

Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 55)

7. A reduction of greater than 50% in relative risk confirms a clinically significant intervention.
8. Treating risk factors reduces adverse outcomes but cannot prevent them completely.

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.

Dasatinib

Sprycel (Bristol-Myers Squibb)

20 mg, 50 mg and 70 mg tablets

Approved indication: chronic myeloid leukaemia and acute lymphoblastic leukaemia

Australian Medicines Handbook section 14.3.5

Most patients with chronic myeloid leukaemia have a chromosomal translocation that produces the Philadelphia chromosome (Ph). This results in an abnormal tyrosine kinase which causes cells to become malignant. This translocation can also occur in patients with acute lymphoblastic leukaemia.

Imatinib (see New drugs, *Aust Prescr* 2001;24:129-31) is an inhibitor of this abnormal tyrosine kinase and is effective in many patients with newly diagnosed chronic myeloid leukaemia. However, some patients are resistant to imatinib when they start therapy or develop resistance during therapy due to mutations in the abnormal tyrosine kinase gene. These mutations interfere with imatinib binding.

Dasatinib is a new tyrosine kinase inhibitor that binds to a broader range of kinases compared to imatinib. *In vitro*, dasatinib has been shown to have inhibitory activity against imatinib-resistant leukaemia cell lines.

After oral administration of dasatinib, maximum plasma concentrations are observed within 0.5-3 hours and it has an overall mean terminal half-life of 5-6 hours. Dasatinib is extensively metabolised, mainly by cytochrome P450 3A4, and is predominantly eliminated in the faeces as metabolites.

Other drugs that inhibit cytochrome P450 3A4, such as erythromycin and other macrolides, may increase exposure to dasatinib and should be avoided. Likewise, inducers of cytochrome P450 3A4, such as dexamethasone, rifampicin, carbamazepine and St John's wort may reduce the

concentrations of dasatinib and are not recommended.

Dasatinib increases the risk of toxicity from other cytochrome P450 3A4 substrates that have a narrow therapeutic index, such as quinidine and ergot alkaloids. H₂ blockers and proton pump inhibitors are likely to reduce the oral bioavailability of dasatinib and are not recommended. If antacids are used, they should be given two hours before or after taking dasatinib.

The efficacy of dasatinib was first assessed in a phase I dose-escalation study in 84 patients with chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia who could not tolerate or were resistant to imatinib. Patients received 15-240 mg of dasatinib orally per day. Following treatment, 68 (81%) patients had a major haematological response (assessed by counting white blood cells, platelets, blasts and myelocytes and metamyelocytes in peripheral blood), and 37 (44%) patients had a major cytogenetic response (based on the percentage of Ph-positive cells in metaphase in bone marrow). Responses were maintained in 95% of patients with chronic-phase disease (median follow-up of 12 months) and 82% of patients with accelerated disease (median follow-up of 5 months). Most patients with lymphoid blast crisis or Ph-positive acute lymphoblastic leukaemia relapsed within six months.¹

An open-label phase II trial studied the efficacy of dasatinib (70 mg taken twice a day) in 186 patients with imatinib-resistant or -intolerant chronic-phase chronic myeloid leukaemia. After eight months, 168 (90%) patients achieved complete haematologic responses and 97 (52%) achieved major cytogenetic responses. Sixteen patients developed progressive disease or died.²

Another study assessed the efficacy of dasatinib (70 mg taken twice a day) from combined data of open-label phase II trials in patients (resistant or intolerant to imatinib) with chronic myeloid leukaemia in blast crisis. Of these patients, 74 had myeloid blast crisis and 42 had lymphoid blast crisis. After 8 months,

dasatinib had induced major haematologic responses in 31–34% of patients. Major cytogenetic responses were observed in 31% of patients with myeloid blast crisis and 50% of patients with lymphoid blast crisis.³

In the phase II trials, response rates to dasatinib were similar in patients with imatinib-resistant tyrosine kinase mutations compared to patients without mutations. However, one particular mutation (T3151) conferred resistance to both dasatinib and imatinib treatment in the phase I and II trials.^{1,2,3} Myelosuppression was a common adverse effect of dasatinib treatment. In the phase I trial of 84 patients, about 60% of them had their treatment interrupted because of myelosuppression and 25% had their dose reduced. Other common adverse events included pleural effusions (18% patients), diarrhoea (23% patients), peripheral oedema (19% patients), nausea (10% patients), dyspnoea or pulmonary oedema (12%), rash (11%), headache (10%) and gastrointestinal haemorrhage (8%).¹ These adverse events were also common in the phase II trials.^{2,3} There have been reports of intracranial haemorrhage, which have been fatal in some patients.

As myelosuppression is common with dasatinib treatment, patients should have regular complete blood counts. Dasatinib should be administered with caution in patients who have or are likely to develop a prolonged QT_c interval.

Dasatinib provides a second-line treatment for patients with imatinib-resistant chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia. However, resistance to dasatinib has been observed in some patients. The effect of this drug on long-term patient survival is unknown.

T T T manufacturer provided clinical evaluation

References

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Dienogest/ethinylestradiol

Valette (Bayer Schering Pharma)

2 mg dienogest/30 microgram ethinylestradiol tablets
(Valette contains 21 active tablets and 7 placebo tablets)

Approved indication: contraception

Australian Medicines Handbook section 17.1.1

Dienogest adds to the choice of progestogens available in combined fixed dose contraceptive pills. The combination with ethinylestradiol has been available in Europe for several years and has been assessed in published postmarketing studies.

In one study there were 11 unplanned pregnancies during 92 146 treatment cycles with the combination. Although irregular bleeding occurred in the first few cycles, 2% of women per cycle reported no withdrawal bleeds. Approximately 4% stopped treatment because of menstrual irregularities. Adverse reactions, including breast pain, weight gain and headache resulted in 3% of the women stopping treatment.¹

Other adverse events include thrombosis, hypertension and alopecia. The contraindications resemble those of other oral combined contraceptive pills.

Open studies confirm that the combination is an effective contraceptive, but it is difficult to judge if it has any advantages over other combined pills. Dienogest has an antiandrogenic action, so it may have a beneficial effect on the skin of some women with acne.

Reference

1. Zimmermann T, Dietrich H, Wisser K-H, Hoffman H. The efficacy and tolerability of Valette: a postmarketing surveillance study. *Eur J Contracept Reprod Health Care* 1999;4:155-64.

Factor VIII inhibitor bypassing fraction

FEIBA-NF (Baxter Healthcare)

vials containing 500 or 1000 units of powder for reconstitution

Approved indication: haemophilia A or B in patients with inhibitors

Australian Medicines Handbook section 7.4

Patients with haemophilia A (factor VIII deficiency) or B (factor IX deficiency) are unable to form a functional tenase complex (calcium, factors VIII, IX and X) which converts factor X to factor Xa and allows normal clotting to occur. Management of these patients usually involves giving a recombinant form of the missing factor. However, patients can develop inhibitory antibodies which neutralise the activity of these clotting factors. Currently in Australia the action of these inhibitors is bypassed by giving patients recombinant factor VIIa to activate the extrinsic clotting cascade (see New drugs, *Aust Prescr* 1999;22:95–8).

If factor VIIa therapy fails or is contraindicated, these patients can be treated with factor VIII inhibitor bypassing fraction. This contains prothrombin, factors IX and X (mainly non-activated), and factor VII (mainly activated).

Factor VIII inhibitor bypassing fraction is administered intravenously. The timing interval of subsequent doses depends on the site and severity of the bleed. As there is a risk of thrombosis, single doses of factor VIII inhibitor bypassing fraction should not exceed 100 units per kg of body weight and

the infusion rate should not be greater than 2 units per kg of body weight per minute. The maximum daily dose should be less than 200 units per kg of body weight.

An open-label trial compared intravenous factor VIII inhibitor bypassing fraction and recombinant factor VIIa in 48 patients with haemophilia A. Each patient was started on one treatment after their first bleeding episode, then crossed over to the alternative treatment for the second bleeding episode. Both products were found to be effective in about 80% of patients six hours after treatment.¹ Similar levels of efficacy have been observed in other trials.

With blood-derived products such as factor VIII inhibitor bypassing fraction, there is always a risk that it may contain infectious agents. A French study collected information about 433 bleeding episodes in 60 patients treated with factor VIII inhibitor bypassing fraction between 1978 and 1993. Of patients who were regularly evaluated, 1 of 52 became positive for human immunodeficiency virus (HIV) and 41 patients became positive for hepatitis C virus.² Plasma from which this product is derived now undergoes viral serologic testing for hepatitis B, hepatitis C and HIV-1 and HIV-2 antibodies. In an effort to remove viruses, the product also undergoes vapour heat treatment and nanofiltration. However, despite the plasma screening and viral removal procedures, there is still a theoretical risk that viruses such as parvovirus B19 and hepatitis A could be transmitted via this product.

In the French study, 17 of 54 evaluable patients had increased inhibitor levels (by more than 50%) after infusion of factor VIII inhibitor bypassing fraction. However, this did not affect the response of these patients to therapy.²

Thrombosis is a recognised complication of factor VIII inhibitor bypassing fraction. In a pharmacovigilance study from 1999 to 2002, the incidence of thrombotic adverse events in patients treated with factor VIII inhibitor bypassing fraction was found to be 8.24 per 100 000 infusions. The most common event was myocardial infarction which occurred five times. Cerebrovascular thrombosis, pulmonary embolism and disseminated intravascular coagulation were also reported.³

Doctors should be aware that tests used to determine clotting time such as activated partial thromboplastin time (APTT) do not correlate with clinical improvement in patients being treated with factor VIII inhibitor bypassing fraction. Therefore clinical outcomes rather than results of these tests should be used to monitor the efficacy of this drug.

Factor VIII inhibitor bypassing fraction provides a second-line therapy for patients who fail to respond to factor VIIa therapy or for whom factor VIIa is contraindicated. However, prescribers should be aware that this product is derived from human plasma and can potentially transmit infectious agents.

T T T manufacturer provided clinical evaluation

References

1. Astermark J, Donfield SM, DiMichele DM, Gringeri A, Gilbert SA, Waters J, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood* 2007;109:546-51.
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3. Aledort LM. Comparative thrombotic event incidence after infusion of recombinant factor VIIa versus factor VIII inhibitor bypass activity. *J Thromb Haemost* 2004;2:1700-8.

Human protein C

Ceprotrin (Baxter)

vials containing 500 IU or 1000 IU as powder for reconstitution

Approved indication: congenital protein C deficiency

Australian Medicines Handbook section 7.4

Protein C is a circulating glycoprotein. When it is activated, protein C has an anticoagulant effect on the clotting system. Patients who have a deficiency of protein C are therefore prone to thrombosis. These patients may need to take warfarin for life.

Starting warfarin in a patient with a severe congenital deficiency of protein C can result in skin necrosis. This is thought to be caused by an imbalance of coagulant and anticoagulant activity which results in capillary thrombosis.

Another presentation of severe protein C deficiency is purpura fulminans. This occurs in babies who are homozygous for the deficient gene. Capillary thrombosis within a few hours of birth results in ecchymoses and skin necrosis. The child may die or require an amputation if gangrene sets in.

It is hoped that concentrates of protein C will help to manage purpura fulminans and coumarin-induced skin necrosis. This product is manufactured from pooled human plasma. One international unit contains the same protein C activity as 1 mL of plasma. An initial dose of 60–80 IU/kg is recommended to restore protein C activity. The half-life is variable and may be shortened in patients with purpura fulminans or skin necrosis so several doses may be needed to maintain the activity of protein C. In acute cases the protein C activity should be checked every six hours.

Although concentrates have been used to treat patients with protein C deficiency due to severe sepsis, a recombinant product (drotrecogin alfa) is already available. As the severe congenital cases of protein C deficiency are rare, clinical trial data are limited. Intravenous injection of the concentrate will help some patients, but it may not prevent death.

As the product is a protein patients can develop hypersensitivity reactions. Its anticoagulant action can also cause bleeding.

T manufacturer provided only the product information

Note: †

Ivabradine

Coralan (Servier)

5 mg and 7.5 mg tablets

Approved indication: angina

Australian Medicines Handbook section 6.2

Atherosclerotic coronary disease can result in the myocardium not receiving all the oxygenated blood it needs. This inadequate perfusion can present as angina. One approach to managing angina is to reduce myocardial oxygen demand by slowing the heart rate. This is one of the actions of beta blockers.

Ivabradine slows the heart rate by its action on the pacemaker activity of the sinoatrial node. It inhibits a current known as the I_f current (F for funny as the current has unusual properties). The I_f current contributes to diastolic depolarisation, so blocking it reduces heart rate and therefore increases diastolic filling time and myocardial perfusion.

Although ivabradine is well absorbed its bioavailability is reduced to 40% by first-pass metabolism. Food delays absorption but increases bioavailability so the twice-daily doses should be taken with food. The metabolism of ivabradine involves cytochrome P450 3A4, so the concurrent use of potent inhibitors of this enzyme, such as macrolide antibiotics and azole antifungals, is contraindicated. Dose adjustment may be needed with less potent inhibitors, or inducers of CYP3A4. The metabolites of ivabradine are excreted in the urine and faeces.

A phase II study randomised 360 patients with chronic stable angina to take 2.5 mg, 5 mg or 10 mg ivabradine or a placebo twice daily for two weeks. This was followed by an open-label extension during which all patients took 10 mg ivabradine twice daily for two or three months and then a randomised withdrawal of treatment for one week. The heart rate reduced in proportion to the dose of ivabradine. After the first two weeks of treatment patients taking ivabradine could exercise for longer before the onset of ECG changes or angina. Exercise tolerance diminished in patients who were randomised to take a placebo during the withdrawal phase.¹

The efficacy of ivabradine has been compared with atenolol in a double-blind trial. After taking the recommended starting dose of 5 mg twice daily, 315 patients had their dose of ivabradine increased to 7.5 mg twice daily and 317 increased to 10 mg twice daily for 12 weeks. The beta blocker group increased their dose from 50 mg to 100 mg atenolol daily. All groups experienced an increase in the time they could exercise for during exercise tolerance tests. The mean number of angina attacks per week decreased by 2.2 with ivabradine 7.5 mg, 2.3 with ivabradine 10 mg and 2.7 with atenolol 100 mg. Overall ivabradine was not inferior to atenolol.²

Ivabradine has also been compared with the calcium channel blocker amlodipine in a trial lasting three months. Again all patients had an increase in total exercise duration at the end of the study. Another study added ivabradine or a placebo to

treatment with amlodipine. After three months, exercise tests, at the peak of ivabradine activity, showed that the patients taking the drug could exercise for longer than those who added a placebo.

In the placebo-controlled trial the main difference in adverse effects was visual disturbances in the patients taking ivabradine.¹ These effects also appeared in the other trials. More than 14% of patients described transient increases in brightness in parts of their visual fields. Most of these 'phosphenes' resolved during treatment. Blurred vision is also common.

Some patients will develop bradycardia so ivabradine is contraindicated in patients with a heart rate less than 60 beats per minute. Heart block can also occur so ivabradine should not be used in patients with atrioventricular block (3rd degree). Other contraindications include sino-atrial block, sick sinus syndrome and heart failure (class III–IV). Ivabradine should not be used to treat arrhythmias or unstable angina. Prescribing it with drugs that prolong the QT_c interval is not recommended as is concurrent treatment with calcium channel blockers, such as verapamil and diltiazem, which can slow the heart rate.

Compared with placebo, ivabradine significantly delays the onset of angina during exercise testing, but the difference is a matter of seconds. For example, after the first two weeks of the placebo-controlled study, patients who had taken ivabradine 5 mg twice daily could exercise for approximately 14 seconds longer than the placebo group before the onset of angina.¹ In the study where it was added to amlodipine, ivabradine had no statistical advantage over placebo if the exercise tolerance test was done at the time of trough drug activity.

It is too early to say if ivabradine will reduce deaths from ischaemic heart disease. The data are limited, but the estimated incidence of death in the trial population is 3.1 per 100 patient years with placebo, 2.4 with ivabradine, 2.1 with amlodipine and 0.5 with atenolol.

As ivabradine appears to have no clear advantage, it seems appropriate to limit its indication to patients with chronic stable angina who are in sinus rhythm and have a contraindication or an intolerance of beta blockers. Unfortunately the main trials of ivabradine were not specifically in people who cannot take beta blockers and the 10 mg twice-daily dose used in some trials exceeds the dose recommended by the product information.

T T manufacturer provided additional useful information

References †

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Ziprasidone hydrochloride

Zeldox (Pfizer)

20 mg, 40 mg, 60 mg and 80 mg capsules

Approved indication: schizophrenia and bipolar I disorder

Australian Medicines Handbook section 18.2

Ziprasidone is one of several atypical antipsychotic drugs now available in Australia.^{1,2} It binds to dopamine and serotonin receptors in the brain. At D₂, 5HT_{2A} and 5HT_{1D} receptors it acts as an antagonist while at 5HT_{1A} receptors it acts as an agonist. The mechanism of action of ziprasidone in schizophrenia and bipolar disorder is unknown.

The recommended dose range for both indications is 80–160 mg a day. It should be taken twice daily with food as this increases its bioavailability. It is eliminated by metabolism with most of the metabolites being excreted in the faeces. The half-life of 6–10 hours is prolonged if the patient has impaired liver function.

Short-term trials (4–6 weeks) of ziprasidone in a variety of doses for schizophrenia have had conflicting results, but in most the drug has been better than placebo. A longer study (52 weeks) of 294 inpatients with stable symptoms of schizophrenia found that those given ziprasidone had a lower rate of relapse and a longer time to relapse than those given a placebo. Its efficacy is probably similar to that of haloperidol.³

Ziprasidone has also been approved for the short-term treatment of acute manic or mixed episodes associated with bipolar I disorder. Two short-term (3 weeks) double-blind phase III studies (of around 200 patients each) compared ziprasidone (80–160 mg a day) to placebo in a 2:1 ratio. In both trials, ziprasidone improved mania-related symptoms.^{4,5}

A trial of 437 patients compared ziprasidone to haloperidol (a typical antipsychotic) or placebo. Both drugs improved the symptoms of mania in patients compared to placebo, although haloperidol seemed to be more effective. This was reflected in the observation that less haloperidol-treated patients discontinued because of 'lack of efficacy' than ziprasidone-treated patients (8.8% vs 20.2%).

In another bipolar disorder trial, ziprasidone was compared to placebo as an additional treatment in 204 patients taking lithium. There seemed to be no obvious extra benefit of taking ziprasidone as well as lithium in terms of recovery from a manic episode.

The number of dropouts in trials of patients with bipolar disorder was generally high. One of the main reasons for discontinuation was 'lack of efficacy', which accounted for 12.9–20.2% of ziprasidone-treated patients, 8.8% of haloperidol-treated patients, 6.9% of ziprasidone plus lithium-treated patients and 13.6% of patients taking lithium alone. In patients treated with placebo, the dropout rate due to 'lack of efficacy' varied from 28.8% to 36.4%.

In terms of safety, the most common ziprasidone-related adverse events in patients with bipolar disorder included somnolence and movement disorders such as extrapyramidal syndrome. However, extrapyramidal effects were less common in ziprasidone-treated patients compared to haloperidol-treated patients.

Severe drug-related adverse events were observed in the trial of patients taking ziprasidone and lithium. These included seizure, neuroleptic malignant syndrome and a higher rate of extrapyramidal syndrome (22 of 101 patients) compared to patients taking lithium alone (3 of 103 patients).

For schizophrenia, somnolence was reported in 14% of patients. Ziprasidone caused fewer extrapyramidal adverse effects than haloperidol, but more nausea and vomiting.³ In the longer-term trial 7–10% of patients discontinued ziprasidone because of adverse effects. Ziprasidone may cause less weight gain than other atypical antipsychotic drugs.³

Some of the adverse effects of ziprasidone may be explained by its action at receptors. Antagonism of alpha₁ adrenergic receptors can produce postural hypotension while antagonism of histamine H₁ receptors may contribute to somnolence. As somnolence is a common adverse event, patients should be cautioned about driving and operating machinery while taking this drug.

There has been concern that ziprasidone prolongs the QT_c interval on the ECG. This has been observed in patients with schizophrenia and patients with bipolar disorder, although these changes were clinically significant in only a few patients. For this reason, ziprasidone should be avoided in patients with a history of cardiac illness and should not be used with other drugs that increase the QT_c interval. Patients may need to have an ECG at baseline and after they have started treatment.

Atypical antipsychotic drugs may have more effect than older drugs on the negative symptoms of schizophrenia, such as apathy. There is little evidence to suggest that ziprasidone is any better than other new drugs for schizophrenia. It appeared to be as effective as risperidone at improving psychotic symptoms in patients with schizophrenia.⁶ A Cochrane review concluded that 'well planned, conducted and reported long-term randomised trials are needed if ziprasidone is to be accepted into everyday use'.³

Prescribers should be aware that ziprasidone should only be used as a short-term treatment for acute bipolar manic and mixed episodes and not for long-term maintenance. It is intended as a monotherapy and so should not be used in combination with other drugs prescribed for the treatment of bipolar disorder.

T T T manufacturer provided clinical evaluation

References

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The T-score (**T**) is explained in 'Two-way transparency', *Aust Prescr* 2007;30:26-7.

† 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.europa.eu)

Answers to self-test questions

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

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