Book review

Handbook of extemporaneous preparation. Jackson M, Lowey A.

Alison Haywood, Senior lecturer, Griffith University, Gold Coast Campus and Beverley Glass, Professor of Pharmacy, James Cook University, Townsville, Queensland

This book presents a thorough examination of some 50 oral liquids prepared extemporaneously from commercially available products, mostly tablets. Since the commercial availability of oral liquids is limited, and the world’s population is ageing with concomitant swallowing difficulties, this resource offers a real advantage to both the prescriber and the pharmacist in the provision of quality oral liquids which can be safely administered to patients unable to swallow solid dosage forms such as tablets and capsules.

This book provides monographs for oral formulations commonly prepared in UK hospitals. Each monograph provides essential information such as: formula, method of preparation, risk assessment, stability, storage and references. The comprehensive list of references for each drug monograph, relating to stability data and in some cases bioavailability, provides the prescriber with evidence that a quality product is being prepared. The first section of the book also provides interesting insight into the appropriate standards with respect to personnel, equipment, documentation, procurements and monitoring required for extemporaneous dispensing.

Of particular use and unique to this text is the inclusion of a ‘risk assessment’ section in each monograph which addresses the clinical and technical risks associated with the extemporaneous preparation of each oral liquid. The attention of the health professional is drawn to the potential risks, for example formulation failure and calculation errors, associated with extemporaneous dispensing, and a checklist is also provided which will assist in managing this risk.

This book is not only a useful resource, but a valuable addition to the texts available on extemporaneous dispensing for those prescribers wanting quick access to suitable oral liquid alternatives when commercially available products are not available.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Apixaban

Eliquis (Bristol Myers Squibb)
2.5 mg film-coated tablets
Approved indication: prevention of postoperative venous thrombosis
Australian Medicines Handbook section 7.1.4

Patients undergoing knee and hip surgery have a high incidence of venous thromboembolism postoperatively. Thromboprophylaxis reduces this risk and current recommendations include heparins (enoxaparin, dalteparin) and the factor Xa inhibitor, fondaparinux. Oral anticoagulants – dabigatran and rivaroxaban – are also available for this indication.

Apixaban is a reversible, direct inhibitor of clotting factor Xa with a similar action to rivaroxaban (Aust Prescr 2009;32:22-7). By blocking factor Xa, it decreases levels of thrombin. The efficacy of oral apixaban has been compared to subcutaneous enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-1 and -2)\textsuperscript{1,2} and hip replacement (ADVANCE-3).\textsuperscript{2} Apixaban was started 12–24 hours after surgery and continued for 10–14 days in the knee trials and for 35 days in the hip trial. The primary outcome was the same in all of the trials and was a composite of deep vein thrombosis (symptomatic or asymptomatic), non-fatal pulmonary embolism, or death from any cause during treatment. Deep vein thrombosis was assessed using bilateral venography.

In ADVANCE-1, apixaban 2.5 mg (twice daily) failed to meet non-inferiority criteria compared to enoxaparin 30 mg (every 12 hours), despite the primary outcome occurring at similar rates (9% vs 8.8%). The enoxaparin dose used in this trial was different from the standard dose used in Australia – enoxaparin 40 mg once daily.\textsuperscript{4} Although the number of deep vein thromboses was similar between groups, pulmonary emboli were more common with apixaban (16/1599 vs 7/1596).\textsuperscript{1}

In ADVANCE-2, apixaban 2.5 mg (twice daily) was non-inferior to enoxaparin 40 mg once daily. The primary outcome occurred
postoperative prophylaxis is often recommended.4,5 However in contemporary Australian practice, and -3 trials, enoxaparin was started 12 hours before the operation. In the ADVAnCE-1 (0.7% vs 1.4%, p=0.053)1, ADVAnCE-2 (0.6% vs 0.9%, p=0.30)2 and ADVAnCE-3 (0.8% vs 0.7%, p=0.54).3 In the ADVAnCE-2 and -3 trials, enoxaparin was started 12 hours before the operation. However in contemporary Australian practice, postoperative prophylaxis is often recommended.4,5

Apixaban was associated with statistically similar rates of major bleeding events compared with enoxaparin in ADVANCE-1 (0.7% vs 1.4%, p=0.053)1, ADVANCE-2 (0.6% vs 0.9%, p=0.30)2 and ADVANCE-3 (0.8% vs 0.7%, p=0.54).3 In the ADVANCE-2 and -3 trials, enoxaparin was started 12 hours before the operation. However in contemporary Australian practice, postoperative prophylaxis is often recommended.4,5

Other adverse events associated with apixaban included nausea (14.1%), constipation (9.4%), vomiting (6.9%), anaemia (2.6%) and bruising (1.5%). Rates were similar to those reported with enoxaparin.

Caution is urged when giving apixaban to patients with an increased risk of bleeding, such as people with ulcerative gastrointestinal disease, bacterial endocarditis, thrombocytopenia, history of haemorrhagic stroke, uncontrolled high blood pressure and recent brain, spinal or eye surgery. Patients taking apixaban should be monitored for signs of bleeding. An unexplained fall in haemoglobin or blood pressure should be investigated. Apixaban is contraindicated with active bleeding and should be stopped if bleeding occurs. Indwelling epidural or intrathecal catheters should be removed at least five hours before the first dose of apixaban because of the risk of developing a spinal haematoma.

Care should be taken when apixaban is given with other drugs that affect haemostasis, such as non-steroidal anti-inflammatory drugs and aspirin. Concomitant use of platelet aggregation inhibitors and other antithrombotic drugs is not recommended. A trial in acute coronary syndrome, comparing apixaban 5 mg twice daily versus placebo in patients receiving antiplatelet therapy, was stopped early because of an increase in major bleeding events with apixaban.6

Drug interactions with apixaban are likely as it is mainly metabolised by cytochrome P450 3A4, and is a substrate of P-glycoprotein. Strong inhibitors (e.g. azole antifungals) are contraindicated, and inducers (e.g. rifampicin) should be used with caution.

Apixaban is rapidly absorbed after administration and can be taken with or without food. It has a half-life of 12 hours and is eliminated predominantly in the faeces, but also in urine. No dose adjustment is required in mild to moderate renal impairment. However, caution is urged in patients with severe renal impairment (creatinine clearance 15–29 mL/minute) and apixaban is contraindicated in patients with creatinine clearance less than 15 mL/minute, or in those undergoing dialysis.

Apixaban should be used cautiously in hepatic impairment and is contraindicated if it is severe or associated with coagulopathy and clinically relevant bleeding risk.

Apixaban is not recommended for patients having hip fracture surgery. As with similar drugs like dabigatran and rivaroxaban, apixaban is being studied in atrial fibrillation.7 Apixaban is effective for preventing venous thrombosis after hip and knee replacement surgery. Although it failed to meet non-inferiority criteria compared to twice-daily enoxaparin 30 mg, it was non-inferior to once-daily enoxaparin 40 mg. The risk of major bleeding with apixaban was statistically similar to once-daily enoxaparin 40 mg. However, it is questionable whether the pre-operative enoxaparin dosing was a valid comparator for Australian practice. There is no antidote for apixaban.

References


Asenapine

Saphris (Schering-Plough)

5 mg and 10 mg sublingual wafers

Approved indication: schizophrenia, bipolar disorder I

Australian Medicines Handbook section 18.2

Asenapine is an atypical antipsychotic drug. Like other drugs in the class it is an antagonist at dopamine D2 and serotonin 5HT2 receptors. It has little affinity for muscarinic receptors.
As asenapine has low oral bioavailability it has to be taken under the tongue. Sublingual administration increases the bioavailability to 35%. Patients will need to be instructed how to take asenapine. It is important that they do not chew or swallow the wafer. They should not eat or drink for 10 minutes after taking the sublingual wafer. Patients may complain of a dry mouth or oral hypoesthesia (asenapine has some anaesthetic effect).

As the drug is metabolised partly by the cytochrome P450 system (mainly 1A2) there is a potential for drug interactions. Apart from an interaction with fluvoxamine, few clinically significant interactions have been recognised. Most of the dose is metabolised with the metabolites appearing in urine or faeces. Asenapine is not recommended for patients with severe liver impairment.

Several short-term studies have shown that asenapine is more effective than a placebo for patients with schizophrenia. In one study 458 patients were randomised to take asenapine, 5 mg or 10 mg, haloperidol 4 mg or a placebo twice daily for six weeks. The total score on the Positive and Negative Syndrome Scale (PANSS) improved with haloperidol and asenapine 5 mg, but asenapine 10 mg had no advantage over placebo. Another trial randomised 182 patients to take twice-daily doses of asenapine 5 mg, risperidone 3 mg or placebo. After six weeks the mean PANSS score with asenapine was significantly better than with placebo. Although there was improvement with risperidone it did not reach statistical significance.

There are longer-term studies of asenapine in schizophrenia, but some are currently unpublished. In a 52-week study 1225 patients were randomised to take asenapine or olanzapine and 528 completed the trial. The change in PANSS score was significantly greater with olanzapine. However, asenapine and olanzapine were not significantly different from each other in a 26-week study of 481 patients with predominantly negative symptoms.

Asenapine has also been evaluated in bipolar I disorder. It was studied with olanzapine and placebo in a trial of 489 patients experiencing mania or mixed episodes. The mean total daily doses used to control the patients’ symptoms were asenapine 18 mg and olanzapine 16 mg. After three weeks the patients taking the active drugs had significantly better scores on the Young Mania Rating Scale (YMRS), than those taking placebo. This superiority was seen from the second day of treatment.

A similar trial involving 488 patients also found that both asenapine and olanzapine reduced the scores on the YMRS rating scale compared to placebo. Post hoc analysis suggested an advantage for olanzapine. The response and remission rates for asenapine were not significantly greater than with placebo after three weeks.

Patients who completed the three-week trials could continue treatment for a further nine weeks. Those who had taken a placebo were switched to asenapine. After 12 weeks asenapine and olanzapine had produced similar changes in the YMRS. The response and remission rates were 77% and 75% with asenapine and 82% and 79% with olanzapine. Following the extension study, 218 patients continued treatment in a study primarily aimed to collect safety data. After another 40 weeks, efficacy appeared to be maintained with asenapine and olanzapine.

Asenapine has also been studied as an adjunct to treatment with lithium or valproate for patients with a manic or mixed bipolar I episode. A total of 326 patients were randomised to add asenapine or a placebo. After three weeks there was a small difference in the YMRS rating scale, and the response and remission rates with asenapine (34% and 34%) were higher than with placebo (27% and 22%). In the intention to treat population, 25% of the asenapine group and 20% of the placebo group had responded by 12 weeks.

Several thousand patients have taken asenapine in clinical trials, but some of the exposures were short-term. Many patients dropped out of the trials, for example because of an inadequate response, but only 9% of the patients taking asenapine in the schizophrenia trials and 10% in the bipolar trials withdrew because of adverse reactions. This was similar to the discontinuation rates in the placebo groups. Asenapine has adverse effects similar to those of other antipsychotic drugs, for example somnolence, akathisia and extrapyramidal symptoms. In the schizophrenia trials, extrapyramidal symptoms were less frequent with asenapine than with haloperidol. In six weeks patients taking asenapine put on an average of 0.47 kg, but this was less than the average gain of 1.6 kg with risperidone.

As asenapine has some antagonist activity at adrenergic receptors it can cause orthostatic hypotension. This may also explain some of the complaints of dizziness.

Like other antipsychotic drugs, asenapine has the potential to cause neuroleptic malignant syndrome, tardive dyskinesia, hyperprolactinaemia and seizures. The drug should not be used in elderly patients with dementia-related psychosis because of an increased risk of death. Patients will need to be monitored for possible metabolic adverse effects.

Successful treatment of schizophrenia requires the efficacy of an antipsychotic drug to be balanced against its adverse effects. While some adverse effects may be less frequent with asenapine than with other antipsychotic drugs, there are questions about its efficacy. The indication for schizophrenia was not approved in Europe as the balance of risk and benefit was considered to be negative.

Asenapine can be used for the treatment of manic or mixed episodes in patients with bipolar I disorder. Its long-term efficacy in preventing relapse is uncertain. While atypical antipsychotic drugs have a role in bipolar I disorder, it is unclear whether asenapine will be as effective as other drugs.

manufacturer declined to supply data
to confirm a treatment effect, there were more patients in the fingolimod. Although the study lacked the statistical power of the lesions was also significantly less in the patients given seen on MRI was 8.4, 5.7 and 14.8 respectively. The volume were randomised to take fingolimod 1.25 mg, 5 mg or placebo. In a phase II study, 281 patients with relapsing multiple sclerosis 6–9 days so it takes several weeks for a steady state to be reached. Fingolimod is eliminated by metabolism with most of the metabolites being excreted in the urine. The terminal half-life is 60–90 hours after taking the first dose. Macular oedema may occur so patients need to be observed for six hours after taking the first dose. Macular oedema may occur so patients also need ophthalmological assessments.3

Adverse events are more frequent with higher doses of fingolimod. In the large placebo-controlled trial 14.2% of patients taking 1.25 mg discontinued treatment because of adverse events compared with 7.5% of the 0.5 mg group and 7.7% of the placebo group.3 As fingolimod reduces the peripheral lymphocyte count there is a potential increased risk of infection. The overall rate of infection is similar, but in one study lower respiratory tract infections were more common with fingolimod than with placebo.3 As fingolimod is slowly excreted, it may take up to two months for lymphocyte counts to return to normal. The patient’s immunity to organisms such as varicella should be checked before treatment begins. Liver function should also be checked as it is more frequently altered by fingolimod than by placebo.3 The risk of adverse reactions may be greater in patients with hepatic impairment. Blood pressure should be monitored as hypertension can occur during treatment. Fingolimod also reduces the heart rate and can cause atrioventricular block.3 Patients need to be observed for six hours after taking the first dose. Macular oedema may occur so patients also need ophthalmological assessments.3

To help establish its place in therapy, oral fingolimod has been compared to intramuscular interferon beta-1a. A total of 1292 patients with relapsing-remitting multiple sclerosis were randomised to receive daily fingolimod 0.5 mg or 1.25 mg, or weekly injections of interferon 30 microgram. After a year the rate of relapse was significantly lower in the fingolimod groups. Approximately 80–83% of these patients had no

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Fingolimod hydrochloride

Gilenya (Novartis)

0.5 mg capsules

Approved indication: multiple sclerosis

Australian Medicines Handbook section 16.6

Multiple sclerosis is thought to be an autoimmune disease. Some patients have therefore been treated with drugs such as glatiramer, interferon and natalizumab. A problem with these drugs is that they have to be injected. Fingolimod is an oral immunomodulator which has been approved for the treatment of relapsing–remitting multiple sclerosis, and secondary progressive multiple sclerosis with superimposed relapses.

Patients take fingolimod once a day. It is metabolised to its active form, fingolimod phosphate. This reduces the release of lymphocytes from lymphoid tissues which may prevent the cells from attacking the myelin sheaths of the nervous system.

Fingolimod is eliminated by metabolism with most of the metabolites being excreted in the urine. The terminal half-life is 6–9 days so it takes several weeks for a steady state to be reached. In a phase II study, 281 patients with relapsing multiple sclerosis were randomised to take fingolimod 1.25 mg, 5 mg or placebo. After six months the mean cumulative number of lesions seen on MRI was 8.4, 5.7 and 14.8 respectively. The volume of the lesions was also significantly less in the patients given fingolimod. Although the study lacked the statistical power to confirm a treatment effect, there were more patients in the fingolimod group who were free of relapses than there were in the placebo group.1

The patients who completed the study could continue treatment. Those who had taken placebo were randomised to one of the fingolimod groups. After a further six months the number of lesions seen in the patients who had switched from placebo reduced, and remained low in those who continued fingolimod. At 12 months 65–67% of those who switched were free of relapse compared with 79% of those who took fingolimod continuously.1

A total of 189 patients completed a further extension of the study. After 24 months the number of lesions seen on MRI remained low. Between 12 months and 24 months the mean number of new lesions was less than one in all groups. Most (75–77%) of the patients who had been treated continuously remained relapse free.2

A larger placebo-controlled trial studied the effect of fingolimod 0.5 mg or 1.25 mg on disability and the rate of relapse. After 24 months, the annualised relapse rate was 0.16 in the 429 patients taking 1.25 mg, 0.18 in those taking 0.5 mg and 0.4 in those taking placebo. Approximately 70–75% of the fingolimod groups were relapse free for two years compared with 46% of the placebo group. The patients' disabilities did not progress in 82–83% of the fingolimod groups and 76% of the placebo group. These differences and the changes seen on MRI were statistically significant.3
relapse compared with 69% of the interferon group. Although there were fewer new or enlarged lesions seen on MRI with fingolimod, there were no significant differences from interferon in the time to progression of disability. Fingolimod 1.25 mg and interferon had similar rates of adverse events, but fewer of the patients taking interferon discontinued treatments. The rates of infection were similar, but atrioventricular block and macular oedema only occurred in patients taking fingolimod. Skin cancers and hypertension were also more frequently found in the fingolimod groups.4

Fingolimod appears to have greater efficacy than interferon over a year, but multiple sclerosis is a long-term disease. Postmarketing studies will be needed to assess not only effectiveness, but also the emergence of any long-term adverse effects.

manufacturer provided the product information

References

Ipilimumab

Yervoy (Bristol-Myers Squibb)

5 mg per 1 mL concentrate solution for infusion
Approved indication: metastatic melanoma
Australian Medicines Handbook section 14.2.1

Patients with metastatic melanoma have a poor prognosis. Although chemotherapy may be given for progressive disease the response rate is low.

Ipilimumab is a recombinant human monoclonal antibody. It binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) on activated T-cells. This enhances immune responses which could lead to tumour regression.

In a phase II study, 155 patients were given ipilimumab after previous treatment of their unresectable melanomas had failed. They were given an intravenous infusion (10 mg/kg) every three weeks (at weeks 1, 4, 7 and 10) then every 12 weeks. The overall response rate was 5.8%. There were no complete responses but nine patients had a partial response to treatment. With a median follow-up of 10 months, the median overall survival was 10.2 months.1

A double-blind dose-finding trial investigated previously-treated patients with advanced melanoma. The 217 patients were randomised to receive doses of 0.3 mg, 3 mg or 10 mg/kg for induction and maintenance therapy. The overall response rate increased with the dose. While nobody responded to the lowest dose, the response rate was 4.2% with 3 mg/kg and 11.1% with 10 mg/kg. The median overall survival was 8.6 months with 0.3 mg/kg, 8.7 months with 3 mg/kg and 11.4 months with 10 mg/kg.2

The 3 mg/kg dose was used in a phase III double-blind trial. In this study, 137 previously-treated patients were randomised to receive ipilimumab alone while 403 were randomised to also receive a peptide vaccine to induce an immune response. Another group of 136 patients were randomised to receive the vaccine alone. The patients were followed up for up to 55 months. Median survival was only 6.4 months with the vaccine alone. This was significantly less than the 10.1 months with ipilimumab alone and the 10 months in the combined treatment group. After 24 months, 21.6% of the ipilimumab group and 23.5% of the combined treatment group were still alive.3

Another trial involved 502 patients with previously untreated metastatic melanoma. They were randomised to receive dacarbazine or dacarbazine plus ipilimumab (10 mg/kg). The median survival was 9.1 months with dacarbazine and 11.2 months with the combination. After 24 months the survival rate was 17.9% with dacarbazine and 28.5% with the combination.4

Stimulating an immune response can provoke severe adverse reactions in any organ system. Gastrointestinal effects are common with ipilimumab and immune-mediated enterocolitis can be fatal. Immune-mediated hepatitis, dermatitis, neutropathy and endocrinopathy can also be life-threatening. In the phase III study of previously treated patients, 2.1% died because of the effects of their treatment (8 patients in the combination group, 4 in the ipilimumab group, 2 in the vaccine group).3 While immune reactions may respond to systemic corticosteroids, a study found that prophylactic oral budesonide does not affect the rate of severe diarrhea.5

Ipilimumab should be infused over 90 minutes. A steady state is reached by the third dose and the terminal half-life is approximately 15 days. Although some of the trials used a higher dose, the recommended dose is 3 mg/kg.

Ipilimumab improves survival in patients with metastatic melanoma. This improvement comes at the risk of severe adverse reactions which may be delayed in onset and can be persistent. However, there could possibly be a relationship between the immune-mediated adverse effects and the likelihood of the melanoma responding. Further research is needed to assess the role of the drug in other presentations of the disease, particularly as some trials excluded patients with brain metastases. At present ipilimumab is only approved
as monotherapy for patients with unresectable or metastatic melanoma who have failed or are intolerant to previous therapy.

**References**


**Ticagrelor**

**Brilianta (AstraZeneca)**

90 mg tablets

Approved indication: prevention of atherothrombotic events in acute coronary syndrome

Australian Medicines Handbook section 7.2.3

Approximately one third of patients with acute coronary syndrome die, have another myocardial infarction or are rehospitalised within six months. Drugs that inhibit platelet aggregation such as clopidogrel can reduce this risk. Similar to clopidogrel, ticagrelor inhibits blood clotting by directly blocking the P2Y12 adenosine diphosphate receptor on platelets. However unlike clopidogrel, this interaction is direct and reversible. Ticagrelor has a rapid onset of action – almost 90% of platelet aggregation is inhibited within 2–4 hours of a 180 mg loading dose.

The approval of ticagrelor is mainly based on a phase III multicentre (42 countries) comparative trial with clopidogrel (PLATElet inhibition and patient Outcomes – PLATO trial).1 In the study, 18 624 patients who had been hospitalised for an acute coronary syndrome with or without ST-segment elevation were randomised to receive ticagrelor (180 mg loading dose, if treatment-naive, then 90 mg twice daily) or clopidogrel (300 mg loading dose, if treatment-naive, then 75 mg daily). All patients were given concomitant aspirin 75–100 mg. Variations in drug doses were allowed depending on the patient’s medications before the trial and on what coronary procedure they were having. After 12 months, the composite outcome of cardiovascular death, myocardial infarction or stroke occurred less with ticagrelor than with clopidogrel (9.8% vs 11.7%, p<0.001, hazard ratio 0.84). However, the rate of stroke alone did not differ significantly between ticagrelor and clopidogrel (1.5% vs 1.3%). Overall in the study, there were fewer deaths with ticagrelor (399/9333) than with clopidogrel (506/9291).1

Although ticagrelor was significantly more effective than clopidogrel in the trial, its efficacy varied between countries. In Canada (401 patients), the USA (1413 patients) and Australia (83 patients), clopidogrel was more effective than ticagrelor (hazard ratios 1.17, 1.27 and 2.45), whereas in countries such as Poland (2666 patients) and the Czech Republic (1021 patients) ticagrelor was favoured (hazard ratios 0.69 and 0.84).2

As with other antiplatelet drugs, bleeding is a risk and patients with an increased risk were excluded from the trial. Despite this, the rates of major bleeding were high, but similar for ticagrelor and clopidogrel (11.6% vs 11.2%). The number of major bleeds not associated with coronary artery bypass grafting was slightly higher for ticagrelor than clopidogrel (4.5% vs 3.8%, p=0.03). There were also more intracranial bleeds with ticagrelor – 11 bleeds were fatal with ticagrelor versus 1 bleed with clopidogrel.1

Ticagrelor is therefore contraindicated if a patient is bleeding or has a history of intracranial bleeding. It should not be given with drugs that may increase bleeding such as clopidogrel and should be used cautiously with non-steroidal anti-inflammatory drugs. Ticagrelor should be stopped five days before elective surgery.

Other adverse effects of ticagrelor include dyspnoea (13.8% of patients), headache (6.5%) and nosebleeds (6%). In the ticagrelor group, 0.8% of patients withdrew because of dyspnoea and 0.4% because of a nosebleed. Patients with asthma or chronic obstructive pulmonary disorder have an increased risk of dyspnoea. There were significantly more discontinuations due to adverse effects with ticagrelor than with clopidogrel (7.4% vs 6.0%).1

Creatinine elevations were observed in some patients so monitoring of renal function is recommended particularly in patients over 75 years, those with moderate or severe renal impairment or patients taking angiotensin II receptor blockers. Ticagrelor is not recommended for patients on renal dialysis. As increases in uric acid have occurred with ticagrelor, caution is urged in patients with a history of hyperuricaemia. Ticagrelor is discouraged in patients with uric acid nephropathy. Caution is recommended in patients with an increased risk of bradycardia as these people were excluded from the trial. Ventricular pauses of three or more seconds (detected during Holter monitoring) were more common in the ticagrelor group than the clopidogrel group in the first week of the trial.1 These were more common in patients with congestive heart failure but were rarely associated with clinical symptoms.
Oral ticagrelor is rapidly absorbed. After metabolism in the liver, ticagrelor is eliminated mainly by biliary excretion. It is contraindicated in moderate to severe hepatic impairment.

As ticagrelor is a substrate for cytochrome P450 3A4, it has the potential to interact with other drugs metabolised by this enzyme such as ketoconazole and diltiazem. Ticagrelor increases concentrations of simvastatin and atorvastatin, so patients may be at increased risk of adverse effects. Ticagrelor is also a substrate for P-glycoprotein and increases the levels of drugs such as digoxin and cyclosporin.

Overall, ticagrelor plus aspirin prevented more myocardial infarctions and cardiovascular deaths (but not strokes) than clopidogrel plus aspirin, without increasing the bleeding risk. However in some countries participating in the trial, including Australia, clopidogrel was more effective than ticagrelor. The reason for this discrepancy is not clear. The safety of ticagrelor use beyond one year is not currently known.

The T-score ($T$) is explained in ‘New drugs: T-score for transparency’, Aust Prescr 2011;34:26–7.

* 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 Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

References

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Answers to self-test questions
1. True 3. False 5. True

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Telephone: (02) 6202 3100 Fax: (02) 6282 6855
Postal: The Editor
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Suite 3, 2 Phipps Close
DEAKIN ACT 2600
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