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CONTENTS

Editorial

Competency for new prescribers

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Key words: nurses.

(Aust Prescr 2007;30:58–9)

In 2006 it became legal under Britain's 'non-medical prescribing programme' for nurses 'to prescribe any licensed medicine for any medical condition within their competence, including some controlled drugs'. This was the culmination of a movement, which started 20 years ago, to extend prescribing rights to more members of the healthcare team. Earlier debate had been keen and prolonged with the British Medical Association, in particular, expressing concerns about the quality and safety of prescribing by non-medical health professionals.

The decision to grant nurses extended prescribing rights was, appropriately, accompanied by the requirement for special training and accreditation. New prescribers undergo a minimum of 25 days formal instruction, including pharmacology and principles of prescribing, and 12 days of medically supervised prescribing practice, usually over a three-month period. Some of the first nurses trained became 'supplementary' prescribers working alongside a doctor. This prescribing was later broadened to allow independent prescribing from a limited list of medicines for selected conditions. A formal evaluation of this program was completed in late 2004 by members of an academic nursing unit (rather than an independent research team). They found satisfactory competence, mostly appropriate prescribing and little evidence of unsafe practice.[1] No direct comparison was made with medical prescribers, but in other comparative studies very few differences have been detected, although clinical outcomes were not reported.[2,3,4]

Perhaps what matters most is not the range of health professionals who may prescribe, but the adequacy of their training and continuing professional development. The extension of prescribing should be done with extreme care, adequate training and ongoing evaluation as the concept is very vulnerable to outside criticism. However, this brings into focus the competence of doctors and pharmacists – the current prescribers in our society. Prescribing worldwide is not uniformly of high quality (for example, overprescription of antibiotics) and until recently training in prescribing has been inadequate. One British medical student contrasted the full program provided for new nurse prescribers with the few **hours** of training in her own medical school.[5,6] Retail pharmacists prescribe, dispense and sell so they have a potential conflict of interest. The sparse evidence that exists suggests that pharmacists – at least in the UK – do not make evidence-based recommendations about over-the-counter products.[7]

The essential ingredients of prescribing competency start with an adequate diagnosis as, in its absence, all prescriptions are likely to be irrational. Specifying a therapeutic goal focuses the prescriber's intent. There must be an appreciation of the pharmacology of the drugs prescribed, whether from a limited or an extended list. Selection of a safe and cost-effective drug from those available can often be aided by evidence-based guidelines. Writing a legal prescription, especially with computer support, is comparatively simple to master. Helping patients adhere to their treatment requires skill and knowledge of the factors that aid or hinder compliance and that help them incorporate the new regimen into their daily lives. In particular, patients must be alerted to the possibility of adverse reactions and know what to do if they occur. This was one of the few areas in which the British evaluation found that nurse prescribers were sometimes deficient.[1]

In Australia, nurse practitioners prescribe from limited lists, often in tightly defined specialty areas. There is clearly support

In this issue…

Extending prescribing rights to health professionals other than doctors is controversial. Tony Smith suggests that no changes should be made until there are improvements in our monitoring of prescribing.

Under the current system, there are still opportunities to enhance the quality use of medicines. Paul Abbott tells us antibiotics are often inappropriate treatments for dental pain, and Michael Abramson, Nicholas Glasgow and Christine McDonald say that many patients are not receiving optimum care for chronic obstructive pulmonary disease.

There remain areas of medicine where the optimum treatment is uncertain. Examples include the role of long-term antidepressants in bipolar disorders, discussed by David Pyle and Philip Mitchell, and the use of metformin during pregnancy, discussed by Bill Hague.

for this, especially in remote and rural areas not served adequately by doctors and pharmacists. The Society of Hospital Pharmacists[8] endorsed the need for special training if prescribing by pharmacists was to be extended to prescription drugs, and emphasised the need to separate wherever possible the prescribing and dispensing roles. Other health professionals (for example optometrists and physiotherapists) commonly have very limited prescribing needs and the convenience of patients must be one factor in deciding whether to extend their prescribing rights. With adequate training, supervision (where necessary) and regular evaluation, non-medical health professionals working with limited formularies should be capable of prescribing to an appropriately high standard.

Medical educators have belatedly awakened to the need to train students for the task of prescribing which, conservatively, will be undertaken at least 200 000 times in a general practitioner's career. The new computer-based prescribing curriculum assembled by the National Prescribing Service is being adopted by medical schools and has received positive support from teachers and senior medical students who have worked with it.[9] It may be useful for training other health professionals.

Any extension of prescribing must be evaluated using routinely generated data. In Australia, prescribing data are captured in pharmacists' computers, but only prescriptions for drugs listed on the Pharmaceutical Benefits Scheme are held in Commonwealth databases. This means that at least 20% of all prescriptions, whoever writes them, are not available for any form of evaluation. This has long been a major stumbling-block for the quality use of medicines. Our legislators appear powerless to take the simple steps needed to make complete, de-identified prescribing data available. This enabling step should be a prior requirement to any extension of prescribing rights.

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Conflict of interest: none declared

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

Can we deny patients expensive drugs?

Editor, – We read with interest the editorial 'Can we deny patients expensive drugs?' (Aust Prescr 2006;29:146–8). We agree with many of the author's arguments, but take exception to the suggestion that Pharmaceutical Benefits Advisory Committee (PBAC) processes be bypassed for drugs targeting rare diseases and for which no PBAC submission has been made. The authors suggest that in such cases the Pharmaceutical Benefits Scheme (PBS) 'subsidise the use of these medicines for an indication after conventional therapies have proven ineffective'. We infer that such medicine be subsidised irrespective of costs. This implies society is willing to accept a higher cost per unit of health (for example a year of life) on the basis that the disease is rare. Some things need to be clarified; rare does not mean severe and expensive does not mean better. We acknowledge that efficiency should not be the only criteria in resource allocation decisions and that equity considerations need to be taken into account also. However, the fact that a person has a rare, as opposed to a common, condition is not a good moral basis for accepting higher opportunity costs. Such a system would send all the wrong signals to the research and development community. Locally, pharmaceutical companies would stop applying for PBS funding for drugs that target rare diseases. On a global

level, such a system signals our willingness to pay infinite amounts for uncertain benefits for rare conditions, at a time when we want more research and development in areas where we can make substantial gains in reducing the health burden.

Gisselle Gallego
Kees van Gool
Research Officers, Centre for Health Economics and Research Evaluation
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Ms Karen Kaye, Ms Christine Lu and Professor Richard Day, authors of the editorial, comment:

We agree that PBAC processes should not be bypassed for medicines targeting rare diseases, but in fact this often happens in our current healthcare system. Expensive treatments for severe and rare diseases that are not PBS-subsidised are instead subsidised through supply by public hospitals. The problem with this process is that it is relatively *ad hoc* and decisions about patients' access to such medicines vary depending on the availability of local expertise and funding. It does not promote consistency or transparency in the decision process, does not guarantee equity of access to medicines for patients with the same condition in different parts of the country, and does not facilitate national monitoring of either costs or outcomes. The current system has not resulted in adequate research or PBS submissions to date and it will not in future unless hospitals refuse to supply these medicines. This is unlikely, especially when the disease is severe **and** there is evidence of clinical effectiveness **and** other therapeutic options have been tried and failed. Such a funding approach is ethically sound; a similar ethical approach forms the basis for the PBS 'rule of rescue' and Australia's Orphan drug program. Carefully monitored supply of expensive but effective medicines via a national system would at least facilitate collation of information to inform government, clinicians, industry and the public about use of these medicines (and associated costs and outcomes) and would help ensure equity of access. Provided supply continues to be reviewed on the basis of such information, there is likely to be benefit to both patients in need and society as a whole.

Should beta blockers remain first-line drugs for hypertension?

Editor, – It was disappointing to read that beta blockers have fallen from favour for the treatment of hypertension (Aust Prescr 2007;30:5–7), particularly at a time when their use as prophylaxis for myocardial ischaemia in the perioperative period is being encouraged.

Myocardial ischaemia related to surgical stress often occurs in patients with no history of coronary artery disease. It is also frequently silent, but causes significant cardiac morbidity and mortality.

Beta blockers are effective prophylaxis for high risk patients[1] and are recommended by the American College of Cardiology/American Heart Association guideline for perioperative cardiovascular evaluation for noncardiac surgery.[2]

The benefit and risk of prophylactic beta blockade in low to moderate risk patients is less clear. The POISE trial, which is currently recruiting 10 000 patients, should soon provide some definitive recommendations.[3]

Beta blockers may not be as effective at achieving target blood pressure as other classes of antihypertensive drugs. However, in the perioperative setting beta blockers should remain first-line therapy for blood pressure control, particularly when risk factors for ischaemic heart disease are present.

James French
Consultant anaesthetist
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Dr Maros Elsik and Professor Henry Krum, authors of the article, comment:

In patients with cardiovascular comorbidities or complications as a result of hypertension, treatment needs to be individualised. In many such cases beta blockers are a reasonable option.

Their use in the perioperative setting, although not specifically discussed in our article, has been shown to improve cardiovascular outcomes mainly by reducing myocardial ischaemic events. This represents another situation where beta blockers should not necessarily be stopped or avoided.

Paracetamol

Editor, – Paracetamol is generally recommended as the first drug of choice in pain largely because of its safety profile and cost. But is it as safe as it seems?

The relative risk of upper gastrointestinal complications from paracetamol is 3.6 for doses greater than 2 g per day. This is compared to a relative risk of 2.4 for low to medium doses of non-steroidal anti-inflammatory drugs (NSAIDs) and 4.9 for high doses.[1]

The relative risk of hypertension with 0.5 g (or more) of paracetamol per day is 1.99 (1.39–2.85) in young women and 1.93 (1.30–2.88) in older women. For NSAIDs, the relative risk of hypertension is 1.60 (1.10–2.32) in young women and 1.78 (1.21–2.61) in older women.[2]

Should we be concerned at this data and is paracetamol a medication that should be taken without warnings being issued to the public?

David Vivian
Medical practitioner
Melbourne

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Expert comment:

Placebo-controlled trials show that paracetamol has no significant effect on the gastrointestinal tract.[1] By contrast, a case-control study on paracetamol reported that there was a dose-related increase in gastrointestinal adverse reactions.[2] We and several others concluded that the finding of gastrointestinal toxicity of paracetamol could be a biased result, a recognised hazard of case-control and observational studies especially when relative risks are low.[3,4,5] Furthermore, another case-control study found that upper gastrointestinal bleeding was not associated with paracetamol[6] indicating considerable uncertainty regarding paracetamol and gastrointestinal toxicity. Paracetamol may, however, cause upper gastrointestinal complaints such as dyspepsia[4], although this does not usually lead to cessation of treatment.

Regarding hypertension, controlled trials of paracetamol generally show no significant effect on blood pressure. Recent reviews recommend that paracetamol is suitable for use in patients 'who may be at increased risk for the blood pressure or fluid effects of NSAIDs'.[7] However, other studies report that the intake of paracetamol is associated with an increased incidence of hypertension.[8,9,10] This finding is not widely accepted and a comment published on one of the studies said, 'I await more compelling data prior to warning my patients that acetaminophen [paracetamol] may have adverse effects on blood pressure'.[11] Furthermore, an epidemiological study found no such association between paracetamol and blood pressure.[12] The reason that patients take regular doses of analgesics may be the confounding factor that explains the risk for increased blood pressure. This is a well known hazard associated with observational studies even when adjustments are made for possible confounding differences between exposed and non-exposed cohorts.[7]

For both questions on the adverse effects of paracetamol, the conclusion that more evidence is needed before changing clinical practice is still very reasonable.[11]

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Professor Graham has received funding from GlaxoSmithKline Australia for research on the mechanism of action of paracetamol. Professor Day has been a member of an advisory board for paracetamol (GlaxoSmithKline consumer) and is currently on an advisory board for over-the-counter ibuprofen (Reckitt Benckiser plc). Honoraria are deposited in audited trust funds of St Vincent's Hospital, Sydney.

New drugs – ziprasidone

Editor, – I would like to update the information in your New Drug comment on ziprasidone (Aust Prescr 2007;30:50–5). Much of the data on schizophrenia comes from a Cochrane review in 2000 which states that 'well planned, conducted and reported long-term randomised trials are needed if ziprasidone is to be accepted into everyday clinical use'. However, more recent studies published since 2000 were omitted from your comment.

Of these studies, a head-to-head trial found that ziprasidone (80–160 mg/day) had comparable efficacy to olanzapine (5–15 mg/day) with differences favouring ziprasidone in observed metabolic parameters.[1] These results are further supported by a 6-month double-blind extension of this study.[2]

Another head-to-head study of ziprasidone (80–160 mg/day) and haloperidol (5–15 mg/day) looking at relapse prevention found that both treatments were effective in reducing overall psychopathology, but ziprasidone was effective for negative symptoms and was better tolerated.[3]

An open-label study suggested that when outpatients who partially responded to conventional antipsychotics, risperidone or olanzapine were switched to ziprasidone their symptom-control was improved or maintained and the switch was well tolerated.[4]

A one-year study in patients with stable, chronic schizophrenia demonstrated that the probability of relapse was significantly lower in the ziprasidone-treated patients than those treated with placebo. In those patients who remained on treatment for at least six months, only 9% subsequently relapsed on ziprasidone compared to 42% on placebo (p=0.001).[5]

Regarding QT_c prolongation, your comment suggests that patients being initiated on ziprasidone may need a baseline ECG and one after starting treatment. This would be ideal practice for all patients receiving any antipsychotic medication and does not apply only to ziprasidone as implied. Prescribing information for ziprasidone states that 'experience with ziprasidone has not revealed an excess risk of mortality compared to other antipsychotic drugs or placebo'.[6] In patients treated with haloperidol, thioridazine, ziprasidone, quetiapine, olanzapine and risperidone, mean QT_c intervals did not exceed 500 milliseconds (the accepted level for clinical significance) in any patient taking any of the antipsychotics studied, in the absence or presence of metabolic inhibition.[7]

It is also important to note that there is six years experience with ziprasidone overseas and that the US prescribing information contains the same precautions as for other antipsychotic medications.

Louise Canny
Associate Medical Director, Neuroscience
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Editorial Executive Committee comments:

It is appropriate that subsequent studies have addressed some of the issues identified by the Cochrane review. The studies cited by Dr Canny are not the only recent studies of ziprasidone. Different studies have reported advantages for other atypical antipsychotic drugs over ziprasidone.[8,9,10] One of the problems in assessing the evidence about antipsychotics is that most trials report outcomes which favour the drug produced by the company funding the trial.[11]

Schizophrenia is a chronic condition, but the head-to-head comparison with olanzapine only lasted six weeks. Although the trial was short, 49 of the 133 patients taking olanzapine and 66 of the 136 taking ziprasidone discontinued treatment.[1] Only 126 patients entered the six-month continuation study and by the end of the trial there were only 17 patients left taking ziprasidone and 21 patients taking olanzapine.[2]

Two of the trials discussed by Dr Canny[3,5] appear to have been included in the Cochrane review so their publication does not change our conclusions.

Another study quoted by Dr Canny pools data from three trials. This open-label switching study does not provide strong evidence for the efficacy and tolerability of ziprasidone.[4]

Ziprasidone seems to cause greater mean increases in QT_c intervals compared to olanzapine, haloperidol, quetiapine and risperidone.[1,2,3,7] Unlike other atypical antipsychotic drugs, the Australian prescribing information for ziprasidone includes a contraindication for patients who have a condition that potentially prolongs the QT_c interval.[6] We believe this is important information for prescribers and may help in treating patients with schizophrenia.

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1–7. See above.

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Managing hepatitis C in the community

Editor, – We have recently been made aware of a dental note by Dr M McCullough of the Australian Dental Association in your journal (Aust Prescr 2006;29:52).

In the comment, Dr McCullough stated that, 'Dentists need to be aware that hepatitis C may be present in the saliva of infected patients. Our infection control practices therefore need to be exemplary to avoid spread of this, and other blood-borne viruses.'

We are perplexed by this comment on two levels. To the best of our knowledge, hepatitis C is a blood-borne virus and is not spread by saliva. We do not believe there has ever been a recorded case of such a transmission route. Secondly, to minimise the risks of transmission of a virus like hepatitis C between patient and health worker, adherence to standard infection control procedures is all that is required. We would be interested to know what 'exemplary' practices mean in this context, and how they differ from standard procedures.

Piergiorgio Moro
Community Development and Education Officer
Hepatitis C Council of Victoria
Melbourne

Dr M McCullough, author of the dental note, comments:

Firstly, I agree that hepatitis C is a blood-borne virus and there has not been a recorded case of spread via saliva. However, in my statement I did not say that it was spread by saliva, but that hepatitis C may be present in the saliva of infected patients. This was based on a recent literature search, which identified several articles on hepatitis C in saliva, and a review article.[1]

Secondly, the use of the term 'exemplary' was not in fact given a great deal of thought at the time. According to the Miriam-Webster dictionary, exemplary means 'deserving imitation because of excellence'. Standard infection control procedures used by Australian dentists are of course adequate to minimise the risks of transmission of a virus like hepatitis C. Furthermore, these standard procedures are at the level of international best practice and should be seen as excellent and deserving of imitation! The intention in the wording was not that we should undertake different procedures, but rather that we, as dentists, should be vigilant in adhering to these standard infection control procedures.

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Managing chronic obstructive pulmonary disease

Michael Abramson, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne; Nicholas Glasgow, Australian Primary Health Care Research Institute, Canberra; and Christine McDonald, Department of Respiratory and Sleep Medicine, Austin Health, Melbourne

Summary

Chronic obstructive pulmonary disease is a common, burdensome and underdiagnosed condition in Australia. Spirometry is the basis of diagnosis and assessing severity in individual patients. Smoking cessation is the keystone for slowing the rate of decline in lung function. Pulmonary rehabilitation reduces breathlessness, anxiety and depression, and improves exercise capacity and quality of life. Multidisciplinary care plans and individual self-management plans may help to prevent or manage crises. Inhaled bronchodilators provide symptom relief and may increase exercise capacity. Systemic steroids reduce the severity and shorten recovery from acute exacerbations. Patients with chronic obstructive pulmonary disease should receive influenza and pneumococcal vaccination.

Key words: bronchodilators, corticosteroids, pulmonary rehabilitation.

(Aust Prescr 2007;30:64–7)

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of disease burden in Australia. The Australian Lung Foundation has conservatively estimated the annual direct costs to exceed $900 million. However, COPD was only the tenth most commonly managed chronic condition in general practice in 2003–04. There is substantial underdiagnosis and many patients are currently not receiving optimal medical care.

The Australian guidelines for COPD (COPD-X), first published in 2003[1], were based upon the Global initiative for Obstructive Lung Disease (GOLD).[2] They are now updated quarterly[3] using the latest evidence from systematic reviews, particularly those published in the Cochrane Library.

C Confirm diagnosis and assess severity

Spirometry remains the basis for diagnosing and assessing the severity of COPD in individual patients[1], however this test is underused in Australia. A recent systematic review found that spirometry, in addition to clinical examination, improved diagnostic accuracy compared to clinical examination alone. The diagnosis of COPD rests on the demonstration of airflow limitation which is not fully reversible. On the other hand, if the airflow limitation is fully or substantially reversible, the patient should be treated as for asthma.[1] Published studies do not support the diagnostic use of trials of therapy with either corticosteroids (both inhaled and oral), short- or long-acting bronchodilators or oral theophylline in COPD.[4]

O Optimise function

Bronchodilators

Inhaled bronchodilators provide symptom relief and may increase exercise capacity in patients with COPD. The dosage and frequency of short-acting beta$_2$ agonists (salbutamol, terbutaline) and anticholinergic drugs (ipratropium) can be titrated against the severity of the disease.[1] Long-acting bronchodilators can provide sustained symptom relief in patients with moderate to severe disease. They include the long-acting beta$_2$ agonists (salmeterol, eformoterol) which are inhaled twice daily and the long-acting inhaled anticholinergic drug tiotropium which is inhaled once daily.

Tiotropium has become first-line therapy in COPD. It has been shown to improve exercise capacity and quality of life. A Cochrane review found that 14 patients would need to be treated with tiotropium for a year to prevent one exacerbation and 30 to prevent one hospitalisation compared to placebo and ipratropium. Controversially, a recent meta-analysis suggested that tiotropium might also be associated with reduced mortality and estimated that 278 patients would need to be treated to prevent one death.[5]

Combination therapy

The combination of short-acting beta$_2$ agonists and anticholinergics may be more effective and better tolerated than higher doses of either drug used alone.[1] Fixed-dose combinations of a long-acting beta$_2$ agonist with a corticosteroid in a single inhaler (salmeterol/fluticasone, eformoterol/budesonide) are widely used in COPD, although this is not yet an approved indication in Australia. In a Cochrane review of six randomised controlled trials, combination therapy

led to clinically meaningful differences in quality of life and symptoms compared to placebo. However, a subsequent critique[6] raised questions about the methodology used in those studies showing benefits in exacerbation rates. The Cochrane review found conflicting results when the different combination therapies were compared with their individual components alone. Firmer conclusions about the effects and optimal dosage of combination therapy require more data, including assessment of the comparative effects with separate administration of the two drugs in double-dummy trials.

Comorbidities and complications

Most patients with COPD have other comorbid conditions. Ischaemic heart disease and lung cancer share cigarette smoking as a common risk factor. There is increased mortality from respiratory failure, pneumonia, pulmonary vascular disease and heart failure. Anxiety and depression are also more common among patients with COPD. Corticosteroid treatment may contribute to the development of osteoporosis or diabetes.

Systemic corticosteroids have a very limited role in COPD

The systemic effects of COPD include nutritional abnormalities and skeletal muscle wasting.[7] Many patients lose fat free mass, due to an increased basal metabolic rate that is not compensated for by increased dietary intake, or to the adverse effects of drugs (including beta$_2$ agonists and theophylline). Nutritional supplementation has not been associated with any improvement in lung function or exercise capacity. Causes of muscle weakness include physical deconditioning, systemic inflammation, oxidative stress, corticosteroid adverse effects, hypoxia, electrolyte disturbances and many other factors. Physical deconditioning can be effectively reduced by pulmonary rehabilitation.

Pulmonary rehabilitation

Pulmonary rehabilitation reduces breathlessness, anxiety and depression, and improves exercise capacity and quality of life in COPD. Comprehensive integrated rehabilitation programs include exercise training, patient education and psychosocial support. Long recommended for patients with moderate to severe disease, there is now evidence that exercise training also benefits those with milder disease. An online toolkit is available to assist health professionals to implement pulmonary rehabilitation programs.[8]

Surgery

In patients with predominantly upper lobe emphysema and low baseline exercise capacity, who remain disabled following pulmonary rehabilitation, there may be a limited place for lung volume reduction surgery. However, high-risk patients with more widespread emphysema should not be referred for surgery because of increased mortality and negligible functional gain.[9]

P Prevent deterioration

Smoking cessation is the keystone for slowing the rate of decline of forced expiratory volume in one second (FEV$_1$) in COPD. The behavioural and pharmacological interventions available to promote complete cessation of smoking and maintain abstinence were reviewed in COPD-X.[1]

Systemic corticosteroids have a very limited role in COPD other than in acute exacerbations. Inhaled corticosteroids are associated with a modest reduction in the rate of FEV$_1$ decline which is of uncertain clinical significance.[3] A slightly greater effect was seen in trials that gave patients 800 microgram or more of budesonide or 1000 microgram of fluticasone per day. The longer-term adverse events associated with these high doses of inhaled corticosteroids are yet to be determined, so the optimum dose is unknown. A recent systematic review which pooled individual patient data from seven clinical trials found a 25% reduction in mortality among patients treated with inhaled steroids compared to placebo.[10] We estimate that 94 patients would need to be treated with inhaled steroids for two years to prevent one death. Patients with COPD should receive annual influenza and five-yearly pneumococcal vaccination.[11]

Domiciliary oxygen

Long-term continuous oxygen therapy

Long-term continuous oxygen therapy for at least 15 hours a day has been shown to reduce mortality in patients whose arterial oxygen (PaO_2) is consistently ≤ 55 mmHg, or 55–59 mmHg with evidence of hypoxic sequelae such as polycythaemia, pulmonary hypertension or cor pulmonale. Oxygen may also improve exercise capacity and mental state.

Intermittent oxygen therapy

A Cochrane review of 31 studies of patients with moderate to severe COPD found that compared to air, ambulatory oxygen improved endurance exercise capacity, dyspnoea and oxygen saturation. This benefit cannot be predicted by a resting test. A six-minute walking test with and without oxygen is required. The available evidence does not allow any firm conclusions to be made about the effectiveness of intermittent ambulatory oxygen therapy used in the **domiciliary** setting by patients who are not significantly hypoxaemic at rest.

D Develop a support network and self-management plan

Patients with COPD can be supported by their general practitioner, respiratory physician, respiratory nurse/educator, physiotherapist, social worker, pharmacist and many other health professionals. Multidisciplinary care plans and individual

self-management plans may help to prevent or manage crises. However, evidence for the beneficial effects of self-management is more convincing in asthma than in COPD. Effective support can help relieve anxiety and depression. If drug treatment is needed, consider using drugs which do not cause sedation. Support groups can provide ongoing education and psychosocial support for patients and their carers.*

X manage eXacerbations

Home management of acute exacerbations of COPD may relieve pressure on acute care facilities. Up to a quarter of carefully selected patients presenting to hospital emergency departments can be safely and successfully treated at home with support from respiratory nurses. A systematic review of seven randomised controlled trials found no significant differences in readmission rates or mortality, and patients preferred 'hospital at home' schemes.

Guidelines for the investigation and initial assessment of severity in acute exacerbations are detailed in COPD-X.[1] Frequent bronchodilators (beta$_2$ agonist with ipratropium) delivered via nebuliser or metered dose inhaler plus spacer are effective treatments for dyspnoea and airflow limitation. The routine use of intravenous aminophylline is no longer recommended because of the potential for severe toxicity. Patients who have acute exacerbations with signs of infection (increased volume and change of colour of sputum and/or fever, leucocytosis) benefit from antibiotic therapy.

Systemic corticosteroids (oral prednisolone, intravenous hydrocortisone) improve dyspnoea and lung function, reduce the severity and shorten recovery from acute exacerbations. A Cochrane review found that it would be necessary to treat nine patients with systemic corticosteroids to avoid one treatment failure. However, one additional acute adverse effect (such as hyperglycaemia) occurred for every six patients treated. Up to two weeks therapy is adequate and longer courses only increase the risk of adverse effects.[1]

Non-invasive positive pressure ventilation with a face mask is effective in patients who develop acute hypercapnic ventilatory failure. It reduces mortality and the need for intubation, with all the attendant complications. Non-invasive positive pressure ventilation results in more rapid improvements in respiratory rate, dyspnoea and blood gas abnormalities and a shorter stay in hospital than conventional therapy alone. However, patients who are unable to protect their airways, who are not breathing spontaneously or who have severe facial injuries may still require endotracheal intubation.

Follow-up at home after discharge from hospital helps to continue the management begun within the acute environment. However, there is no current evidence to show a benefit from nurse-led chronic disease management for people with COPD.

* See Patient support organisation: The Australian Lung Foundation, page 79.

Conclusion

The challenge remains to improve the recognition and management of COPD in Australia. A large multicentre trial of combination therapy is due to report shortly. However, there is a pressing need for more randomised controlled trials of non-drug therapies for COPD. The latest full version of the guidelines approved by the Australian Lung Foundation can be consulted at www.copdx.org.au.

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Self-test questions

The following statements are either true or false (answers on page 83)

1. Anticholinergic bronchodilators are ineffective in chronic obstructive airways disease.
2. Lung volume reduction surgery reduces mortality in patients with widespread emphysema.

Medicinal mishap

Interstitial nephritis associated with omeprazole

Prepared by Chin Soon Ng, Senior Registrar, Department of Clinical Pharmacology, Medical Specialties, Princess Alexandra Hospital, Woolloongabba, Qld

Case

A 62-year-old man presented with acute renal failure. On examination, there were no allergic features such as rash, fever or eosinophilia. Urine examination was normal. Previous renal function was normal. His creatinine peaked at 470 micromol/L. Investigations included tests for anti-neutrophil cytoplasmic and antinuclear antibodies, antibodies against extractable nuclear antigens, double-stranded DNA, complement, hepatitis serology, serum paraprotein concentration and renal ultrasound, all of which were normal. Renal biopsy showed florid interstitial nephritis.

A few weeks earlier, he was diagnosed with Helicobacter gastritis and treated with triple therapy (omeprazole, amoxycillin, clarithromycin) followed by omeprazole 40 mg daily. He had previously been taking pantoprazole for dyspepsia. Other medical history included a knee injury six months earlier. This had been treated with diclofenac, which was associated with the development of a rash and was substituted with rofecoxib. The exact duration of treatment with rofecoxib was unclear.

Omeprazole was changed to ranitidine and the man was treated with tapering doses of prednisolone, commencing at 75 mg daily. On examination three years later, his creatinine had improved to 123 micromol/L.

Comment

Acute interstitial nephritis is due to a hypersensitivity reaction and is typically associated with reversible acute renal failure. Drugs account for 71% of cases of acute interstitial nephritis.[1] Medicines commonly implicated include non-steroidal anti-inflammatory drugs (NSAIDs), penicillins, cephalosporins, sulfonamides and proton pump inhibitors. Drug-induced interstitial nephritis is not dose dependent and can recur with rechallenge. The classic triad for interstitial nephritis of fever, rash and eosinophilia occurs in less than 10% of cases.[2] Urine examination including microscopy may show haematuria, proteinuria, white cells, casts and eosinophiluria, but may be unremarkable.

Interstitial nephritis may occur with all of the proton pump inhibitors, although most reports to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) have been with omeprazole.[3] To date (14 May 2007) ADRAC have 82 reports associated with proton pump inhibitors. Of these cases, 50 were associated with omeprazole, 12 with esomeprazole, 6 with pantoprazole and 14 with rabeprazole. The duration of proton pump inhibitor treatment before presentation is usually between two weeks and nine months.[4]

The temporal relationship in this case suggests that omeprazole was the most likely cause of interstitial nephritis, although the possibility that amoxycillin, pantoprazole or the NSAID were implicated cannot be excluded.

Recommendation

Maintain a high index of suspicion for interstitial nephritis in patients who develop acute renal failure while on a proton pump inhibitor. The diagnosis can only be confirmed on renal biopsy. Management involves drug withdrawal and supportive treatment. The efficacy of corticosteroids has not been demonstrated in controlled trials.[4]

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Metformin in pregnancy and lactation

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Summary

Metformin improves insulin sensitivity and reduces hepatic glucose output in patients with diabetes. It offers potential benefits for pregnant women with gestational or type 2 diabetes because both conditions are associated with increased insulin resistance. Some cohort data are available and randomised trials are currently in progress to compare metformin with insulin, but strong evidence is not yet available to guide management. There are no long-term follow-up data to provide reassurance about the safety of metformin, given its passage across the placenta, although recent evidence suggests that there is no significant risk of teratogenesis. Limited amounts of metformin are transferred into breast milk, but the risk of neonatal hypoglycaemia is negligible.

Key words: birth defects, gestational diabetes, hypoglycaemic drugs, insulin.

(Aust Prescr 2007;30:68–9)

Introduction

Oral hypoglycaemic drugs have been viewed with suspicion for many years in the management of women with diabetes during pregnancy or breastfeeding. Pregnant women with type 2 diabetes are often switched to insulin. However, there is long experience with use of the biguanide metformin in pregnant women in South Africa. Metformin increases insulin sensitivity, reduces hepatic glucose release and is associated with a tendency to lose weight.[1]

Increasingly metformin is being used in the management of women with polycystic ovary syndrome, as the syndrome is associated with insulin resistance. Metformin reduces hyperandrogenaemia and, as it allows more effective ovulation to occur, it is now widely used in the management of infertility.[2] If a woman with polycystic ovary syndrome becomes pregnant while taking metformin, a decision has to be made whether to continue treatment.

Teratogenicity

Caution is needed when using metformin in pregnancy. In the Australian categorisation of risk metformin is in category C. The product information recommends switching to insulin during pregnancy. It is important for any changeover to insulin to be done under specialist supervision to maintain optimum glucose control and reduce the risk of congenital anomaly from maternal hyperglycaemia.

Limited data are available about the pharmacokinetics of metformin during pregnancy. In one small study of seven women, the clearance of metformin increased with gestation and the associated increased renal elimination.[3] More data are required to clarify the possible need for dose adjustment as pregnancy proceeds. Studies of the passage of metformin across the placenta suggest that there is a rapid transfer of metformin into the fetal circulation.[4]

Recent data provide some reassurance about the safety of metformin in respect of lack of teratogenicity when taken in early pregnancy, although no long-term follow-up data are available.[5] Properly conducted randomised trials are required, as well as a large enough database to exclude rare unanticipated adverse outcomes, such as birth defects.

Outcomes

It is not known if continuation of metformin in early pregnancy provides any better outcome than either ceasing the drug (in women with polycystic ovary syndrome) or changing to insulin (in women with type 2 diabetes). In some circumstances, use of metformin may be preferred, but patients should be individually advised of the harms and benefits.[6] Ideally they should be recruited into appropriately designed studies.

Non-randomised data from New Zealand, where a number of pregnant women with type 2 diabetes have been treated with metformin, suggest that there may be no difference in outcomes when compared with similar women treated with insulin.[7] A small randomised trial in Australia showed no difference in fetal beta cell activity, as measured by cord C-peptide concentrations at delivery, between the babies of women with gestational diabetes treated with metformin and the babies of women treated with insulin.[8]

The randomised Metformin in Gestational Diabetes trial is currently underway to establish the efficacy of metformin compared with insulin, using neonatal outcome as a primary end point. The results may be available soon. After reviewing the results from 600 women, the independent data monitoring committee recommended that the trial continue as there was no indication for early closure.

Metformin improves plasma concentrations of some markers of endothelial activation in people with impaired glucose tolerance,

unrelated to changes in glycaemia, lipids, weight or insulin sensitivity.[9] This is a potential benefit for pregnant women with diabetes, as they are at increased risk of problems associated with endothelial activation, such as pre-eclampsia. Few data are currently available to assess the outcome of such therapy. A secondary outcome in a small randomised placebo-controlled trial in 38 pregnant women with polycystic ovary syndrome was significantly fewer severe pregnancy complications in the women taking metformin.[10]

Any potential benefit of metformin on future childhood obesity and later development of diabetes is hypothetical. Long-term follow-up data from the current studies are required.

Lactation

There are three published studies of metformin in breast milk. The milk:serum or milk:plasma ratio varied between 0.18 and 1.00, while the estimated mean infant dose as a percentage of the mother's weight-adjusted dose varied between 0.18% and 1.08%. This dose is much less than the usual 10% level of concern.[11] Women can be reassured that it is unlikely that there will be any significant effect on their babies. In particular, there is no risk of neonatal hypoglycaemia, in contrast to the use of drugs stimulating insulin release, such as the sulfonylureas. Maintenance of maternal euglycaemia during lactation remains an important principle to reduce the risk of subsequent obesity in the child.[12]

Conclusion

Evidence is emerging that metformin may improve insulin sensitivity during pregnancy. This may be of benefit in gestational diabetes, but further evidence is required. Metformin can be used by women who are breastfeeding.

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[R] randomised controlled trial

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

3. Women with polycystic ovary syndrome who are planning pregnancy should not take metformin.
4. Metformin is contraindicated in breastfeeding because of the risk of neonatal hypoglycaemia.

Australian Prescriber

Thank you to all the readers who participated in the recent surveys of the paper and electronic versions of *Australian Prescriber*. The thousands of responses were very encouraging and the Editorial Executive Committee is pleased that *Australian Prescriber* is having a positive influence on prescribing. The results of the surveys will help to ensure that the journal meets the needs of Australian prescribers.

Maintenance treatments for bipolar disorders

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Summary

Bipolar disorders are disabling and, for most patients, recurrent illnesses. Lithium is the 'gold standard' mood stabiliser in terms of efficacy, but many patients find it difficult to tolerate. The anticonvulsants sodium valproate and carbamazepine are useful despite minimal controlled evidence for their prophylactic efficacy. The approval of olanzapine and lamotrigine for maintenance treatment increases the choice of drug therapy. These new drugs, in conjunction with the development of effective psychological interventions, mean that the clinician has an increasing range of effective options to offer patients with these disabling and challenging conditions.

Key words: carbamazepine, lithium, lamotrigine, olanzapine, sodium valproate.

(Aust Prescr 2007;30:70–3)

Introduction

Bipolar disorders (see box) are relatively common conditions with a lifetime prevalence of up to 4%.[1] They lead to levels of disability which are greater than those associated with major depressive disorder (unipolar depression).[2] Rates of disrupted relationships are high and many sufferers are unemployed and in receipt of government benefits. At least a quarter have a history of suicide attempts, with 10–20% of all patients ending their life by their own hand.

While effective and rapid management of acute episodes of mania and bipolar depression are critical components of treatment, the prevention of relapse is probably the most important aspect of management. Bipolar disorders are highly recurrent for most patients. It is the recurring nature of the condition that, unless adequately treated, gradually takes its toll in terms of the patient's capacity to maintain relationships, career and self-esteem. The average patient experiences a major relapse every 17 to 30 months, with episodes frequently lasting between three and six months. At least 25% will go through phases of rapid-cycling illness in which they experience at least four episodes in a year.[3]

The challenge for the treating clinician – be that a general practitioner[4] or psychiatrist – is to ensure adequate long-term control of the illness. Effective maintenance treatment can make an enormous difference to the lives of those with bipolar disorders. The benefits observed can be some of the most dramatic seen in medical practice.

Which patients should be commenced on maintenance treatment?

There are different guidelines, but the basic principle is that most patients with recurrent, severe or disabling illness are highly likely to benefit from prophylactic treatment. Usually (but not always) the maintenance treatment will be a continuation of the drug that was effective for acute treatment (Table 1). Some of these drugs are currently not subsidised for maintenance treatment (Table 2).

Lithium

Although lithium was first discovered to be effective in mania in 1949, by the Melbourne psychiatrist John Cade, it is still the 'gold standard' therapy. Despite the intervening 58 years, no treatments of greater potency have yet been developed. Many patients are unable to tolerate lithium and it has limited effectiveness for the depressive phase of bipolar disorders.

Bipolar I disorder	At least one episode of mania (current or past) Usually (but not necessarily) episodes of depression
Bipolar II disorder	Episodes of hypomania and depression No manic episodes
Mania	Pathologically elevated or euphoric mood (often also irritable) lasting at least one week. There is evidence of marked impairment of functioning. Delusions or hallucinations may occur and hospitalisation may be required.
Hypomania	Pathologically elevated (or irritable) mood lasting at least 2–4 days. While mood and behaviour are distinctly different from normal, functioning is not severely impaired. Psychotic features do not occur and hospitalisation is unnecessary.

Table 1

Relative efficacy of drugs in preventing manic and depressed episodes

	Preventive potency	
	Mania	**Depression**
Lithium	++	+
Carbamazepine	+	+
Valproate	+	+
Lamotrigine	+/–	++
Olanzapine	++ *	+

++ strong evidence
+ reasonable evidence
+/– equivocal evidence
* one (unreplicated) study demonstrated superiority to lithium for prophylaxis in mania

Table 2

Status of drugs currently approved in Australia for bipolar disorders

	Marketing approval		Subsidised indications	
	Acute mania	**Maintenance**	**Acute mania**	**Maintenance**
Lithium	✓	✓	✓	✓
Carbamazepine	✓	✓	✓	✓
Valproate	✓	✗	✓	✗
Lamotrigine	✗	✓*	✗	✗
Olanzapine	✓	✓	✗	✓
Quetiapine	✓	✗	✗	✗
Risperidone	✓	✗	✗	✗
Ziprasidone	✓	✗	✗	✗

* Approved for prevention of episodes of bipolar depression only. This approval is not presently listed in the product information.

There is no drug or medicine specifically approved in Australia for the acute treatment of bipolar depression.

There are more positive randomised double-blind controlled trials for lithium as a maintenance therapy than for any other treatment. Several meta-analyses have confirmed the efficacy of lithium, particularly in preventing manic relapse.[5] Its capacity to prevent depressive relapse is less clear-cut. Consequently, many patients on lithium suffer from frequent and prolonged depressive episodes, despite dramatic suppression of the periods of elevated mood. Non-compliance is common (20–50% of patients) and if lithium is abruptly discontinued, the chance of sudden relapse into mania is considerable.

The main drawbacks of lithium are the need for serum concentration monitoring, the possibility of serious toxicity, and the risk of thyroid (and less commonly renal) impairment. Tremors, increased muscle tone, hyperreflexia and disorientation are signs of severe toxicity.

Anticonvulsants

In Australia sodium valproate is an anticonvulsant drug that is approved for acute treatment of mania. It is also commonly used as an alternative to lithium for maintenance treatment of bipolar disorders. Carbamazepine, another anticonvulsant, is approved for the management of mania and the maintenance treatment of bipolar disorder.

The only placebo-controlled trial of carbamazepine in prophylaxis failed to show superiority over placebo. However, most of the five randomised double-blind comparisons with lithium reported no difference between lithium and carbamazepine. There has been only one double-blind trial of sodium valproate in the prophylaxis of bipolar disorders. This found no differences between either valproate or lithium when compared to placebo.[6] Despite this lack of evidence from controlled trials, clinical experience worldwide has seemed to confirm the benefit of these drugs in reducing relapse rates.

Lamotrigine

Lamotrigine is an anticonvulsant that may also be used in Australia for the prevention of bipolar depressive episodes. This indication is not subsidised by the Pharmaceutical Benefits Scheme (PBS). There is evidence from one placebo-controlled trial for the efficacy of lamotrigine in the acute treatment of bipolar depression, but this was not replicated in several subsequent trials. Lamotrigine is neither acutely nor prophylactically effective in unipolar depression. It is not significantly superior to placebo in the acute treatment of mania.

In two trials of maintenance treatment involving 638 patients with bipolar I disorder over 18 months, lamotrigine was superior to placebo in the prevention of depressive episodes, while lithium was more effective than placebo in the prevention of mania.[7] A pooled analysis of both studies showed that lamotrigine was more effective than placebo for preventing depression, and lithium was more effective for mania. It also showed that lamotrigine was statistically more effective than placebo in the prevention of manic episodes, but this appeared to be of limited clinical significance.[8]

The main safety problem with lamotrigine is serious rash. The development of Stevens-Johnson syndrome is a major concern as it may be fatal. Major risk factors for serious rash are rapid dose escalation and failure to reduce the dose of lamotrigine on co-administration with sodium valproate.

Antipsychotics

The antipsychotic olanzapine has been approved in Australia for prevention of relapse in bipolar I disorder and this indication is

included in the PBS. Olanzapine is also approved for the acute treatment of mania.

The strongest evidence for the prophylactic efficacy of olanzapine comes from a 12-month randomised double-blind comparison with lithium.[9] Olanzapine was superior to lithium in the prevention of manic and mixed episodes and equivalent to lithium for reducing bipolar depressive episodes even in the absence of psychosis. As yet, no other studies have confirmed that olanzapine has greater efficacy than lithium in preventing manic relapse.

At present there are few reports about the long-term preventive efficacy of other atypical antipsychotics, although the effect of olanzapine may turn out to be a class effect. Risperidone has been approved in Australia for continuation for six months following acute treatment of mania.

The major safety concerns with olanzapine and some other atypical antipsychotics are substantial weight gain, hyperlipidaemia and diabetes. During long-term treatment with olanzapine, lipids and glucose should be monitored, and active means instituted to encourage diet and exercise.

Combination therapy

There is minimal evidence to support the use of combinations of drugs for maintenance treatment. The main evidence comes from a study in the 1990s which found that patients unresponsive to monotherapy with lithium or anticonvulsants often responded to combined therapies. The effective combinations were lithium and carbamazepine, and lithium and valproate.[10]

Is there a role for long-term antidepressants?

For many patients, the episodes of mania are relatively easily treated, but depressive episodes are frequently less amenable to treatment. There is currently considerable controversy internationally over adding long-term antidepressants to the maintenance treatment of bipolar disorders. Antidepressants may induce manic episodes or even a rapid-cycling pattern, but the frequency of this is debated as there is some evidence that suggests induction of mania is relatively uncommon. There is some evidence that continuing antidepressants in patients who respond acutely to them has a prophylactic benefit. In one study 70% of the patients who stopped their antidepressants early relapsed into depression, compared to 36% of the patients who continued their antidepressants.[11] Some (particularly US) authorities argue that antidepressants should rarely be used in long-term treatment.

Psychological interventions

Strong evidence for the benefits of psychological interventions in reducing the likelihood of relapse (particularly depressive episodes) is accumulating from a series of randomised controlled trials. Educational techniques, empowering the patient to take responsibility for the management of their illness, have been shown to reduce relapse and improve social functioning and employment. Cognitive therapy is aimed at improving skills in managing stress and symptoms, and in identifying early warning signs of impending relapse, and teaching skills to challenge and alter unhelpful thinking styles.[12] It improves mood, coping and adherence, and reduces recurrence.[13] Interpersonal and social rhythm therapy teaches patients to regulate their social habits, sleep patterns and daily routines at times of stress.[14]

Conclusion

New treatments, in conjunction with the development of effective psychological interventions for bipolar disorders, mean that the clinician has an increasing range of effective maintenance therapies to offer patients with these disabling and challenging conditions. While none of the newer drugs has been shown to be more effective than lithium, they are better tolerated by some patients.

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Professor Mitchell has received honoraria from GlaxoSmithKline, Eli Lilly and AstraZeneca for lectures, and has served on an advisory board for Eli Lilly in the last three years.

Self-test questions

The following statements are either true or false (answers on page 83)

5. In bipolar disorders, lithium is more effective at preventing manic relapse than depressive relapse.
6. Adding an antidepressant to the maintenance treatment of bipolar disorders may induce mania.

Book review

Therapeutic Guidelines: Antibiotic. Version 13.

Melbourne: Therapeutic Guidelines Limited; 2006. 422 pages. Price $39, students $30, plus postage

Sophie Dwyer, Academic General Practice registrar, Discipline of General Practice, University of Adelaide

Therapeutic Guidelines: Antibiotic is the original and most widely distributed book in the Therapeutic Guidelines series. There have been revisions and additions to the content, but there have been few changes to the concise and easy-to-use format of this book.

The primary use of Therapeutic Guidelines: Antibiotic is as a quick evidence-based reference guide for practitioners in selecting an appropriate antibiotic. The succinct discussion relevant to clinical diagnosis and common organisms is as valuable as the actual recommendations. Where the use of antibiotics is controversial or not indicated for a particular condition, this is discussed, as is non-pharmacologic management. Importantly for infectious diseases, the content is distinctly Australian.

The book commences with a discussion of the principles of antimicrobial use that covers basics such as antibiotic choice, duration of treatment and resistance. The 'Getting to know your drugs' chapter looks briefly at antimicrobials by class. Later chapters discuss administration routes, pregnancy and lactation with a detailed section on dose reduction in renal failure. Specific information on particular drugs is better covered by books such as the Australian Medicines Handbook.

The largest component of the book is arranged by system with conditions ordered alphabetically. Recommendations for first-line antimicrobial treatment are generally accompanied by at least one alternative. Chapters are devoted to specific infections such as malaria, HIV and mycobacteria. A whole chapter is now dedicated to the management of pneumonia. The chapter on the management of severe sepsis has been expanded and includes more information on initial management than the previous version. Newly included treatment algorithms cover important conditions such as pneumonia and meningitis. The rationale for medical and surgical antibiotic prophylaxis is also covered.

This guide is a well entrenched source of reliable information for general practitioners, hospital staff and specialists. The pocket-sized book is also available in 'updateable' versions for desktop computers and personal digital assistants (PDAs) which means many practitioners have several avenues to access this information. These electronic versions have the advantage of including all the titles in the Therapeutic Guidelines series.

C-reactive protein

Glenn Reeves, Staff Specialist in Immunology and Immunopathology, Hunter Area Pathology Service Immunology, John Hunter Hospital, Newcastle, New South Wales

Summary

C-reactive protein elevation is part of the acute-phase response to acute and chronic inflammation. It out-performs erythrocyte sedimentation rate in terms of responsiveness and specificity for inflammation. While C-reactive protein elevation is suggestive of inflammation or infection in the appropriate clinical context, it can also occur with obesity and renal dysfunction. Conversely, a lack of C-reactive protein elevation in inflammation may be seen with hepatic failure, as well as during flares of conditions such as systemic lupus erythematosus. Using C-reactive protein in refining cardiac risk assessment is not currently recommended outside of research settings.

Key words: acute-phase reaction, erythrocyte sedimentation rate, inflammation.

(Aust Prescr 2007;30:74–6)

Introduction

An elevated concentration of C-reactive protein in the blood is an indicator of inflammation. The bulk of C-reactive protein tests are requested for the detection of inflammatory responses associated with microbes, autoimmune diseases and drug allergies (especially to antibiotics).

The inflammatory response

Inflammation is a protective reaction of vascular connective tissue to damaging stimuli. The inflammatory response is associated with vasodilatation, increased vascular permeability, recruitment of inflammatory cells (especially neutrophils in acute inflammation), and the release of inflammatory mediators from these cells, including vasoactive amines, prostanoids, reactive oxygen intermediates and cytokines. Cytokines derived from macrophages and monocytes include tumour necrosis factor alpha (TNF-α), interleukin-1 and interleukin-6. These cytokines are primarily responsible for mediating the 'acute-phase response'.[1] They cause a change in the production of various plasma proteins by hepatocytes, including an increase in C-reactive protein. The effects of inflammation on some of the more important acute-phase proteins are shown in Table 1.

C-reactive protein

C-reactive protein plays a key role in the host's defence against infection.[2] It was so named because it reacts with the C-polysaccharide of *Streptococcus pneumoniae*. In the presence of calcium, C-reactive protein specifically binds to polysaccharides such as phosphocholine moieties present on the cell surface of many pathogenic microbes. C-reactive protein binding activates the classical complement pathway and opsonises (prepares) ligands for phagocytosis. It also neutralises the pro-inflammatory platelet-activating factor and down-regulates polymorphs.

C-reactive protein is predominantly made in the liver and is secreted in increased amounts within six hours of an acute inflammatory stimulus.[3] The plasma concentration can double at least every eight hours, reaching a peak after about 50 hours. After effective treatment or removal of the inflammatory stimulus, concentrations can fall almost as rapidly as the 5–7 hour plasma half-life of labelled exogenous C-reactive protein. C-reactive protein responses may be reduced by severe hepatocellular impairment, but renal dysfunction can elevate concentrations of C-reactive protein.

Normal ranges

The median normal concentration of C-reactive protein is 0.8 mg/L, with 90% of apparently healthy individuals having a value less than 3 mg/L and 99% less than 12 mg/L. Elevated values are abnormal and suggest the presence of organic disease, although minimal C-reactive protein rises can be seen with obesity.

C-reactive protein test results can vary between laboratories. It is therefore recommended that serial C-reactive protein assessments be undertaken through a single laboratory if possible, to minimise error.

'Ultra-sensitive' or 'highly-sensitive' C-reactive protein refers to the measurement of small changes in C-reactive protein concentrations occurring below the 'normal' cut-off used to define significant infection and inflammation.

Table 1

Acute-phase proteins

	Increased concentrations	Decreased concentrations
Protease inhibitors	alpha$_1$-antitrypsin antichymotrypsin	
Coagulation proteins	fibrinogen prothrombin factor VIII plasminogen	
Complement proteins	C1s, C2, C3, C4, C5 factor B C1 esterase inhibitor plasminogen	
Transport and storage proteins	haptoglobin haemopexin caeruloplasmin ferritin	transferrin
Miscellaneous	C-reactive protein procalcitonin serum amyloid protein fibronectin alpha$_1$-acid glycoprotein	albumin pre-albumin

Clinical utility of C-reactive protein

While an elevated C-reactive protein value is not specific for any condition, it is a fairly sensitive marker of inflammation (greater than 90%), and so provides a valuable adjunct to a careful clinical assessment. There is often no clear correlation between C-reactive protein concentrations and disease severity. The commonest conditions associated with major elevations of C-reactive protein concentrations are shown in Table 2. Despite unequivocal evidence of active inflammatory disease and/or tissue damage, some conditions are often associated with only minor (or no) elevation of C-reactive protein concentrations (see Table 2). In many of these conditions C-reactive protein remains normal in some patients despite severe disease. The mechanism of this 'selective' failure of the acute-phase C-reactive protein response is currently uncertain.

Monitoring the extent and activity of disease

In inflammatory conditions, C-reactive protein may be used to monitor the patient's response to therapy. For instance in rheumatoid arthritis, C-reactive protein concentrations correspond well to disease activity and treatment efficacy.

Screening for infection

As an adjunct to clinical assessment, a C-reactive protein test may be useful in differentiating between bacterial and viral infections. A very high C-reactive protein (greater than 100 mg/L) is more likely to occur in bacterial rather than viral infection, and a normal C-reactive protein is unlikely in the presence of significant bacterial infection. However, intermediate C-reactive protein concentrations (10–50 mg/L) may be seen in both bacterial and viral conditions. Measurement of another acute-phase reactant, procalcitonin, has been advocated as an alternative marker in these circumstances, but data are too preliminary to recommend its universal adoption.

Detection and management of intercurrent infection

The possibility of intercurrent infection must always be kept in mind, especially when immunosuppressants are being administered. Bacterial infections usefully monitored by C-reactive protein concentrations include pyelonephritis, pelvic infections, meningitis and endocarditis. Serial C-reactive protein measurements are important adjuncts to the use of temperature charts in clinical practice, as C-reactive protein concentrations are not affected by antipyretic drug therapy or thermoregulatory factors.

In conditions such as systemic lupus erythematosus and ulcerative colitis, a major diagnostic dilemma is often posed between a disease flare and superinfection. Elevation of the C-reactive protein above usual baseline concentrations for a particular patient may provide a valuable clue to the presence of infection.

Table 2

Conditions causing elevation of C-reactive protein

Major elevations	
Bacterial infections	pyelonephritis pelvic infections meningitis endocarditis
Hypersensitivity complications of infections	rheumatic fever erythema nodosum
Inflammatory disease	rheumatoid arthritis juvenile chronic arthritis ankylosing spondylitis psoriatic arthritis systemic vasculitis polymyalgia rheumatica Reiter's disease Crohn's disease familial Mediterranean fever
Transplantation	renal transplantation
Cancer	lymphoma sarcoma
Necrosis	myocardial infarction tumour embolisation acute pancreatitis
Trauma	burns fractures
Minor or no elevations	
Inflammatory disease	systemic lupus erythematosus systemic sclerosis dermatomyositis ulcerative colitis Sjogren's syndrome
Transplantation	graft versus host disease
Cancer	leukaemia

The 'metabolic syndrome'

The metabolic syndrome refers to a constellation of risk factors for cardiovascular disease and type 2 diabetes, which are generally associated with obesity and insulin resistance. The role of inflammation in the pathogenesis of metabolic syndrome is increasingly being recognised. While an association between ultra-sensitive C-reactive protein and vascular risk exists at a population level[4], data suggesting a role for ultra-sensitive C-reactive protein in assessing an individual's cardiovascular risk and offering interventions are conflicting and inconclusive.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR) also provides a measure of inflammation. It reflects concentrations of fibrinogen and alpha-globulins.[5] However, ESR is also influenced by immunoglobulins that are not acute-phase proteins. These proteins all have half-lives of days to weeks, and there is a significant lag time between changes at the clinical level and variations in the ESR. This, plus the influence of various other factors on the ESR such as diurnal variation, anaemia, food intake and red cell morphology, makes it an imprecise guide to disease activity in most cases.

C-reactive protein or ESR?

C-reactive protein is superior to ESR in terms of rapidity of response and specificity for inflammation. Measuring C-reactive protein is also more precise and reproducible and a quicker test to perform. However, ESR measurements remain helpful in certain clinical situations such as the detection of paraproteinaemias, which often do not elicit an acute phase response.

Conclusion

When used in conjunction with clinical assessment, C-reactive protein measurement is a useful tool for evaluating possible infective or inflammatory disease. However, as with any diagnostic test, false positives and false negatives can occur, and no test represents a replacement for thorough clinical review.

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Conflict of interest: none declared

Medical management of dental and oral pain

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Summary

Patients may consult medical practitioners because of painful dental or oral conditions. Medical practitioners need to be aware of common dental and oral diseases in order to manage the patient's pain, but it is even more important to encourage the patient to see a dentist. Typically there is an underlying disease that must be managed by dental or surgical means rather than medication alone. Pain-relieving drugs are considered to be an adjunct to dental treatment rather than a 'first-line' approach. When drugs are needed, anti-inflammatory drugs are appropriate as most dental pain is caused by inflammation. Antibiotics are not necessary in many cases.

Key words: antibiotics, anti-inflammatory drugs, dental pain, infection, inflammation.

(Aust Prescr 2007;30:77–9)

Introduction

Patients will sometimes present to medical practitioners for the management of pain or other dental and oral problems.[1,2] There are several reasons why patients may seek medical assistance rather than going to a dentist. These reasons include:

- the lack of timely access to a dentist – especially in rural and remote areas
- dentists are not always available, particularly for 'after-hours' emergencies
- the cost of dental treatment
- a fear of pain associated with dental treatment
- trauma to the face, mouth, teeth
- ignorance or a lack of knowledge about the role of dentists and the scope of dental practice – especially regarding the management of soft tissue problems and infections
- not realising their problem has a dental or oral origin
- drug dependent patients seeking opioids.

The majority of medical practitioners have little, or no, formal training in the diagnosis and management of dental and oral diseases, but they are likely to feel obligated to assist a patient in pain. They can prescribe drugs to relieve the pain or to reduce the effect of swellings or other problems. Medical practitioners should advise patients with dental and oral problems to seek dental assessment and management as soon as possible. If a patient is suffering from intense pain, then analgesics may be indicated, but antibiotics should only be prescribed when there are definite signs of an active and spreading infection. In some cases, drug treatment may mask the signs and symptoms which then complicates, or even prevents, the dentist's task of diagnosing the disease. This may delay appropriate treatment.

Dental diseases

There are many dental and oral diseases that cause pain, swelling or other acute symptoms. Some general principles can assist medical practitioners to understand the common dental disorders, but more detailed information is available in other publications.[1,2]

The common dental conditions are inflammatory in nature rather than being infections. Although they are caused by the presence of bacteria in or on the tooth, the bacteria are not necessarily causing all the problems that would be seen when other tissues of the body become infected. Infections do occur in some cases and these may manifest in the form of abscesses (periapical or periodontal) or facial cellulitis.

Dental caries

The most common dental disease is dental caries or tooth decay. It can be painless, but can cause pain ranging from mild to severe pain with swelling and spreading infection. Dental caries is essentially a bacterial disease process which breaks down tooth structure. Once the tooth's outer protective layer of enamel has been breached, the bacteria can progress through the underlying dentine via its network of many tubules. Eventually, the pulp becomes inflamed and if left untreated, it will necrose as the bacteria spread further down into the tooth root. Infection of the root canal system then occurs and this leads to apical periodontitis, an inflammatory response within the periodontal ligament that surrounds the tooth root. Acute apical periodontitis is typically a very painful condition that is likely to lead a patient to seek medical or dental assistance.

Gum disease

The second most common oral condition that can lead to pain and symptoms is periodontal disease. There are various forms

of periodontal disease and they are generally the result of the build-up of plaque and calculus on teeth. Plaque is a biofilm of bacteria and this causes inflammatory changes within the gingival tissues and the periodontal ligaments that support the teeth. Most of these conditions are chronic and usually do not cause pain, but some patients will develop acute conditions as a result of certain bacteria or other predisposing factors.

Other conditions

Pain can arise from aphthous ulcers, mucosal diseases (for example lichen planus, pemphigoid), trauma to the teeth or oral tissues, impacted teeth, occlusal (bite) problems, temporomandibular disorders, inflammation of the muscles of mastication, tumours and cysts. Some of these conditions are uncommon and difficult to identify. They generally do not require any emergency or urgent treatment by a medical practitioner unless the patient has severe pain. These conditions should always be assessed and managed by a dentist.

Managing dental pain

The most effective way to manage pain of dental or oral origin is to remove the cause of the pain.[3] This requires an accurate diagnosis otherwise the treatment may be inappropriate. It must be emphasised that the common conditions that cause dental pain should not be treated by using drugs alone. Drugs only give symptomatic relief at best leaving the underlying problem *in situ* so that it will progress and become more severe over time. There are likely to be subsequent periods of pain or discomfort as the condition fluctuates between chronic and acute stages until it reaches the point where the patient is unable to tolerate the pain and will seek appropriate treatment. Dental diseases should be considered as being continuously progressive until they have been halted by the appropriate dental management.

The '3-D principle' is used by dentists to manage dental pain. In order, this is **d**iagnosis, **d**ental treatment, and then **d**rugs if required.[3] The emphasis is on making a correct diagnosis so the appropriate dental treatment can be provided. If this is done, then drugs are rarely necessary. Typical dental treatments to reduce pain include removal of the caries and placement of a sedative dressing in the tooth, root canal therapy, periodontal treatment, and extraction. The exact nature of treatment provided depends on the presenting problem.

If any drugs are required, then they should only be considered as an adjunct to the dental treatment. Their duration of use can be minimised since they are only required to help resolve any pain that remains after dental treatment while the tissues are recovering. At that stage the pain will be inflammatory and not due to infection.[3] The most effective drug in this situation will therefore be an anti-inflammatory drug such as a non-steroidal anti-inflammatory drug (NSAID). Analgesics such as paracetamol (with or without codeine) can be used, but their effectiveness is limited to blocking pain in the central nervous system rather than peripherally at the site of inflammation. The NSAIDs are far more effective pain relievers as they reduce inflammation at the site of injury.[3]

Managing infections

Some dental or oral pain arises from infections that require antibiotic therapy. In some cases the treatment will be urgent in order to prevent life-threatening conditions such as Ludwig's angina and other deep, spreading infections of the head and neck.[4] Infections resulting from dental or oral diseases are usually readily identified as infections and distinguished from inflammatory conditions due to the presence of swelling, severe pain, generalised malaise, cervical lymph node involvement and fever. If the signs and symptoms have developed rapidly, then urgent treatment is essential to avoid further spread.[4] These patients should ideally be rapidly referred to a dentist or oral surgeon, but if this is not possible then immediate administration of antibiotics is required. These severe cases require intramuscular or intravenous antibiotics rather than oral tablets or capsules.[4] Most odontogenic infections will respond rapidly to penicillin although in more severe cases it may be necessary to combine the penicillin with metronidazole to broaden the spectrum of antibacterial action.[4,5,6,7]

In the absence of signs and symptoms of infection, medical practitioners should refrain from prescribing antibiotics as a means of relieving pain.[5] In some cases, the antibiotics may provide symptomatic relief which may last for some time (several months or even a year or more), but it is inevitable and quite predictable that the problem will return in the future as the underlying cause of the pain has not been removed or managed. In these circumstances, the medical practitioner may actually be providing a disservice to the patient in the long term unless referral to a dentist is also advised. Even with referral, it is still preferable to desist from prescribing antibiotics since this may complicate the dentist's diagnostic processes which may in turn mean that the appropriate treatment is not provided expediently.

Conclusion

The most effective way to manage dental and oral pain is to diagnose the condition and then to provide the appropriate dental treatment. This implies referral to a dentist. Medical practitioners should avoid the temptation to prescribe antibiotics to manage dental or oral pain except when there are signs of severe or life-threatening infections and a dentist is not immediately available. Drugs are rarely required and should only be used as an adjunct to dental treatment since they may complicate further dental management.

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Further reading

Therapeutic Guidelines: Oral and dental. Version 1. Melbourne: Therapeutic Guidelines Limited; 2007.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

7. Most dental pain is caused by tooth infection.
8. Most of the bacteria causing dental infections are resistant to penicillin.

Patient support organisation

The Australian Lung Foundation

The Australian Lung Foundation promotes understanding, management and relief of lung disease. It has over 100 patient support groups in metropolitan and regional areas of all the states and territories. For patients and carers the Foundation produces a range of fact sheets and illustrations, written in non-scientific language, about respiratory diseases and lung health. These fact sheets can be ordered or downloaded from the website, which also contains lists of pulmonary rehabilitation programs, internet support groups, links to further information, and materials for healthcare professionals.

Contacts

Phone 1800 654 301
Website www.lungnet.com.au
Email enquiries@lungnet.com.au

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.

Darunavir

Prezista (Janssen-Cilag)

300 mg tablet

Approved indication: HIV infection

Australian Medicines Handbook section 5.4.3

Darunavir is a new protease inhibitor that can be used in combination with other antiretroviral drugs to treat patients infected with HIV.[1] It works by selectively inhibiting the cleavage of viral polyproteins in infected cells, which prevents the formation of mature virus.

Darunavir is extensively metabolised by CYP3A. Ritonavir inhibits this enzyme and, when co-administered, increases the bioavailability of darunavir 14-fold. After an oral dose of 600 mg darunavir with 100 mg ritonavir, peak plasma concentrations are reached within 2.5–4 hours. The terminal half-life is around 15 hours and most of the drug is excreted in the faeces. This drug should be taken with ritonavir and food to increase its bioavailability.

The efficacy of darunavir (with ritonavir 100 mg) has been compared to other protease inhibitors in a phase II dose-finding trial. The 318 patients who were enrolled had previously been treated with antiretroviral drugs and many of them had HIV that was resistant to commercially available protease inhibitors. Before the patients were allocated to a treatment group, they were prescribed an optimised background regimen of two

or more nucleoside analogue reverse transcriptase inhibitors with or without enfuvirtide. Patients were then randomised to receive darunavir or another protease inhibitor (lopinavir, saquinavir, fosamprenavir, atazanavir or indinavir) selected by the investigator. After 24 weeks of treatment, 53% (32) of patients taking 600 mg darunavir (twice daily) had less than 50 viral copies/mL of blood compared to 18% (11) of patients taking another protease inhibitor. Corresponding to this, mean CD4 cell counts increased by 124 cells/microlitre of blood in the darunavir group and 20 cells/microlitre in the comparator group.[2]

Viral resistance to darunavir has been noted in patients previously treated with other protease inhibitors. This is associated with amino acid substitutions in the viral proteases. HIV strains that are resistant to darunavir may also have decreased susceptibility to other protease inhibitors.

Headache and gastrointestinal symptoms are the most common adverse events associated with darunavir. Skin rashes have also been reported.

Darunavir interacts with many drugs as it is metabolised by CYP3A. It must not be prescribed with drugs that rely on this enzyme for their clearance such as ergot derivatives and midazolam and triazolam. Darunavir can also interact with complementary medicines such as St John's wort. Other antiretroviral drugs (lopinavir/ritonavir and saquinavir) also affect the bioavailability of darunavir.

Darunavir is indicated in combination with other antiretroviral drugs for the treatment of HIV in heavily pre-treated adults who already have resistance to multiple protease inhibitors. So far, it has only been tested in a limited number of patients. The effectiveness of this drug depends on the treatment history of the individual patient and the genotype of their HIV strain.

[X] manufacturer declined to supply data

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Laronidase

Aldurazyme (Genzyme)

5 mL vials containing 100 U/mL

Approved indication: mucopolysaccharidosis I

Mucopolysaccharidosis I is a lysosomal storage disease caused by an inborn error of metabolism. Severe cases are also known as Hurler disease. The patient has a deficiency of the enzyme α–L–iduronidase which leads to an accumulation of substrates inside the lysosomes. This gradually impairs cell function and results in developmental delay, hepatosplenomegaly, joint stiffness, neurological problems, airway obstruction and abnormal facial features. Children with Hurler disease usually die before the age of 10 years, less severe cases may live into their 20s.

Laronidase is a recombinant form of the deficient enzyme. It is genetically engineered, using Chinese hamster ovary cells, to have exactly the same amino acid sequence as the human enzyme.

The aim of treatment is to metabolise the stored substrate and prevent further accumulation. To achieve this laronidase is diluted and given as an infusion over four hours. Although the half-life of laronidase is 2–4 hours, only a weekly dose is required. The molecule is metabolised by peptide hydrolysis.

In a 52-week study of 10 patients there was a 25% decrease in the size of the liver and a 20% decrease in the size of the spleen. There was a 63% reduction in the amount of substrate appearing in the urine. The range of joint movement increased and the prepubertal patients showed improved growth. Lung function also improved.[1]

A larger double-blind trial randomised 22 patients to receive laronidase and 23 to receive a placebo for 26 weeks. Active treatment resulted in a significant reduction in liver size and the excretion of substrates.

Infusing patients with peptides can cause hypersensitivity reactions. As 32% of patients may have a reaction to the infusion, it is important that they are given antipyretics and antihistamines before their infusions. Many patients will produce antibodies to laronidase, but they can also develop an immune tolerance.[2] It is therefore unknown if these antibodies will alter the long-term effectiveness of treatment.

Although the efficacy studies show some improvements for patients, not all of the benefits are statistically significant. In the larger trial the forced vital capacity significantly improved, but there was no significant change in the apnoea/hypopnea index. Although, after 26 weeks of treatment, the patients could walk nearly 20 metres further in six minutes, the advantage over placebo was not statistically significant. The effect of laronidase on the nervous system is uncertain and it is only indicated for non-neurological manifestations of the disease.

Although bone marrow transplantation can be helpful it will not be an option for many patients. Treatment with laronidase will be an expensive alternative and the long-term outcomes will remain unknown for many years.

[T] manufacturer provided only the product information

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Olmesartan medoxomil

Olmetec (Schering-Plough)
20 mg and 40 mg tablets

Olmetec Plus (Schering-Plough)
20 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide tablets
40 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide tablets
40 mg olmesartan medoxomil/25 mg hydrochlorothiazide tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.4.5

Olmesartan is the sixth angiotensin receptor antagonist to be marketed in Australia. Like the other members of its class it blocks the binding of angiotensin II to the angiotensin (AT_1) receptor (see 'Angiotensin receptor antagonists for the treatment of hypertension', Aust Prescr 1998;21:95–7).

As olmesartan medoxomil is a prodrug it has to be converted to active olmesartan. This metabolism occurs during absorption. The bioavailability is 26%, but this is unaffected by food. Up to half of the absorbed drug is excreted in the urine. Renal and hepatic impairment will increase concentrations of olmesartan.

The efficacy of the drug has been shown in several placebo-controlled trials. Approximately 70% of patients with hypertension will respond. The mean reductions in ambulatory blood pressures with a daily dose of 20 mg olmesartan are 11 mmHg diastolic and 14 mmHg systolic.[1] The maximum effect of olmesartan occurs by the eighth week of treatment.

Olmesartan has been compared with other antihypertensive drugs. Olmesartan 20 mg had a greater effect on blood pressure than 50 mg losartan, 150 mg irbesartan and 8 mg candesartan.[2]

When combined with hydrochlorothiazide the efficacy of olmesartan is similar to that of atenolol and hydrochlorothiazide. The combination product should only be used when the patient's hypertension has not been controlled by olmesartan or hydrochlorothiazide alone.

The most common adverse effect of olmesartan is dizziness. Cough does not appear to be a major problem, but angioedema has been reported. Like other angiotensin receptor antagonists and ACE inhibitors caution is needed when prescribing for patients who may have renal impairment or be volume depleted by diuretics. Similarly, taking a non-steroidal anti-inflammatory drug with olmesartan could cause renal failure.

Hypertension is a chronic disease, but most trials of efficacy only last a few months. Although it may have a greater effect on blood pressure, the long-term effects of olmesartan are uncertain. As currently available angiotensin receptor antagonists have been more widely used and as some have also been approved for heart failure and diabetic renal disease, olmesartan should probably not become the first choice until it has more outcome data.

T manufacturer provided only the product information

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Ranibizumab

Lucentis (Novartis)

1.8 mg/0.3 mL or 3.0 mg/0.3 mL in single-dose vials

Approved indication: neovascular age-related macular degeneration

Australian Medicines Handbook section 11.7

Age-related macular degeneration is the leading cause of irreversible blindness in Australia. It is a progressive disease that causes loss of 'straight ahead' vision. Approximately 10% of people with this condition have the neovascular or 'wet' form. This is caused by abnormal blood vessels under the macula leaking fluid and bleeding, which eventually leads to scarring. Using fluorescein angiography, these lesions can be classified as 'classic' or 'occult'.[1] One current treatment for this disease in Australia is verteporfin, which is given intravenously and then followed by photodynamic therapy (see New drugs, Aust Prescr 2000;23:137–9).

Ranibizumab is a humanised monoclonal antibody fragment which blocks vascular endothelial growth factor A (VEGF-A), a key mediator in neovascular age-related macular degeneration.

Following intravitreal injection very little ranibizumab is absorbed systemically and any that is, is rapidly cleared. The terminal half-life of ranibizumab in the vitreous humour is approximately 10 days.

Most of the published efficacy data for ranibizumab comes from two randomised controlled trials. One trial compared monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) with sham injections (pressing a needleless syringe against the conjunctiva) in 716 patients with age-related macular degeneration. Patients had either occult or minimally classic choroidal neovascularisation. After 12 months of treatment, around 94% of patients given ranibizumab and 62% of patients receiving a sham injection maintained their vision. This was defined as losing less than 15 letters of visual acuity on the chart used in the Early Treatment Diabetic Retinopathy Study. The chart consists of 14 rows of 5 letters each. For patients in the ranibizumab groups, visual acuity increased by an average of 6.5 letters for the 0.3 mg dose and 7.2 letters for the 0.5 mg

dose and decreased by an average of 10.4 letters in the sham injection group. After 24 months of treatment visual improvements were largely maintained in the patients receiving ranibizumab, whereas vision continued to decline in patients receiving sham injections.[2]

In the other efficacy trial, monthly injections of ranibizumab (0.3 mg or 0.5 mg) were compared with an active treatment, verteporfin photodynamic therapy, in 423 patients who mostly had predominantly classic neovascular age-related macular degeneration. After 12 months of treatment, around 95% of patients given ranibizumab and 64% of patients receiving verteporfin therapy maintained their vision. On average, visual acuity in patients receiving ranibizumab increased by 8.5 letters in the 0.3 mg group and 11.3 in the 0.5 mg group and decreased by 9.5 letters in the verteporfin group.[3]

Within both of these trials, the difference between the efficacy of ranibizumab and the sham injection or verteporfin therapy was statistically significant, whereas the difference between the two ranibizumab doses was not.[2,3]

In the larger efficacy trial, serious uveitis, endophthalmitis and retinal tear occurred in the ranibizumab groups but not in the sham group. Increases in intraocular pressure (of 30 mmHg or more) occurred more often after ranibizumab injections than sham injections.[1] In both trials, non-ocular haemorrhage was more common in patients treated with ranibizumab compared to control patients.[2,3] Some trials have reported an increase in arterial thromboembolism in patients given intravitreal ranibizumab.

After two years of treatment, 4.4% of patients given 0.3 mg of ranibizumab and 6.3% of those given the 0.5 mg dose tested positive for circulating antibodies to ranibizumab. This did not seem to affect the efficacy of ranibizumab.[2]

Doctors should be aware that only one eye should be injected at each visit. As ranibizumab is injected into the vitreous cavity, aseptic technique is important and patients should be monitored during the week following treatment in case infection occurs. Advise patients to administer antimicrobial eye drops for three days before and after the injection.

Increases in intraocular pressure and changes in perfusion of the optic nerve head may occur within 60 minutes of the injection and so these should be monitored. Ranibizumab can temporarily affect vision and patients should be warned not to drive or operate machinery if this occurs.

Ranibizumab seems to offer a promising alternative to current therapy for neovascular age-related macular degeneration. Ongoing trials are investigating whether patients can have the same benefit from less frequent injections of ranibizumab.[4]

T manufacturer provided only the product information

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1. Guymer R. Drug treatment of macular degeneration. Aust Prescr 2002;25:116-9.
2. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
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4. Rosenfeld PJ, Rich RM, Lalwani GA. Ranibizumab: phase III clinical trial results. Ophthalmol Clin N Am 2006;19:361-72.

The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

* 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.emea.europa.eu).

Withdrawal of thioridazine

Thioridazine is an old antipsychotic drug. Its use has declined partly because of concerns about it causing serious cardiac arrhythmias.

The current manufacturer is ceasing production of thioridazine in Australia. It is expected that stocks will be exhausted in August 2007.

No protocol has been published to assist prescribers switch patients to other therapy. Some information was made available to Canadian prescribers when thioridazine sales ceased in Canada during 2005 (see www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/thioridazine_hpc-cps_e.html).

Your questions to the PBAC

Influenza vaccination

I found the article on influenza vaccination (Aust Prescr 2007;30:35–7) very informative. I would like clarification on the eligibility of healthcare workers to receive influenza vaccination under the Pharmaceutical Benefits Scheme (PBS). My copy of the Schedule states that influenza vaccine is a restricted benefit for 'Persons at special risk of adverse consequences from infections of the lower respiratory tract'. My understanding of this restriction means that only individuals who are themselves at risk are eligible for PBS subsidy. The fact that immunisation prevents disease in someone else is not an indication for PBS subsidy, by my understanding. I hope I can prescribe it for health workers on the PBS so I am asking for further elucidation.

Peter Annetts
General Practitioner
Glen Innes, NSW

PBAC response:

Dr Annett's understanding of the restriction on influenza vaccine is correct – only those individuals who are themselves at special risk of adverse consequences from infections of the lower respiratory tract are eligible for subsidy under the PBS.

Certainly, use in healthcare workers who are contacts of high risk patients is recommended by the National Health and Medical Research Council immunisation guidelines. However, subsidy of the influenza vaccine for this occupation-related indication is not covered by the Commonwealth, but by decisions made at the state, territory or employer level. For example, in the Australian Capital Territory (ACT) public hospitals will cover the cost of vaccinating their own health workers who want it, nursing home owners provide the same for their staff, while the ACT Health Department operates a program to supply the vaccine free of charge to staff working in general practice. In summary, the subsidy of influenza vaccine for an individual patient at risk is covered by the PBS, while for healthcare workers the subsidy is a matter for their employer.

Correction

Influenza vaccination for healthy adults (Aust Prescr 2007;30:35–7)

Although the National Health and Medical Research Council recommends influenza vaccination for a number of groups, not all of these groups are eligible for free vaccine under the National Immunisation Program (see www.immunise.health.gov.au).

Answers to self-test questions

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

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