of outcomes, including increased rates for birth defects such as neural tube defects and an increased risk of obstetric complications. Theoretical concerns about a relative folate deficiency have prompted some experts to suggest that women planning pregnancy while taking olanzapine should take 5 mg folate rather than the usual 0.5 mg to try and reduce the risk of neurodevelopmental disabilities.[6]

Lactation

Limited information shows that maternal doses of olanzapine up to 20 mg/day produce low levels in milk and undetectable levels in breastfed infants. Generally, short-term adverse effects have not occurred, and sedation has not been reported. Limited long-term follow-up of infants exposed to olanzapine has been reassuring, particularly with monotherapy.

Conclusion

The potentially harmful effects of taking an antipsychotic drug in pregnancy have to be balanced against the harm of untreated psychotic illness. Data are limited, particularly for the atypical antipsychotic drugs, but there are no clear associations with specific congenital abnormalities.

The benefits of breastfeeding are likely to outweigh the potential harm of medication. Women who wish to breastfeed should be managed with a single antipsychotic drug if possible. All antipsychotic drugs are sedating and have relatively long half-lives, so babies should be observed for lethargy, sedation and appropriate developmental milestones particularly if multiple antipsychotic drugs are used.

Note: A national register of antipsychotic medication in pregnancy has been developed. For information phone (03) 9076 6988 or email H.Gilbert@alfred.org.au

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Conflict of interest: none declared

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.

Abatacept

Orencia (Bristol-Myers Squibb)

vials containing 250 mg lyophilised powder

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2

The primary goal of treatment for rheumatoid arthritis is to preserve and restore physical function as well as modify the disease process and slow down the development of joint damage. In Australia, methotrexate is initially used to manage the disease. It is often given with other disease-modifying antirheumatic drugs (DMARDs) for moderate to severe disease (Aust Prescr 2003;26:36–40). If these drugs are not effective or not tolerated, biological agents such as tumour necrosis factor (TNF) inhibitors may be considered.

Abatacept, a genetically-engineered protein, is a biological drug for rheumatoid arthritis which is designed to suppress T cell-mediated inflammatory reactions. It is made up of the extracellular part of the human cytotoxic lymphocyte-associated antigen (CTLA-4) linked to a fragment of human immunoglobulin G. Abatacept works by binding to two signal molecules (CD80 and CD86) on antigen-presenting cells, thereby preventing them from activating T cells.

Abatacept should be given as a 30-minute intravenous infusion. The dose is dependent on the patient's body weight. The infusion should be repeated at two and four weeks and then every four weeks after that. Following multiple 10 mg/kg intravenous infusions of abatacept, the serum concentration reaches a steady state after 60 days. The mean half-life is approximately 13 days in patients with rheumatoid arthritis, and clearance increases with body weight.

When given as a monotherapy to patients with severe active rheumatoid arthritis, more patients responded to abatacept (10 mg/kg) than to placebo. After 85 days, a 20% clinical improvement (based on the criteria of the American College of Rheumatology) was observed in 53% of patients on abatacept compared with 31% on placebo.[1] This study was primarily a dose-finding trial and so there were only 32 patients in the abatacept 10 mg/kg group.

Abatacept appears to be efficacious when given in combination with other DMARDs.[2,3,4,5,6] In a trial of patients with active disease despite methotrexate, 652 patients were randomised to also receive abatacept or placebo. After a year, 73% of patients given abatacept had a 20% clinical improvement compared to only 40% of those given placebo. There was slower radiological progression of joint damage in the abatacept group.[4]

In another trial patients who had not responded to anti-TNF therapy received either abatacept or placebo with another DMARD. More patients in the abatacept group than in the control group had a 20% improvement (50% vs 20% of patients after six months). However, reduced progression of joint damage was not established in these patients.[5]

Infusion-related reactions, such as dizziness and headache, are common with abatacept. In a one-year safety trial of 1441 patients, serious infections were more frequent with abatacept than with placebo (2.9% vs 1.9%). Pneumonia was the most common type of serious infection. In patients receiving other biological drugs as well as abatacept, the rate of serious infections increased to 5.8%. Overall, the incidence of neoplasms was similar with abatacept compared to placebo (3.5%). However, this rate increased to 6.8% in patients who were also taking other biological drugs. In patients with chronic obstructive pulmonary disease, there were more adverse events with abatacept than with placebo.[7]

As abatacept inhibits T cell activation, it may affect a patient's ability to fight infections or malignancies. Caution is needed when treating patients who have a history of recurrent infections and patients should be checked for latent tuberculosis infections and viral hepatitis before starting treatment. Live vaccines should be avoided.

Abatacept in combination with methotrexate is indicated for patients with moderate to severe rheumatoid arthritis who have had an inadequate response or intolerance to other DMARDs. Non-biological DMARDs can be used with abatacept, however, it should not be given with biological drugs such as adalimumab, anakinra, etanercept and infliximab.

As rare but potentially fatal adverse effects can occur with abatacept, longer-term safety studies are needed. It is not known how abatacept compares with other treatments for rheumatoid arthritis as there do not appear to be any comparative studies.

T T T manufacturer provided clinical evaluation

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Exenatide

Byetta (Eli Lilly)

250 microgram/mL in 1.2 mL and 2.4 mL pre-filled pen injectors

Approved indication: type 2 diabetes

Australian Medicines Handbook section 10.1.4

An oral dose of glucose causes more insulin secretion than the same dose given intravenously. This is because glucose in the gut stimulates the release of hormones called incretins which increase insulin secretion. As this action would have a favourable effect in diabetes researchers have tried to develop drugs with a similar action.

One of the incretins is a glucagon-like peptide (GLP-1). The venom of a lizard *(Heloderma suspectum)* contains a peptide with a similar structure and this led to the development of exenatide, an injectable synthetic peptide that acts as a GLP-1 agonist.

Unlike GLP-1, exenatide is not rapidly inactivated. Instead it is cleared by the kidneys at a rate which enables twice-daily dosing. Plasma concentrations peak two hours after a subcutaneous injection so exenatide should be injected before morning and evening meals.

Postprandial and fasting glucose concentrations are reduced by exenatide. It also moderates glucagon secretion, slows gastric emptying and decreases appetite.

A 28-day study investigated different regimens of exenatide in patients being treated for type 2 diabetes. Compared to the 28 patients randomised to receive placebo, the 81 patients injecting exenatide had significantly greater reductions in glycated haemoglobin (HbA1c).[1]

A longer-term study looked at adding exenatide to the treatment of patients whose diabetes was not controlled by the maximum dose of sulfonylureas. Placebo injections were given to 123 patients, while 125 injected exenatide 5 microgram and 129 injected 10 microgram. All injections were given twice daily. At the start of the study the HbA1c averaged 8.6%. In the 30th week of the trial this had fallen by 0.46% with exenatide 5 microgram and by 0.86% with 10 microgram. In the placebo group HbA1c increased.[2]

A similar study compared the two doses of exenatide with placebo in 336 patients taking at least 1.5 g metformin daily. After 30 weeks HbA1c had declined by 0.4% with 5 microgram exenatide, 0.78% with 10 microgram, while it had increased in the placebo group.[3]

Another 30-week study enrolled patients who were already taking metformin and the maximum dose of a sulfonylurea. There were 247 patients who injected a placebo twice daily, 245 who injected exenatide 5 microgram and 241 who injected 10 microgram. At the end of the study, HbA1c had declined by 0.6% with exenatide 5 microgram, 0.8% with 10 microgram and had increased with placebo.[4]

Exenatide has also been studied in patients whose diabetes has not been controlled by a thiazolidinedione with or without metformin. A group of 121 patients injected exenatide and 112 injected a placebo twice daily. After 16 weeks the HbA1c had decreased by 0.89% with exenatide 10 microgram and increased by 0.09% in the placebo group.[5]

After the placebo-controlled trials, 668 patients who had taken exenatide continued using it in open-label extension studies. A total of 314 patients completed a further 52 weeks of treatment. The reduction in HbA1c seen at the end of the placebo-controlled studies was maintained.[6]

In the medium-term placebo-controlled studies, more patients dropped out of the exenatide groups because of adverse effects.[2,3,4,5] In the trial adding exenatide to a thiazolidinedione, 16% of the patients withdrew because of adverse effects compared with only 2% of the patients who added a placebo.[5] A common problem with exenatide is nausea. It affects more than 40% of patients some of whom will vomit. Diarrhoea and dyspepsia are also more frequent than with placebo. There is an increased frequency of hypoglycaemia when exenatide is added to regimens containing a sulfonylurea. The dose of sulfonylurea may need to be reduced.

The exenatide molecule is not identical to human GLP-1. Some patients will develop antibodies against exenatide. Hypersensitivity reactions may occur and it is possible that high antibody titres could reduce the efficacy of exenatide.

During the 30-week trials, patients randomised to take exenatide lost 1–3 kg in weight.[2,3,4] This continued in the open-label extension studies.

Exenatide's role in therapy is unclear. If optimum therapy with oral hypoglycaemic drugs does not control a patient's type 2 diabetes, introducing insulin is the next step. Although exenatide appears to have a similar effect on HbA1c to once-daily insulin glargine[7] or twice-daily insulin aspart[8] in open-label studies, it causes more adverse effects. In the comparison with insulin glargine, 19.4% of the 282 patients injecting exenatide dropped out, compared with 9.7% of the 267 patients injecting insulin.[7] In the comparison with insulin aspart the corresponding figures were 21.3% of the 253 patients injecting exenatide and 10.1% of the 248 patients injecting insulin.[8] Gastrointestinal adverse reactions were common with exenatide and contributed to these withdrawals.

In Europe there is a risk management plan to monitor for safety concerns such as pancreatitis and anti-exenatide antibodies. Long-term outcomes with exenatide are currently unknown.

As it is relatively expensive, the use of exenatide may be limited to obese patients with insulin resistance, but this will require further study. At present, the Australian approval is for adjunctive therapy in patients who are not achieving adequate glycaemic control with metformin, a sulfonylurea, or both.

☒ manufacturer declined to supply data

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Telbivudine

Sebivo (Novartis)

600 mg tablets

Approved indication: chronic hepatitis B

Australian Medicines Handbook section 5.3

Worldwide, hepatitis B is the most common form of viral hepatitis. Some people who are infected develop chronic hepatitis B which may lead to serious liver disease such as cirrhosis and hepatocellular carcinoma. Chronic hepatitis B infection is usually diagnosed by detecting viral antigens and their corresponding antibodies, and viral DNA in serum.[1] Current drugs used to treat chronic hepatitis B include interferons and nucleotide/nucleoside analogues (lamivudine, adefovir and entecavir).

Telbivudine is a synthetic thymidine analogue which inhibits the replication of hepatitis B virus by binding to its DNA polymerase and causing DNA chain termination. It is indicated for chronic hepatitis B (irrespective of whether the patient has the hepatitis B e antigen (HBeAg) or not) in patients who have compensated liver disease, evidence of viral replication and liver inflammation and who have not previously been treated with another nucleoside analogue such as lamivudine.

Following oral administration of telbivudine (600 mg), peak plasma concentrations occur within 1–4 hours. Telbivudine has an overall terminal half-life of around 42 hours and is eliminated mainly unchanged in urine. Patients with impaired renal function may need a dose interval adjustment.

In a phase I placebo-controlled trial, the safety, antiviral activity and pharmacokinetics of telbivudine were assessed in 43 adults with HBeAg-positive chronic hepatitis B. Patients were given one of six different daily doses of telbivudine for four weeks and were followed up for 12 weeks after treatment. The antiviral activity of telbivudine, measured by quantifying serum viral DNA (using the polymerase chain reaction), appeared to be higher at doses of 400 mg or above.[2]

A subsequent phase II trial compared the safety and efficacy of telbivudine (400 or 600 mg/day) and lamivudine (100 mg/day) alone or in combination, in 104 patients with HBeAg-positive chronic hepatitis B. At week 52, there was no detectable viral DNA in 61% of patients on telbivudine monotherapy compared to 32% of patients on lamivudine monotherapy ($p<0.05$). Likewise, a greater proportion of patients taking telbivudine monotherapy had improved liver function (normalisation of alanine transferase) compared to those taking lamivudine monotherapy (86% vs 63%, $p<0.05$). Combination treatments with telbivudine were no more effective than telbivudine alone.[3]

Results of a two-year multicentre phase III trial comparing telbivudine (600 mg/day) and lamivudine (100 mg/day) are currently unpublished. This trial included approximately 1300 patients with HBeAg-positive or -negative chronic hepatitis B. Interim results suggest that viral suppression was greater in patients treated with telbivudine than in those treated with lamivudine. Improvements in liver function were not statistically different between the two treatments.

The efficacy of telbivudine has also been compared to adefovir in an open-label trial of 136 HBeAg-positive patients. After a year of treatment, there seemed to be greater viral suppression with telbivudine than with adefovir.[4]

In the phase II and III trials, genetic evidence of viral resistance was found following viral breakthrough in some patients.[3] In *in vitro* studies, some viral strains that showed resistance to other nucleotide/nucleoside analogues, such as lamivudine or adefovir, also had reduced susceptibility to telbivudine.

The safety profiles of telbivudine and lamivudine were comparable in the phase III trial, with muscle-related symptoms being the most common treatment-emergent clinical adverse events, occurring in 2% of all patients. Creatine kinase elevations occurred in 9% of telbuvidine-treated patients and 3% of lamivudine-treated patients.

Telbivudine comes with a warning about the risk of myopathy. Patients taking telbivudine should therefore be advised to report any unexplained muscle aches, pain, tenderness or weakness. Treatment should be stopped if myopathy is diagnosed.

Health professionals should also be aware that discontinuing telbivudine treatment may lead to severe acute exacerbations of hepatitis B infection. Hepatic function should be monitored for a minimum of several months once therapy has been stopped. When monitoring hepatic function in patients taking telbivudine, check for flares in alanine transferase.

Telbivudine offers a new therapy for patients diagnosed with chronic hepatitis B infection. While telbivudine seems to be effective at reducing viral loads, we do not know if viral resistance will become a problem. It is not known if this drug will reduce the long-term complications associated with chronic hepatitis B.

T manufacturer declined to supply data

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The T-score (T) is explained in 'Two-way transparency', Vol 28 No 4, 2005 (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 Medicines Agency (www.emea.eu).

Answers to self-test questions

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

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