3]

Solifenacin will reduce urgency and this may improve the patient's quality of life. However, the efficacy is modest and the patient may have to endure adverse effects to obtain the benefit.

T T manufacturer provided some data

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Tigecycline

Tygacil (Wyeth)

vials containing 50 mg lyophilised powder for reconstitution

Approved indication: complicated skin and soft tissue infections and complicated intra-abdominal infections

Australian Medicines Handbook section 5.1.11

Tigecycline is structurally related to the tetracycline class of antibiotics and is a derivative of minocycline. It has broad spectrum *in vitro* activity against Gram-positive, Gram-negative and anaerobic organisms and also tetracycline-resistant bacteria. Coverage includes multiresistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Tigecycline has poor activity against *Pseudomonas* species.

Tigecycline is not absorbed from the gut so it must be administered by slow intravenous infusion. It is extensively distributed in the body and has a serum half-life of 40 hours. The tissue half-life is not known. Tigecycline is not extensively metabolised and so most of the drug is excreted unchanged in the urine and faeces.

The safety and efficacy of tigecycline were evaluated for the treatment of skin and skin-structure infections from pooled data of two trials totalling 1116 hospitalised adults. Soft tissue infections, abscesses and infected ulcers were the most common type of infections in these patients. In both trials, tigecycline (100 mg intravenously followed by 50 mg every 12 hours) was compared to a combination of vancomycin and aztreonam for 5–14 days of therapy. Microbiological data were available for 540 patients and clinical data were available for 833 patients. Cure rates for tigecycline and vancomycin/aztreonam were similar in both sets of data, with approximately 86% of tigecycline recipients responding to treatment compared to approximately 88% of vancomycin/aztreonam recipients. Both treatments were equally effective in patients with underlying comorbidities such as diabetes mellitus and peripheral vascular disease.[1]

The safety and efficacy of tigecycline were also evaluated for the treatment of complicated intra-abdominal infections, such as complicated appendicitis, from pooled data of two studies totalling 1642 hospitalised adults. Patients received tigecycline or a combination of imipenem and cilastatin for 5–14 days. Of the 685 patients with clinically evaluable data, a total of 594 responded to tigecycline, compared to the 607 of the 697 patients with clinically evaluable data in the comparator group. Similar levels of drug efficacy were reflected in the 1025 patients who were microbiologically evaluable.[2]

Although tigecycline has *in vitro* activity to multidrug resistant bacteria, there were limited data in these trials to support its use in patients with these infections. However, tigecycline was effective at eradicating MRSA in 25 out of 32 patients with complicated skin infections.[1]

There were two reports of bacterial resistance to tigecycline in the intra-abdominal infection pooled analysis. Both patients infected with these resistant isolates failed to respond to tigecycline treatment.[2]

In all four trials, there were slightly more drug-related adverse events reported by tigecycline recipients (986 of 1383 patients) than by patients receiving the comparator treatments (927 of 1375 patients). The most common events in the tigecycline-treated patients were nausea and vomiting. Nausea was experienced by 394 of the patients given tigecycline and 202 patients in the comparator group. Vomiting occurred in 268 patients taking tigecycline and 138 patients taking the comparator treatments. Overall there were 30 deaths in the tigecycline groups and 18 deaths in the control groups. One

death of a tigecycline recipient, after septic shock, was possibly related to the study drug.

Tigecycline is not recommended for pregnant women or children. Tetracycline class effects, such as photosensitivity, may also occur in patients taking tigecycline.

Tigecycline provides an alternative antibiotic therapy for the treatment of serious infections in hospitalised adults. However, its effectiveness in treating multidrug resistant infections remains to be fully evaluated. Advice from an infectious disease specialist or bacteriologist should be sought before using tigecycline.

T T T manufacturer provided all requested information

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The T-score (T) is explained in 'Two-way transparency', Aust Prescr 2005;28:103.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int)

Correction

Epoetin beta (New drugs, Aust Prescr 2006;29:112–5)
The brand name for epoetin beta is NeoRecormon.

Answers to self-test questions

1. True
2. False
3. True
4. False

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Editorial office

For general correspondence such as Letters to the Editor, contact the Editor.

Telephone: (02) 6202 3100
Fax: (02) 6282 6855
Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA
Email: info@australianprescriber.com
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