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CONTENTS

- 58 **Discharge medication**
(Editorial) S.N. Hilmer & S.J. Ogle
-
- 59 **Letters**
-
- 63 **Starting steroids for asthma**
C. Jenkins
-
- 67 **Managing patients taking
tumour necrosis factor
inhibitors**
T.Y-T. Lu & C. Hill
-
- 70 **Book review**
Pocket guide to lung function tests
-
- 71 **Medicinal mishap**
Serotonin syndrome precipitated
by an over-the-counter cold remedy
-
- 72 **Drug treatment of
neuropathic pain**
R.D. Helme
-
- 75 **Patient support organisation**
Trigeminal Neuralgia Association
-
- 76 **Treatment of adult leukaemias**
I. Kerridge
-
- 79 **Book review**
Therapeutic Guidelines:
Palliative Care
-
- 80 **Travelling with medicines**
N. Zwar
-
- 82 **Dental notes**
Drug treatment of neuropathic pain
-
- 83 **Medicinal mishap**
Dosing errors with Donnalix Infant
Drops
-
- 84 **New drugs**
bortezomib, disodium gadoxetate,
eflornithine, posaconazole,
tazarotene

Discharge medication

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Keywords: drug information, quality use of medicines.

(Aust Prescr 2006;29:58–9)

There are many barriers to the transfer of a patient's medication history between the hospital and the community. It is just as important to have good information on discharge as it is to have an accurate medication history when the patient is admitted. Discharge summaries may be illegible, inaccurate and inconsistent in the use of generic and trade names. Timely transfer of discharge information is also a challenge. Telephone calls are helpful for discussing changes to medications, but must be used in conjunction with a written list of discharge medications. There is currently limited use of fax and email to transfer discharge medication information. Many hospitals issue a limited supply (3–5 days) of medication, so the patient may need another prescription before the general practitioner receives the discharge summary by conventional mail.

There is a need to transfer more information than a list of current drugs. Changes made to treatment and the reasons for those changes should be communicated. This should include information about drugs which have been tried and found to be ineffective or to have caused adverse reactions. Specialist knowledge about the use of medications (for example, the need

to monitor for adverse drug reactions) and about compliance should also be transferred. The hospital staff must communicate with the community pharmacist if a blister pack is needed (increasingly required in residential aged care) and with the family or community nurses if they are needed to assist with drug administration.

Trials of interventions to improve the transfer of drug information from the hospital to the community have been disappointing. We found that hand-held medication cards given to patients were infrequently used and often inaccurate.¹ A South Australian study of patients discharged from hospital to residential care used a pharmacist to co-ordinate medication management transfer summaries, timely medication reviews by community pharmacists, and case conferences with physicians. These interventions prevented a post-discharge decline in the quality of prescribing (measured by the Medication Appropriateness Index) and prevented worsening of pain, but had no effect on adverse drug events, falls, mobility, behaviour or confusion eight weeks after discharge.² In Sydney, workshops and audits were used to improve the exchange of medication information between hospitals and general practitioners. The intervention increased the proportion of general practitioners receiving discharge summaries directly by fax from 2% to 27%.³ However, only 29% of general practitioners reported receiving a discharge referral which included the reasons for changing medications.

Healthcare agreements between the Commonwealth and state governments aim to implement the Australian Pharmaceutical Advisory Council's guiding principles for achieving continuity in medication management.⁴ To implement the 'provision of a sufficient supply of medicines in a planned and timely way', public patients in most states will soon receive up to one month's supply of medication through the Pharmaceutical Benefits Scheme (PBS) on discharge from hospital. Medications can be prescribed in hospital and, where possible, dispensed from the hospital pharmacy.

Provision of a PBS prescription on discharge will allow time for the discharge summary to reach the general practitioner by mail before a new prescription is required. However, issuing PBS prescriptions from the hospital requires training of junior medical officers and an investment of their limited time, in

In this issue...

The importance of communication as a component of prescribing is underlined in several articles. Sarah Hilmer and Susan Ogle suggest that communication could be improved when patients are admitted to or discharged from hospital. This is illustrated in the two 'Medicinal mishaps'. Treatment summaries are also useful for travellers, as discussed by Nick Zwar.

Asthma can be exacerbated by travel so it is important for people to take their regular medication. Christine Jenkins considers how to use inhaled corticosteroids to control asthma.

Controlling neuropathic pain can be challenging. Rob Helme reminds us that drugs are just one part of management.

Drugs have a central role in treating leukaemias. Ian Kerridge explains how therapy is changing as our understanding of these diseases increases.

addition to writing medication lists on discharge summaries. In our hospital, discharge prescriptions are screened by clinical pharmacists and errors are detected for about 12% of patients.⁵ Issuing PBS prescriptions from the hospital will require new systems to check discharge drugs and to transfer instructions about their use.

Accurate, timely transfer of discharge medication information from the hospital to the community requires co-operation between doctors, pharmacists and nurses in the hospital and in the community. Lists of discharge medications should be typed to improve legibility and include reasons for any changes. The drugs must be ordered in time for the pharmacist to check them, dispense them (or organise dispensing in the community) and provide the patient with the information to manage their medications. There should be timely transfer of the discharge information by as many routes as possible to the patient and/or carer and the general practitioner. The community pharmacist needs to know if a blister pack is required and the community nurse needs to be informed if administration is required. Medication cards can provide the patient with their own record on discharge.

Electronic systems can transfer computerised discharge summaries and medication lists rapidly by fax or email, but require new processes for checking and correcting discharge prescriptions. The Commonwealth Government has trialled a 'MediConnect' record for consenting patients.⁶ An electronic medication list was stored by Medicare Australia and could be added to and accessed by doctors, pharmacists and hospital staff. The findings will be implemented as part of the 'HealthConnect' strategy for electronic health information. However, for all records, paper or electronic, accuracy depends upon timely and accurate data entry. For example, it is important that electronic prescribing records are updated to reflect changes in treatment. Ultimately the most useful and accurate record of patients' medications may be the 'plastic bag' or basket (Fig. 1) containing all their drugs, including discharge medications.¹

Fig. 1

Medicines brought to a geriatric outpatients clinic by a patient



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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.

Assisting Aboriginal patients with medication management

Editor, –The article 'Assisting Aboriginal patients with medication management' (*Aust Prescr* 2005;28:123–5) included many useful suggestions. However, one of the most important barriers facing people with chronic ill health was only mentioned in passing, namely medication

co-payments. A particular sub-group of the Aboriginal population is severely affected by co-payments. These are the growing number who normally live in remote communities but move temporarily or permanently into capital cities. By moving, they lose access to free medications provided under Section 100 (*National Health Act 1953*). Due to the high burden of chronic disease experienced by Aboriginal

people, many require multiple medications and, not surprisingly, come to grief being unable to afford the additional costs. Extension of Section 100 eligibility to the whole Aboriginal population of Australia has been the subject of a joint position paper by the National Aboriginal Community Controlled Health Organisation (NACCHO), the Australian Medical Association (AMA) and the Pharmacy Guild. This paper is available online.¹ Implementation of its recommendations would not be expensive, but would do much to improve the health status of Aboriginal people with chronic conditions.

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What now for Alzheimer's disease?

Editor, –The review of the AD2000 trial (Aust Prescr 2005;28:134–5) fails to note that this trial has been heavily criticised. It permitted enrolment of people with cerebrovascular disease, enrolled less than 20% of its recruitment target and carried on with too few patients for too short a time to tell whether the drugs delayed institutionalisation. There was a complicated double randomisation method with an extra four-week washout period every 12 months. Of 566 people entering the study only 111 completed two years of the trial and only 20 completed the third year of a planned five-year study. Many prominent researchers in the UK chose not to be involved because of the questionable ethics of offering treatment only as part of a randomised controlled trial. The researchers skirted this ethical dilemma by asking doctors to recruit only patients about whom they were 'substantially uncertain that the individual would gain a worthwhile clinical benefit from donepezil'. About the only conclusion that can be drawn from this study is that donepezil produces a measurable but small improvement in a crude cognitive measure which is sustained in individuals receiving treatment compared to those receiving placebo over at least one and possibly two years.

The review contains a footnote saying that the results of a recent study were 'very similar to those of the AD2000 trial'. This is misleading. The recent trial assessed the usefulness of donepezil and vitamin E for a completely different indication (mild cognitive impairment, not Alzheimer's disease) and returned negative, not weakly positive, results on measures of cognition.¹

Cholinesterase inhibitors have modest efficacy for some patients with Alzheimer's disease, but it is not possible to

tell in advance who will respond. It is therefore appropriate to offer people with mild to moderate Alzheimer's disease a trial of treatment, monitor their response and then decide about continuation. The requirement for at least a 2-point improvement in the mini-mental state examination goes some way towards ensuring that the patients who receive continuing treatment will be those who have shown some response.

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Professor Ames and Professor Brodaty have both received research support, honoraria and financial assistance to attend conferences from companies marketing cholinesterase inhibitors.

Professor J. Attia and Professor P. Schofield, authors of the editorial, comment:

In our editorial, we clearly acknowledged the drawbacks of the trial, including the low recruitment and the complex design. Despite the contention that the trial was too short, it was the only trial up to that point to have looked at outcomes beyond one year. Despite criticism of the inclusion criteria, even Ames and Brodaty acknowledge the difficulty of prospectively identifying responders. We would contend that the study has some strengths, including the focus on clinical end points, caregiver burden, and economic analyses. It tempers the enthusiasm generated by the results from short-term, largely drug company-sponsored studies and this cautionary note has been sounded by others.¹

The recent study examined the effect of donepezil and vitamin E on conversion rates from incipient to diagnosed Alzheimer's disease, and thus was concerned with the same disease entity as was AD2000, albeit at a milder stage. The similarity that we see between the two three-year trials is that they both indicated a small beneficial effect in primary outcomes at 6–12 months, which was not sustained in the long term.

However, 'evidence alone is never sufficient to make a clinical decision'.² The translation of evidence into practice is subject

to an evaluation of the risks and benefits, costs, patient values and circumstances. We agree with Ames and Brodaty that an N of 1 trial is the highest level of evidence to apply!

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Management of bite injuries

Editor, –The article 'Management of bite injuries' (*Aust Prescr* 2006;29:6–8) is helpful in determining appropriate antibiotics for bites, but the most important message is that all bite wounds, other than those where there is a clear cosmetic problem such as in the face, should be treated by wound excision and topical use of povidone-iodine, providing the patient is not allergic to iodine. Under no circumstances should wounds be sutured primarily.

Unless this point is stressed unfortunately tragedies will still occur because of the inexperience of emergency doctors who feel obliged to suture all wounds that present to the emergency department.

The primary treatment of the wound is far more important than the use of antibiotics, although they are an important adjunct to management.

Chris Haw
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Dr Marion Woods and Dr Jennifer Broom, authors of the article, comment:

Our article was concerned primarily with appropriate antibiotic management of bite wounds. We reiterate that debridement of devitalised tissue and thorough irrigation of bite wounds is an essential part of management. We made the point that early surgical consultation is advised for bite wounds, particularly for hand wounds, to prevent loss of function. Early surgical consultation will also optimise the cosmetic results of treatment particularly for bites on the face.

We agree that most bite wounds should not be primarily closed unless there is a specific need. Of note, however, is a best evidence topic report of closure of bite wounds¹ stating that dog bites on the hands should be left open (primarily closed hand wounds had double the infection rate [$p < 0.01$]), but that non-puncture wounds elsewhere may be safely

treated by primary closure after thorough cleaning (7.6% infection rate in primary closure group vs 7.7% infection rate in open group).²

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Editor, – In addition to the useful information in the article 'Management of bite injuries' (*Aust Prescr* 2006;29:6–8), readers should be aware of the forensic implications of bite marks.

Marks made by the teeth may be inflicted either on skin or inanimate objects in cases of criminal assault, sexual assault, child abuse or homicide. Bite marks may be used as evidence in court, either to identify a perpetrator or exclude suspects.¹

While prompt medical attention for bites is necessary, medicolegal consideration must also be given to correct documentation of the injury, with biological swabs for DNA testing and photographs (including scale).² Without good evidence collection criminal or civil legal proceedings may be hampered.

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MRSA: the storm clouds travel from hospital to community

Editor, – We read with interest the article 'Community-acquired methicillin-resistant *Staphylococcus aureus* infection' (*Aust Prescr* 2005;28:155). In a developing country like India, a significant number of methicillin-resistant *Staphylococcus aureus* (MRSA) infections are being acquired from the community.¹ We need to curtail infection as quickly as possible and alter any long established practices which may be enhancing the development and spread of MRSA.²

The major problem is the inappropriate use of antibiotics. Given the increasing ecological pressure of antibiotics globally, bacteria respond by becoming resistant. Faced with the established scientific evidence of a relationship between antimicrobial use and MRSA prevalence, we

suggest restricting the use of certain antimicrobial classes as an adjunct to infection control practices, which should be reinforced to fight MRSA in hospitals. The prescribing that led to the selection of MRSA can be identified by studying local retrospective data.

Basic hygiene is also important in the continued fight against pathogens.³ One needs to consider the epidemiological and physical properties of staphylococci, and each component of their transmission cycle between man and the environment. There is evidence to support hygienic measures at every stage.⁴

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Medication overuse headache

Editor, – It is of great interest to note the high prevalence of medication overuse headache (*Aust Prescr* 2005;28:143–5) yet a corresponding paucity, or in many cases, absence, of warning statements on many common over-the-counter analgesics. Likewise, little prominence is given in consumer medication information leaflets about the potential for developing this disorder, signs and symptoms to be aware of, and the importance of seeking medical help should the disorder become apparent. Given the ready availability of codeine-containing combination analgesics without a prescription, the prevalence of this undiagnosed disorder in people who are unknowingly trapped in a vicious circle must be cause for concern. Moreover, it is disappointing to note a corresponding lack of suitable warnings in some of the 'triptan' product information for healthcare professionals

– a factor which must be considered in the over-prescribing of these products in the first place.

Karen Honson
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Transparency of drug information

Editor, – We have tried to emulate your T-score (*Aust Prescr* 2005;28:103) in our French drug bulletin, *la revue Prescrire*, in order to expose pharmaceutical companies' readiness to respond to our requests for information on their products.

Our rating system is similar to yours, but it specifies the provision of unpublished data and packaging information. We presented our rating system in January this year during our Pill Awards, a ceremony which recognises new drugs which have genuine benefits.

We wish you all the best with your T-score, and hope our approach will also improve access to key data. Thanks for showing the lead!

Christophe Kopp
Managing Editor
Prescrire International
Paris, France

1 - manufacturer provided detailed information, including unpublished data and packaging items



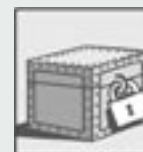
2 - manufacturer provided information limited to administrative and published data

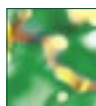


3 - manufacturer provided minimal information, mainly administrative data



4 - manufacturer provided no information





Starting steroids for asthma

Christine Jenkins, Clinical Professor, Central Clinical School, University of Sydney, Head, Asthma Group, Woolcock Institute of Medical Research, and Senior staff specialist, Thoracic Medicine, Concord Hospital, Sydney

Summary

Inhaled corticosteroids are indicated for everyone with persistent asthma. For most patients low doses are sufficient to improve clinical outcomes. Increasing the dose may not cause a proportionate improvement in the patient's symptoms and lung function. After the patient's asthma has been well controlled and stable for six to eight weeks, the dose of inhaled corticosteroid should be gradually decreased. The aim is to find the lowest dose that maintains asthma control. Inhaled corticosteroids may slow the rate of growth in children, but they do not appear to have a significant effect on their final height.

Key words: beclomethasone, budesonide, ciclesonide, corticosteroids, fluticasone.

(Aust Prescr 2006;29:63–6)

Introduction

The indications for inhaled corticosteroids and the choice of dose are two of the most important questions in asthma management today. In the past asthma management guidelines have given conflicting advice, but new data have now enabled a more consistent approach. Underpinning the recommendations in guidelines is the acknowledgement that even seemingly mild asthma can be associated with serious morbidity and even death.

The case for commencing corticosteroids

One reason why there is uncertainty regarding optimal treatment is that the natural history of mild asthma in adults is not well documented. The Global Initiative for Asthma (GINA) guidelines define patients with mild asthma as those who experience symptoms at least once a week but less than once a day over a three-month period, including exacerbations which may affect sleep and activity.¹ Australian mortality studies from almost 20 years ago suggest that some people with apparently mild asthma can have fatal attacks, although there are no longitudinal prospective studies of mild asthma to confirm this.²

Several recent, shorter studies shed light on the consequences of untreated asthma and the relative merits of treatment.^{3,4,5}

These suggest that some untreated patients with mild asthma have a frequency of severe exacerbations approaching that for moderate to severe asthma. Their symptoms will improve with low-dose inhaled corticosteroids, but if left untreated some patients will have significantly poorer lung function over time.⁶

Inhaled corticosteroids vs placebo

The largest study of asthma treatment ever undertaken⁷ involved 7241 patients who had not received regular inhaled corticosteroids. These patients had mild asthma (wheeze, cough, dyspnoea or chest tightness at least once a week but less frequently than daily) of less than two years' duration. The active treatment group received either budesonide 400 microgram daily (or 200 microgram daily if aged under 11 years) for three years. Approximately 5% of the patients taking placebo and 3% of the patients taking budesonide had at least one severe asthma exacerbation (hazard ratio of 0.56 (95% CI 0.45–0.71%)). There were also fewer courses of oral corticosteroids and better lung function in the budesonide group. However, in children under 11 years old, three-year growth was reduced by 1.34 cm compared to placebo, although the magnitude of this difference decreased over each of the three years.

In another comparative study in children⁸, budesonide (400 microgram daily) was compared to nedocromil sodium or placebo over 4–6 years. Budesonide again resulted in better lung function than placebo and was superior to nedocromil and placebo in symptom control and prevention of exacerbations. There was an effect on height, but only at 12 months and not subsequently.

Inhaled corticosteroids vs short-acting bronchodilators

In an early study of patients with newly diagnosed asthma³, an inhaled corticosteroid (budesonide 1200 microgram daily) was compared to a short-acting beta₂ agonist (terbutaline 500 microgram twice a day). After two years, patients given budesonide had better lung function, symptom control and airway responsiveness. Twelve months after patients taking terbutaline were changed over to budesonide, their lung function had not caught up to that of the patients who had taken budesonide continuously. In addition, improvement was maintained in only 33% of the patients who ceased budesonide after two years.⁴ This shows that in some patients the improvements achieved by taking a low daily dose of

budesonide for two years may be temporary. However, improvement in airway responsiveness was maintained suggesting that inhaled corticosteroids may have a disease-modifying effect at least in some patients. This study has also been interpreted as indicating that failure to use inhaled corticosteroids in asthma may permit airway remodelling which is not fully reversible, although it must be remembered that the control group received regular beta agonist, not placebo.³

Inhaled corticosteroids vs inhaled corticosteroids plus long-acting bronchodilators in mild asthma

A large study compared the effects of adding formoterol to low doses of budesonide over one year. It included 698 people with mild asthma who had not previously taken corticosteroids. They were assigned to twice-daily treatment with 100 microgram budesonide, 100 microgram of budesonide plus 4.5 microgram of formoterol, or placebo.⁵ Budesonide alone reduced the risk of severe exacerbations by 60% and the number of poorly-controlled asthma days by 48%. Adding formoterol increased lung function but had no effect on other end points. By contrast, in the 1272 patients who had previously received inhaled corticosteroid, adding formoterol was more effective than doubling the corticosteroid dose.

The case against inhaled corticosteroids

The evidence suggests that inhaled corticosteroids confer important benefits in mild persistent asthma. Although in children this may be at the price of some initial growth slowing, studies show that children taking inhaled corticosteroids over longer periods attain their predicted adult height. However, a recent multicentre study appears to challenge the role of regular inhaled corticosteroids.⁹

In this study, patients with mild persistent asthma received either budesonide 200 microgram twice a day, zafirlukast 20 mg twice a day or placebo. All patients had monthly telephone contact with the study nurse, a detailed written action plan, and were advised to use inhaled or oral corticosteroids if their asthma symptoms worsened. After one year, the group on placebo had neither significantly poorer morning peak flows nor a greater frequency of asthma exacerbations than those receiving regular corticosteroids. The authors estimated that the only treatment required was a 10-day course of inhaled budesonide on average every two years and oral corticosteroids on average every eight years. However, patients receiving intermittent inhaled corticosteroids had 26 more days of asthma symptoms over a year, and less improvement in their asthma control scores and airway hyperresponsiveness than patients taking regular budesonide.⁹

The findings of this study must be interpreted with great care because the selection criteria and an initial period of intense treatment may make the population unrepresentative of that seen in general practice.

What do asthma management guidelines currently say?

The Australian Asthma Management Handbook recommends inhaled corticosteroids for patients with mild asthma characterised by occasional symptoms, exacerbations more than 6–8 weeks apart and a normal forced expiratory volume in one second (FEV₁) when asymptomatic.¹⁰ It also states that preventive treatment is indicated if patients require reliever medication 3–4 times a week or more.

The British Thoracic Society guidelines advise starting inhaled corticosteroids when a reliever is taken three or more times a week, exacerbations of asthma have occurred in the last two years, symptoms are occurring three or more times a week, or are causing night waking one night a week.¹¹ Although the British guidelines state that a threshold for introducing inhaled steroids has never been firmly established, in recent years several large studies and meta-analyses have been published. These enable firmer recommendations and an assessment of the strength of evidence supporting the guidelines.

Who should be treated?

All the large randomised controlled trials provide strong evidence that patients with mild persistent asthma achieve and maintain control of their asthma more effectively on inhaled corticosteroids than on no treatment. These trials support the current recommendations in guidelines, that patients who are symptomatic or needing a reliever three or more times a week should receive low-dose inhaled corticosteroids, at doses up to the equivalent of budesonide 400 microgram daily or fluticasone 250 microgram daily.

The assessment of severity is important. Some patients who present with symptoms suggestive of mild asthma may have more severe disease on objective measures. By contrast, many patients who present with poor control or acute severe symptoms actually have untreated mild–moderate asthma. In patients with moderate to severe asthma, combination therapy with long-acting bronchodilators achieves greater and more rapid asthma control than inhaled corticosteroids alone.

Which starting doses should be used?

All guidelines agree that inhaled corticosteroids are the first choice preventer for adults with asthma and that the starting dose should be appropriate to the severity of the disease. For mild persistent asthma, they advise starting with low doses of inhaled corticosteroids, up to 250 microgram daily of fluticasone or beclomethasone, or 400 microgram daily of budesonide. An equivalent dose of the halogenated inhaled corticosteroid ciclesonide is 160 microgram daily.

In moderate to severe asthma, the GINA guidelines and the British Thoracic Society guidelines, based on evidence from several large trials, advocate commencing treatment with an

inhaled corticosteroid (budesonide 400–1000 microgram or fluticasone 250–500 microgram daily) and a long-acting bronchodilator.

The question of whether to start with a low dose or a higher dose has been partly answered by a recent systematic review of 13 clinical trials of inhaled corticosteroids.¹² The trials compared different starting doses in adults who had not previously taken inhaled corticosteroids for asthma of varying severity. Meta-analysis showed that there was no significant difference between high or moderate doses of inhaled corticosteroids for day and night symptom scores, and reliever use. Comparison of studies using a step-down approach versus constant low–moderate doses of inhaled corticosteroid showed no difference in lung function, symptoms or reliever medication use. Meta-analysis of the change in peak expiratory flow showed no significant difference in morning values.

The same review compared low doses (beclomethasone less than 400 microgram daily) with moderate doses (beclomethasone 400–800 microgram daily). It showed that while moderate doses improved morning peak expiratory flow and night symptom scores, there was no difference in daytime symptom scores, symptom-free days or reliever use. This review did not analyse exacerbations as the studies were relatively short (average 4–12 weeks) and did not always report exacerbations as an end point.

It is important to note that several studies show smokers with mild persistent asthma have a poor response to low-dose inhaled corticosteroids, but may respond to higher doses.¹³

Is increasing the dose of inhaled corticosteroids worthwhile?

Clinical trials and a meta-analysis show that the dose-response curve for inhaled corticosteroids is relatively flat. In a meta-analysis of eight studies in 2324 adults and adolescents, the fluticasone dose-response curve began to flatten out at 100–200 microgram a day¹⁴ with 90% of the ultimate benefit of fluticasone 1000 microgram a day achieved, on average, at 100–250 microgram a day. Therefore, in the majority of patients there is little benefit in increasing the dose above 250 microgram daily for a range of outcomes including lung function, symptom scores and reliever use.^{12,14,15,16}

Some caution should be exercised here as these studies were all of 6–12 weeks duration and were also primarily undertaken in people with sub-optimally controlled asthma who were already receiving inhaled corticosteroids. Some studies suggest this is a less steroid-responsive population than those who receive inhaled corticosteroids for the first time.¹⁷ A meta-analysis of the dose-response curve for budesonide found similar results with 90% of the maximum response being achieved with 300–600 microgram daily.¹⁸

In all these studies it is clear that a minority of patients do respond to higher doses. Importantly, the relationship between dose and adverse effects shows a much stronger dose-response effect. High doses are associated with a steep rise in the risk of adverse effects, both local and systemic.¹⁵

All guidelines emphasise the importance of ensuring good device use and checking compliance, inhaler technique and reviewing trigger factors before considering further increases in treatment if patients have not achieved good asthma control. Reduce the dose of any inhaled corticosteroid when the patient's asthma is stable to the lowest clinically effective dose that maintains good control. If good asthma control is not achieved by low-dose inhaled corticosteroids, a long-acting bronchodilator should be added.

Comparative efficacy of different inhaled corticosteroids

When an appropriate dose is chosen (see Table 1), the available inhaled corticosteroids are of similar efficacy so the choice of steroid may depend on delivery device. There is inadequate evidence to draw firm conclusions about the relative safety of each of the inhaled corticosteroids and the comparative risks of systemic adverse effects in relation to their clinical effects.

Should inhaled corticosteroids always be used alone as first-line therapy for mild asthma?

A recent meta-analysis undertaken for the National Asthma Campaign in preparation for the revised Asthma Management Handbook showed that combination therapy with an inhaled corticosteroid and a long-acting beta agonist achieved statistically greater improvements in lung function tests than inhaled corticosteroids alone in patients aged 4–80 years who had previously not received corticosteroids. These improvements may not always be of clinical importance, but combination therapy also resulted in fewer exacerbations in patients who were symptomatic on inhaled corticosteroids alone.

Conclusion

Mild persistent asthma in adults and children has better outcomes if it is treated with low-dose inhaled corticosteroids. These doses have an extremely low risk of adverse effects

Reduce the dose of any inhaled corticosteroid when the patient's asthma is stable

Table 1

Approximate dose equivalence of inhaled corticosteroids

Inhaled corticosteroid	Dose (microgram)
Beclomethasone CFC-free	100
Fluticasone	100
Budesonide	200
Ciclesonide	80

in adults. They may slow growth in children, but do not affect the attainment of final predicted height. The benefits of protection against symptoms, exacerbations and impaired lung function are strongly in favour of treatment, but this should always be considered in the context of each individual patient's needs. Low-dose inhaled corticosteroids alone achieve excellent outcomes in mild asthma, but adding a long-acting bronchodilator is indicated if optimal control is not achieved.

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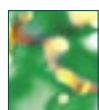
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Professor Jenkins has received honoraria for presentations at educational meetings and membership of advisory boards from GlaxoSmithKline, AstraZeneca and Altana, all manufacturers of respiratory drugs, including inhaled corticosteroids. The Woolcock Institute of Medical Research also receives research funding from these companies to perform clinical trials in asthma.

Self-test questions

The following statements are either true or false (answers on page 87)

1. The dose of inhaled corticosteroid should be gradually reduced after a patient's asthma has been stable for several weeks.
2. A large increase in the dose of an inhaled corticosteroid is unlikely to have a proportionate effect on lung function.



Managing patients taking tumour necrosis factor inhibitors

Tim Y-T. Lu, Registrar, and Catherine Hill, Staff specialist, Department of Rheumatology, Queen Elizabeth Hospital, Adelaide

Summary

Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or juvenile chronic arthritis that is unresponsive to standard disease-modifying antirheumatic drugs can now be treated with tumour necrosis factor inhibitors. These biological drugs all antagonise the actions of tumour necrosis factor, a key cytokine central to the inflammatory cascade. Their adverse effects can be severe and include sepsis, reactivation of pulmonary tuberculosis, blood dyscrasias, demyelinating syndromes, lymphoproliferative disease and precipitation of cardiac failure. Careful monitoring of patients is important.

Key words: adalimumab, etanercept, infliximab, rheumatology.

(*Aust Prescr* 2006;29:67–70)

Introduction

In recent years the treatment of inflammatory joint diseases has undergone a dramatic change with the advent of biological drugs. Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile chronic arthritis are potential candidates for this new therapy. Biological drugs are usually prescribed if the patient's condition has been resistant to treatment with standard disease-modifying antirheumatic drugs or if the patient has been unable to tolerate them.¹ In clinical trials biological drugs have been superior to disease-modifying antirheumatic drugs in achieving disease remission and retarding bony destruction. The most common biological drugs

used today belong to the class known as tumour necrosis factor (TNF) inhibitors. This class includes infliximab, adalimumab and etanercept. As these drugs are being used more frequently, it is important to be familiar with the principles of managing patients during treatment in the community.

Mechanism of action

Tumour necrosis factor is a critical pro-inflammatory cytokine in the cascade of inflammatory joint diseases.² It mediates many of the inflammatory processes in rheumatoid arthritis including immune-cell activation and proliferation, apoptosis and regulation of leucocyte movement. TNF inhibitors act to neutralise the actions of this cytokine by binding to TNF or its receptor. Infliximab and adalimumab are recombinant monoclonal antibodies while etanercept is a soluble TNF-receptor fusion protein.

In randomised double-blind placebo-controlled trials TNF inhibitors have significantly improved the clinical and radiological outcomes for patients whose rheumatoid arthritis has been poorly controlled by standard disease-modifying antirheumatic drugs. The majority of trials involved combination therapy with methotrexate.

Administration of TNF inhibitors

Infliximab is given by intravenous infusion while adalimumab and etanercept are self-administered as subcutaneous injections (Table 1). For rheumatoid arthritis infliximab is commenced at 3 mg/kg of body weight at 0, 2 and 6 weeks, then every 8 weeks. (In patients with an incomplete response, the maintenance dose may be gradually increased to a maximum of 10 mg/kg.) The dose of adalimumab is 40 mg fortnightly, while etanercept is given at 25 mg twice weekly or 50 mg once a week.

Table 1

Dose schedule for TNF inhibitors

Drug	Presentation	Route of administration	Dose in rheumatoid arthritis
Infliximab	Powder for reconstitution	Intravenous infusion	3 mg/kg repeated after 2 weeks and 6 weeks, then every 8 weeks
Adalimumab	Pre-filled syringe	Subcutaneous injection	40 mg repeated every 2 weeks
Etanercept	Powder for reconstitution	Subcutaneous injection	25 mg twice a week, or 50 mg once a week

TNF tumour necrosis factor

Indications

TNF inhibitors are indicated for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile chronic arthritis, however they are not subsidised by the Pharmaceutical Benefits Scheme for all these indications. The prescription of TNF inhibitors by a rheumatologist or clinical immunologist for adult inflammatory joint diseases must follow strict guidelines as set out in the Schedule of Pharmaceutical Benefits. These guidelines are under constant review and are updated to reflect results from new clinical trials. Psoriatic arthritis, for example, is an indication currently under review. As of June 2005 all TNF inhibitors are indicated for rheumatoid arthritis irrespective of the patient's rheumatoid factor status. In addition, infliximab and etanercept are indicated for ankylosing spondylitis. Only etanercept has been approved for juvenile chronic arthritis.

The efficacy of TNF inhibitors on the signs, symptoms, function, quality of life and retardation of radiological progression in patients with rheumatoid arthritis has been shown in a variety of roles. These include monotherapy, combination with methotrexate and in patients who have not previously been treated or have failed to respond to disease-modifying drugs. Combining a TNF inhibitor, especially infliximab, with methotrexate increases efficacy.

As there have been no direct head-to-head trials, no single TNF inhibitor can be said to be more effective than another. The choice of drug therefore depends on the patient's preference and the prescriber's experience with the particular TNF inhibitor. This includes considering the contraindications (see Box 1).

Before treatment

As part of the pre-treatment assessment, patients should have a chest X-ray to exclude latent pulmonary tuberculosis and congestive cardiac failure. The full blood count, liver function tests, hepatitis B and C serology, inflammatory markers

Box 1

Contraindications to TNF inhibitors¹¹

Previous untreated tuberculosis
Recurrent chest infections/bronchiectasis
Septic arthritis within 12 months
Infected prosthesis
Indwelling urinary catheter
Multiple sclerosis/demyelinating illness
Malignancy within 10 years (apart from fully resected basal cell carcinoma more than five years before)
Pregnancy and lactation
Congestive heart failure
Chronic cutaneous ulceration (but not pyoderma gangrenosum)

(CRP, ESR), and anti-nuclear and anti-double-stranded DNA autoantibodies should be checked before therapy. The presence of latent pulmonary tuberculosis warrants eradication therapy, usually for nine months, before starting a TNF inhibitor. This is best managed by a physician experienced in tuberculosis care.

Adverse effects

Given that TNF inhibitors are relatively new drugs, their long-term safety is still being established. From their mechanism of action it is predicted that there will be an increase in the incidence of infection and possibly secondary malignancy.

The pharmacovigilance database of the Australian Rheumatology Association contains many case reports of toxicities related to TNF inhibitors. These include severe injection-site reactions, infection (particularly mycobacterial and opportunistic organisms), lymphoproliferative disorders, lupus-like autoimmune disease, demyelinating disease, haematological abnormalities including aplastic anaemia, and precipitation of cardiac failure. These findings are important as infection (particularly pulmonary infection), cardiovascular disease and osteoporosis are the three conditions that cause the greatest morbidity and mortality in rheumatoid arthritis.³

Injection-site reactions

In patients receiving adalimumab and etanercept, injection-site reactions present as mild erythema, itching, pain or swelling, usually lasting a few days. It is important that patients mix etanercept correctly before injecting it. During infusion of infliximab some patients complain of headache and nausea. An immediate hypersensitivity response suggested by the development of rash, urticaria or anaphylaxis is rare. Patients rarely cease therapy because of injection-site reactions.

Infection

Many infections can occur. These include serious bacterial infections, tuberculosis, atypical mycobacterial infection, aspergillosis, histoplasmosis, listeriosis, *Pneumocystis jiroveci* pneumonia and cryptococcal infections. Infections may be more common in patients over 65 years of age than in younger patients.⁴

Latent viral infections may be reactivated. These include herpes simplex virus (including genital herpes), herpes zoster virus and cytomegalovirus.

Reactivation of tuberculosis has been reported in association with all TNF inhibitors. This usually occurs within the first 2–5 months of commencing treatment. The majority of cases present as extra-pulmonary and disseminated tuberculosis. A recent study has shown that screening for previous pulmonary tuberculosis with chest X-ray and Mantoux testing followed by appropriate treatment before starting TNF inhibitors, significantly reduces the incidence of tuberculosis.⁵

Lymphoproliferative disease

Cases of lymphoma have been reported in patients taking TNF inhibitors. The incidence of lymphoma and leukaemia is already increased in patients with rheumatoid arthritis, particularly those with high disease activity. Epidemiological studies differ on whether there is an additional risk of lymphoproliferative disorders among patients with rheumatoid arthritis who are treated with TNF inhibitors.^{6,7} There is no indication that patients with rheumatoid arthritis taking TNF inhibitors are at increased risk of other tumours.

Blood dyscrasias

Medically significant thrombocytopenia and leucopaenia have been reported with TNF inhibitors. However, pancytopenia including aplastic anaemia rarely occurs. These abnormalities are generally reversible upon cessation of the drug.

Lupus-like autoimmune responses

Positive antinuclear antibodies develop in over 50% of patients with rheumatoid arthritis during treatment with infliximab and 13% develop antibodies to double-stranded DNA.⁸ With etanercept, 11% of patients develop a new antinuclear antibody and 2% develop double-stranded DNA antibodies.⁹ Despite the high rate of autoantibodies, clinical manifestations of drug-induced systemic lupus erythematosus are rare.

Demyelinating syndromes

Exacerbations of previously quiescent multiple sclerosis and the onset of other demyelinating diseases (such as optic neuritis) have been reported in patients taking TNF inhibitors. Symptoms included paraesthesia, visual disturbance and confusion.

Cardiac failure

Patients with heart failure have elevated concentrations of TNF. Trials of etanercept and infliximab in heart failure were stopped early because there was no evidence that TNF inhibitors were of benefit. In the case of infliximab, mortality increased.¹⁰ TNF inhibitors are therefore contraindicated in patients with heart failure (New York Heart Association class III and IV).

Pregnancy and lactation

There are no clinical data for pregnant or lactating women being treated with TNF inhibitors. Animal studies were inconclusive with regard to the embryofetal toxicity so their use during pregnancy is not recommended. Women of childbearing age should be advised to use effective contraception during therapy.

Practice points (Box 2)

Before starting a patient on TNF inhibitors, immunisations should be brought up to date. Live vaccines should not be given to people receiving TNF inhibitors. There is no contraindication to yearly influenza and five-yearly pneumococcal vaccination. Varicella vaccination should be considered for individuals who

are seronegative. Routine screening for latent tuberculosis is mandatory before treatment. It is also important to remain clinically vigilant for reactivated tuberculosis, as a delayed diagnosis may lead to increased morbidity. Patients are reassessed after 8–12 weeks of treatment to see if they qualify for continuation of the drug. Routine clinical examination for signs of cardiac failure and pulmonary sepsis should be performed at each visit. Measurement of the full blood count at baseline and at regular intervals (initially monthly then three-monthly thereafter) is needed to monitor for blood dyscrasias. This may differ if patients are on other therapy such as methotrexate or leflunomide.

Cold application, simple analgesic drugs such as paracetamol, and antihistamines are adequate for treating minor injection-site reactions in patients administering adalimumab and etanercept. Rotation of injection sites is also a useful strategy to prevent skin irritation. Slowing the rate of infusion may ameliorate the infusion-related adverse reactions to infliximab.

The development of systemic or localised infection warrants cessation or postponement of TNF inhibitor therapy. Treatment can be continued after the infection has resolved. For patients exposed to chickenpox or shingles during therapy their serological status should be obtained. Those with a negative serology will require treatment with zoster immunoglobulin to prevent disseminated infection. For patients undergoing major surgery, it is prudent to interrupt TNF inhibitor treatment until the risk of postoperative infection has declined. Minor surgery such as dental procedures does not require cessation of therapy. When patients develop serious complications during treatment, the TNF inhibitors are to be stopped. Specialist advice should be sought immediately.

Box 2

Practice points

- Update immunisations, including yearly influenza vaccines
 - avoid live vaccines during treatment
- Clinical examination for signs of cardiac failure and pulmonary sepsis
- Monthly complete blood count, renal and liver function tests if on methotrexate, C-reactive protein and erythrocyte sedimentation rate
- Monitor for drug toxicities
- Withhold treatment if:
 - hypersensitivity
 - active sepsis
 - malignancy
 - pregnancy or lactation
 - worsening congestive cardiac failure
 - surgery

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

3. Tumour necrosis factor inhibitors can reactivate tuberculosis.
4. Influenza vaccination is contraindicated during treatment with tumour necrosis factor inhibitors.

Book review

Pocket guide to lung function tests: explanations without equations. 2nd edition. Hancox B, Whyte K.

Sydney: McGraw-Hill; 2006. 176 pages. Price \$34.95

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This little book first appeared in 2001 with a reprint in 2003. The appearance of a second edition shows that it has found a market. Although not specifically spelt out, it appears that the second edition has been 'revised throughout' with the addition of chapters 12 and 13 dealing with the preoperative assessment for thoracic surgery and fitness for flying. The basic approach in the interpretation of tests is of pattern recognition rather than requiring much knowledge of pure respiratory physiology and I have no quarrel with that. Most of us read an ECG without much knowledge of cardiac electrophysiology.

In nine chapters covering the commonly used tests, from spirometry to cardiopulmonary exercise tests, the authors present a commonsense approach in a compact yet highly readable text laced with clear diagrams and clinical examples. Things become a little more esoteric and perhaps premature

in chapter 10 (exhaled nitric oxide) and some 'non-routine tests' are discussed in chapter 11.

With so much useful information packed into a small book (the pages are 18 x 11.5 cm) it is hard to be critical, but a few minor things caught my eye. There is inconsistency in the use of the symbols so beloved by respiratory physiologists (for example VD in the glossary and V_D in the text). Despite stating that the book uses mmHg rather than kPa units, chapter 13 uses kPa. Mixed spirometric patterns would be better introduced in chapter 1 rather than chapter 4. A pitfall not mentioned with oximetry is the dependence on adequate circulation. The delay in elevation in carbon dioxide tension in ventilation/perfusion mismatching has less to do with solubility and more to do with the complexity of the carbon dioxide-oxygen-haemoglobin relationships in hypoxia, and even multi-breath nitrogen clearance will only be linear if plotted semi-logarithmically.

The book can be read slowly in 90 minutes and this would be time well spent by candidates for postgraduate exams, advanced trainees in general and thoracic medicine, respiratory scientists and nurses. There are good references for further study and an excellent index. Whether it will be carried around in many pockets is another matter, but it is a compact reference which deserves a wide readership.

Medicinal mishap

Serotonin syndrome precipitated by an over-the-counter cold remedy

Prepared by Chris Cameron, Advanced trainee in general medicine, Hutt Hospital, Lower Hutt, New Zealand

Case

A 46-year-old man presented to the emergency department with a three-day history of headache and vomiting, and one day of confusion and fevers. His medical history included an old spinal injury and his usual medications were methadone 70 mg daily, gabapentin 3.6 g daily and citalopram 40 mg daily. One week before admission he had a tooth extracted and two days later developed a 'head cold', from which he recovered.

At presentation the patient was febrile (39.1°C) and sweating. His pulse fluctuated between 80 and 140 beats/minute, and his blood pressure between 170/86 and 214/100 mmHg. He had a score of 12 on the Glasgow Coma Scale and was unable to sustain conversation. His dental socket looked clean and there was no clinical evidence of infective endocarditis, but he had generalised abdominal tenderness. Neurological examination revealed dilated reactive pupils and no meningism, but he had increased tone in both legs, with brisk reflexes and clonus at both ankles. Investigations revealed a white cell count of 21.1×10^9 , predominantly neutrophils, and a C-reactive protein of 15. Chest and abdominal X-rays and urine were normal.

The diagnosis was sepsis, probably from an intracerebral or abdominal source, so broad-spectrum antibiotics were started. However, the patient had a normal brain scan and the lumbar puncture found no evidence of infection. The patient's condition remained unchanged over the next 24 hours. An abdominal CT scan and an echocardiogram were ordered, but were normal.

On reviewing the history, the patient recounted taking 'Night and Day' capsules containing dextromethorphan as a cough suppressant for his head cold for two or three days before becoming unwell. A presumptive diagnosis of serotonin syndrome was made and the creatine kinase was found to be elevated (354 IU). After 48 hours without citalopram, the patient recovered fully.

Comment

Serotonin syndrome is a triad of mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities¹, with a mortality of about 11%. It is caused by excessive stimulation of serotonin receptors, often as a result of interactions between serotonergic drugs.² Severe cases of serotonin syndrome can cause rhabdomyolysis, with raised creatine kinase and metabolic acidosis.¹

Many drugs have been implicated, including monoamine

oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), opioid analgesics including tramadol, antimigraine treatments and antibiotics, for example linezolid. Over-the-counter cough and cold remedies have occasionally been implicated³, but no case reports involving dextromethorphan and citalopram were found in a literature search.

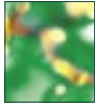
Several mechanisms may have contributed to the development of serotonin syndrome in this patient. Firstly, dextromethorphan is a potent inhibitor of serotonin reuptake, similar to SSRIs.⁴ The combination with citalopram would therefore be expected to markedly increase the concentration of serotonin at the synapse. Secondly, SSRIs act as cytochrome P450 2D6 inhibitors⁵, and although citalopram is a weak inhibitor, this may have contributed to elevated concentrations of dextromethorphan, which is a substrate of CYP 2D6.⁶ Finally, methadone increases brain serotonin in laboratory animals⁷, but the patient had been taking methadone and citalopram for two years, without ill-effect.

Estimates from previous studies are that 85% of doctors may be unaware of serotonin syndrome as a clinical entity.⁸ Some community pharmacists may also be unaware that serotonin syndrome can be precipitated by over-the-counter cold remedies. As it can cause significant morbidity and mortality, health professionals need to consider the possibility of serotonin syndrome. This case also shows the value of taking a thorough drug history, including over-the-counter preparations.

Acknowledgement: Dr Sisira Jayathissa

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Drug treatment of neuropathic pain

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Summary

The distress evident in many patients with neuropathic pain demands a trial of drug treatment. Evidence for satisfactory outcomes is limited so patients must be fully informed of the likely benefits and adverse effects of any trial. Antidepressants, anticonvulsants and opioids are the main drugs used to treat neuropathic pain. Management by a multidisciplinary pain clinic should be considered for patients with chronic, severe and disabling neuropathic pain.

Key words: anticonvulsants, antidepressant drugs, opioids.

(Aust Prescr 2006;29:72-5)

Introduction

Neuropathic pain is defined as pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. One example is the phantom limb pain patients feel after amputation, but there are many possible causes (Table 1). The pain may be spontaneous, stimulus-evoked, or a combination of both. Its characteristics are often different from those of other types of pain, such as the nociceptive pain experienced after an injury.

In neuropathic pain the central neurons are sensitised, so that they fire spontaneously, or abnormally. If this sensitisation persists the pain becomes chronic and is often difficult to treat.

Clinical evaluation

Doctors are familiar with taking a history of spontaneous pain to establish its location, temporal pattern, quality, severity, exacerbating and relieving factors. In neuropathic pain this approach needs to include other components:

- cognitive (that is, psychological determinants of pain such as fear, avoidance and catastrophising)
- affective (for example, anxiety, depression, frustration, anger, demoralisation)
- functional (for example, the impact of pain on activities and quality of life).

There are considerable overlaps in the pain descriptors between nociceptive and neuropathic pain. Some patients may have nociceptive and neuropathic pain. Clues to a neuropathic origin are its continuous nature (as opposed to movement-induced pain), burning and shooting qualities. There are also associated

symptoms (derived from irritation to non-noxious afferent neurons) such as numbness, dysaesthesia and formication in anatomically recognised patterns.

Important components of the assessment are the examination of the patient for evidence of abnormal stimulus-evoked pain¹ (see box), usually indicating central sensitisation, and routine neurological examination for sensory loss, particularly warm and cold sensibility, in recognisable anatomic patterns. The most confusing element is the extension of areas of stimulus-evoked pain beyond the anatomical boundary of the area receiving the stimulus. This occurs because central sensitisation does not respect these boundaries.

Table 1

Common causes of neuropathic pain

Peripheral	Central
Trauma blunt trauma (5%) radiculopathy iatrogenic (surgery)	Stroke (8%)
Ischaemia	Multiple sclerosis (58%)
Entrapment	Spinal cord injury (50%)
Polyneuropathy hereditary metabolic (diabetes 11%) toxic immune infections paraneoplastic nutritional	Syringomyelia/bulbia (75%)
Stump and phantom pain	
Post-herpetic neuralgia	
Neuralgias trigeminal glossopharyngeal occipital	
Neoplastic tumour invasion radiation surgery chemotherapy	

The percentages are the reported proportions of patients with each condition who have neuropathic pain. For example, 11% of patients with diabetes have neuropathic pain.

Sensory abnormalities in neuropathic pain ¹

Hypoaesthesia	– reduced touch sensation
Hypoalgesia	– reduced response to painful stimuli
Paraesthesia	– tingling sensation
Hyperalgesia	– increased response to painful stimuli
Allodynia	– pain due to a stimulus which does not normally produce pain
Hyperpathia	– an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. (This often explosive reaction is associated with continuing pain after cessation of the stimulus.)
Dysaesthesia	– an unpleasant abnormal sensation, whether spontaneous or evoked

The investigations of neuropathic pain vary according to the suspected cause of each syndrome. A cause should be sought in each case, and treatment of that cause may contribute to alleviation of symptoms and retard progression of the condition. For example, irritation caused by a prosthesis may be contributing to a patient's pain following amputation.

Mechanisms of neuropathic pain

Both peripheral and central neuropathic pain syndromes rely on sensitisation of neurons in central pathways normally associated with the transmission of noxious stimuli. These pathways are the dorsal horn of the spinal cord, the spinothalamic tract (for somatic structures) and dorsal columns (for viscera), the thalamus, and the sensorimotor, limbic, prefrontal and insula cortex.

The sensitisation of neurons is characterised by increased background activity, a lowered threshold for activation (for example, by non-noxious stimuli), and the spread of receptor fields (increased firing of spatially diverse neurons ensuring larger areas of the body are represented in the conscious recognition of pain). Sensitisation is usually associated with partial denervation plus stimulation from continuously active afferent input (peripheral or central) which depends on activation of axonal sodium channels. Pain in the presence of complete deafferentation is rare, but much feared because of its lack of response to treatment.

The sensitisation of nociceptive neurons is the result of increased activity in excitatory pathways where substance P, excitatory neurotransmitters and adenosine triphosphate act via voltage-gated calcium channels and/or diminished activity in inhibitory pathways via gamma-aminobutyric acid (GABA) and glycine.

The most difficult chronic neuropathic pain syndromes to treat are associated with the irreversible loss of neurons. Mostly, this is by apoptosis initiated through both intrinsic calcium modulated systems in neurons, or by extrinsic inflammatory processes. This has led to the concept of chronic pain as an

(irreversible) disease within the nervous system. The implication is that neuropathic pain should be treated early in the course of its development to prevent it becoming chronic.

Treatment

Non-drug treatments can help to control the patient's pain. A multidisciplinary approach may be required.

Current drug treatments are focused on dampening the neuronal input to consciousness by suppressing axonal function (for example sodium channel blockade) or interfering with neurotransmission (blockade of excitatory and inhibitory neurotransmitters and modulators). This approach is likely to be greatly modified over the next few years as the biology underlying these processes is better understood.

There are significant weaknesses in the trials that underpin current treatments for neuropathic pain. Large studies have been undertaken predominantly in patients with pain from diabetic neuropathy and post-herpetic neuralgia. The results of these studies are then extrapolated to other neuropathic pain states. When one considers that a successful outcome is deemed to be a 50% reduction in pain in 50% of patients, it is easy to appreciate we have a long way to go before we have highly effective treatments for neuropathic pain.

Unfortunately, the cost of trials is high, and they are generally only undertaken by drug companies. This limits the likelihood of 'head to head' trials and trials of drug combinations.² This means comparisons between drugs and drug classes must depend on analysis of numbers needed to treat and numbers needed to harm, despite criticisms of this methodology. These comparisons generally favour tricyclic antidepressants over anticonvulsants and opioids.³

Neuropathic pain is likely to be an ongoing complaint. A trial of treatment in an individual patient can therefore be planned. Due consideration is given to selection of measures of pain, activity, mood and adverse effects, in agreement with the patient before and after an agreed trial period. One drug should be trialled at a time, although later consideration may be given to trials of drug combinations.

The drugs used to treat neuropathic pain can be conveniently divided into two types: medications used to treat other conditions but found to be useful in reducing pain from nervous system damage, and analgesics.

Antidepressants

Tricyclic antidepressants have long been used to treat all forms of neuropathic pain.³ Clinical experience would suggest that antidepressants are often very helpful, especially in cases of peripheral neuropathic pain, as long as the starting dose is low (for example amitriptyline 10–12.5 mg at bedtime) and is increased slowly at intervals of a few days to a week. The maximum effective dose is disputed, but usually 75 mg at night is sufficient. The mean numbers needed to treat to obtain

a beneficial outcome, set at 50% reduction of pain, calculated in the early studies of amitriptyline were impressive at 2–3, but failed to take account of high dropout rates. Doses higher than 75 mg are associated with anticholinergic adverse effects on brain, bladder, bowel and blood pressure. Dry mouth is inevitable but weight gain is uncommon. If a benefit is to be obtained, it occurs within a few days of starting treatment. This benefit appears to be independent of the antidepressant effect.

Evidence for the use of other antidepressants apart from tricyclics is very limited. Venlafaxine may be useful.⁴ Again, the dosing advice is to 'start low and go slow'. The effective dose may be as much as 225 mg daily.

Anticonvulsants

There is a long tradition of using antiepileptic drugs in neuropathic pain, but they can all cause adverse effects such as drowsiness, dizziness and ataxia. Until recently there was almost no evidence of efficacy, but newer drugs such as gabapentin and pregabalin have been more extensively studied in patients with diabetic neuropathy and post-herpetic neuralgia. These two drugs modify the action of voltage-gated calcium channels of primary afferents so appear to interfere with the release of substance P, noradrenaline and the excitatory amino acid neurotransmitter glutamate.

The number of patients who need to be treated with gabapentin for one to have a 50% reduction in pain has been calculated as five.^{3,5,6} Gabapentin should be started at 100 mg daily in older frail people and those with renal impairment, and the dose increased every few days to achieve symptomatic relief of pain. The effective dose ranges widely.

Pregabalin has a similar action to gabapentin, but caution is needed as experience of the drug is limited. Efficacy data are available in post-herpetic neuralgia⁷ and painful diabetic neuropathy.⁸ The number needed to treat is 4.2.³ Caution is needed with the old and frail, and a slow increment from 75 mg daily to 75 mg twice a day by the end of the first week is likely to be better tolerated. Patients rarely want to exceed 150 mg twice a day because of the adverse effects common to antiepileptic drugs, plus blurred vision and oedema. Gabapentin and pregabalin should only be used after checking renal function, preferably by calculated creatinine clearance, as they are renally excreted.

Lamotrigine is another antiepileptic drug which has been used in neuropathic pain, but of the six randomised controlled trials so far reported, none has exceeded 40 patients. Similarly, there are no large randomised controlled trials of valproate and trials of topiramate have had conflicting results. There are no substantive studies to support the use of carbamazepine in the treatment of neuropathic pain, in contrast to its use in the true neuralgias. Drug concentration monitoring is not used in the treatment of neuropathic pain with antiepileptic drugs. Tolerance of the adverse effects is the limiting factor.

Analgesics

Simple analgesics are often ineffective in neuropathic pain, but frequently there is a nociceptor component to the patient's pain. All analgesics have adverse effects and are therefore introduced incrementally over weeks to achieve a balance between pain relief and tolerance of adverse effects.

Opioids

Pain which has not been responsive to other drugs may respond to opioids. This benefit is not seen in pain syndromes of uncertain origin including complex regional pain syndrome type 1 (reflex sympathetic dystrophy), fibromyalgia, irritable bowel syndrome and tension headache.

Opioids are started at low doses, such as oxycodone 5 mg or morphine 10 mg twice daily. These are increased progressively over days to a level which provides symptomatic relief with tolerable adverse effects. Patients can then be switched to controlled release formulations twice daily. If patients do not respond to moderate doses, such as oxycodone 40 mg or morphine 60 mg twice daily, do not increase the dose further as they are unlikely to respond to higher doses which have an increased risk of adverse effects.⁹ Although prophylactic use before a pain-inducing activity is sometimes warranted, slow-release formulations, taken at fixed time intervals regardless of the presence of pain, are to be preferred to using analgesia only when pain occurs. Other medications to treat the common adverse effects of opioids may be needed. Constipation will almost invariably need to be treated.

For tramadol the number needed to treat was 3.9 in one meta-analysis³, but the doses used were relatively high. This may increase the chance of adverse effects such as headache, seizures and, especially when used in combination with an antidepressant, the serotonin syndrome.¹⁰

Other medications

There is a limited role for other drugs when antidepressants, anticonvulsants and opioids have not worked. This often occurs during exacerbations of pain. The drugs tried have included ketamine, an N-methyl-D-aspartate antagonist delivered by parenteral and nasal routes, usually in a specialist setting, clonidine by the intrathecal and epidural routes, and local anaesthetics by topical, oral, parenteral, epidural and intrathecal routes. There is no indication for the use of non-steroidal anti-inflammatory drugs in patients with neuropathic pain unless there is clear clinical evidence that a nociceptor pain source is contributing to the patient's pain.

Neuralgias

The treatment of neuralgias, apart from post-herpetic 'neuralgia', can be considered separately as they have a somewhat different pathophysiology and are not associated with sensory abnormalities on examination. They are triggered by non-noxious stimuli, leading to ectopic spread of afferent

impulses from large to small neurons, predominantly in dorsal root ganglia rather than sensitisation in central pathways as occurs in neuropathic pain. This manifests clinically as explosive high frequency bursts of paroxysmal pain.

These syndromes are generally responsive to carbamazepine, presumably acting as a sodium channel blocker. It is used in doses sufficient to alleviate paroxysms without producing unacceptable adverse effects. The starting dose varies, but, because these patients are often old and frail, should usually be 50 mg or 100 mg. Carbamazepine may even be effective at this dose, but usually needs to be increased over a few days according to the patient's tolerance of adverse effects such as drowsiness and dizziness. When to decrease the dose once an attack is controlled is always problematic. An attempt should be made to do so 1–2 weeks after control has been achieved. Despite gradual reduction it is often difficult to cease the dose and so a maintenance dose may be needed.

If carbamazepine is unhelpful, there are a number of second-line drugs, none of which has been adequately studied. They include oxcarbazepine, lamotrigine, gabapentin and baclofen. Early referral for surgery should be considered if control is difficult to obtain in patients with trigeminal neuralgia.

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[R] randomised controlled trial

[S] company sponsored trial or publication

Dr Helme is a member of the neuropathic pain advisory board for pregabalin, manufactured by Pfizer.

See also **Dental notes**, page 82

Self-test questions

The following statements are either true or false (answers on page 87)

5. A sensory deficit is often present in areas of the body affected by neuropathic pain.
6. Selective serotonin reuptake inhibitors can effectively reduce neuropathic pain in most patients.

Patient support organisation

Trigeminal Neuralgia Association of Australia

The Trigeminal Neuralgia Association provides information and support to patients, families and friends of those with trigeminal neuralgia. In addition there are support groups in most states (New South Wales, Victoria, Queensland and South Australia). Members receive monthly newsletters. The Association is affiliated with the US Trigeminal Neuralgia Association.

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US website: www.tna-support.org



Treatment of adult leukaemias

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Summary

Improved understanding of the molecular causes of leukaemia is altering the approach to management. Acute myeloid leukaemia is managed with chemotherapy according to the patient's prognostic factors, but stem cell transplantation may be an option. Imatinib is now available for the treatment of chronic myeloid leukaemia, but whether it should be preferred over transplantation is uncertain. When chronic lymphocytic leukaemia progresses, it can be managed with chemotherapy, in which fludarabine has an increasing role.

Key words: antineoplastics, imatinib, stem cell transplantation.

(*Aust Prescr* 2006;29:76–9)

Introduction

Leukaemia in adults is not a single disease entity. It includes a number of different diseases with widely varying molecular and cytogenetic features, clinical characteristics, prognoses and responses to treatment. The most common leukaemias in adults are acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia. (Acute lymphoblastic leukaemia occurs in adults as well as children, but at only around 10% the frequency of acute myeloid leukaemia. Although adults are given the same treatment as children, the outcomes are worse.)

Over the past decade there have been major advances in the diagnosis, classification and management of leukaemia in adults. This is due largely to improved understanding of the molecular basis of these diseases. Improvements in supportive care, the introduction of targeted therapies and increasing use of non-myeloablative conditioning regimens for allogeneic stem cell transplantation have all transformed the treatment of patients with leukaemia. This means that more patients may be offered treatment and that more can be expected to survive for longer periods.

Acute myeloid leukaemia

The incidence of acute myeloid leukaemia increases with age. It accounts for 80% of adult acute leukaemias. Most patients present with clinical features of bone marrow failure such as recurrent infection, bleeding and fatigue. Many experience bone

pain, weight loss, sweats and fevers. While the majority have no predisposing factors to explain the development of the disease, some patients will have a history of a haematological disorder (such as myelodysplasia) or exposure to cytotoxic drugs.

Studies of outcomes after treatment for acute myeloid leukaemia have shown that the most important prognostic factor is the type of cytogenetic abnormality present at diagnosis.¹ There are three main prognostic groups:

- a favourable group (30%) comprising patients with acute promyelocytic leukaemia and patients with acute myeloid leukaemia with chromosomal translocations involving the core-binding factor genes [t(8;21), inv(16)]
- an unfavourable group (20%) comprising patients with complex cytogenetic abnormalities and with abnormalities of chromosomes 5, 7, 11
- an intermediate group (50%).

Other than the cytogenetic risk category, the main determinant of management is the patient's age. Patients older than 65 years are more likely to have drug-resistant disease and frequently have major comorbidities. They are less able to tolerate intensive chemotherapy, so they are often offered palliative therapy, supportive care and/or palliative chemotherapy with drugs such as oral hydroxyurea, oral etoposide or intermittent intravenous cytosine arabinoside.

Younger patients with acute myeloid leukaemia require treatment with intensive chemotherapy, which is generally given in a specialist haematology unit. Chemotherapy for acute myeloid leukaemia currently involves the pyrimidine analogue cytarabine arabinoside. This is given alone in high doses or in lower doses in combination with an anthracycline (such as idarubicin or daunorubicin) and a podophyllotoxin (etoposide). A treatment course consists of induction therapy followed by 1–3 cycles of consolidation therapy. Multicentre studies show that about 80% of patients under 60 years of age achieve remission, 10% die of treatment-related complications and 10% have primary resistance. Overall, 30–45% of patients remain disease-free long term.² There are limited data to support maintenance therapy for acute myeloid leukaemia.

Allogeneic haematopoietic stem cell transplant (see box) may be an option in first complete remission for patients with HLA*-identical sibling donors. Patients with poor risk factors may be offered a transplant during their remission from either

* HLA human leucocyte antigen

sibling or unrelated donors. Transplantation is the treatment of choice for patients with relapsed disease who achieve a second complete remission. If haematopoietic stem cell transplantation is not an option following relapse, the patient is generally given palliative treatment.

Acute promyelocytic leukaemia

Acute promyelocytic leukaemia accounts for about 15% of all cases of acute myeloid leukaemia (almost always in patients under the age of 60). It results from a translocation between chromosomes 15 and 17. This alters the function of a receptor protein for vitamin A derivatives (retinoids) in the cell nucleus and ultimately prevents apoptosis.

The combination of a synthetic retinoid (all-*trans*-retinoic acid (tretinoin)) and the anthracycline idarubicin, induces maturation and apoptosis of leukaemic cells. This leads to remission in most cases and to long-term disease-free survival in over 70% of patients.³ Arsenic trioxide has also shown promise in the treatment of *de novo* and relapsed/refractory disease. Its role in therapy is the subject of intense research interest.

Chronic myeloid leukaemia

Chronic myeloid leukaemia accounts for 7–15% of all adult leukaemias. It is thought to result from the clonal transformation of a haematopoietic stem cell and is historically significant because it was the first disease in which a specific chromosomal abnormality was directly linked to pathogenesis.

In chronic myeloid leukaemia a reciprocal translocation of the Abelson oncogene (c-abl) from chromosome 9 to the breakpoint cluster region (bcr) on chromosome 9 leads to the

formation of a new fusion gene (bcr-abl) on chromosome 22 (the Philadelphia chromosome). This in turn leads to the production of an abnormal protein product (bcr-abl fusion protein) with increased tyrosine kinase activity which functions to promote cell survival and proliferation and to inhibit apoptosis.

Chronic myeloid leukaemia is characterised by leucocytosis, thrombocytosis and splenomegaly, although 40% of patients are asymptomatic. Chronic myeloid leukaemia has three phases: chronic, accelerated and blastic. The natural history is progression from a 'benign' chronic phase to fatal blast crisis over three to five years.

The aim of treatment is to eliminate all evidence of the Philadelphia chromosome or bcr-abl mRNA from the bone marrow and blood (as detected by polymerase chain reaction (PCR) or fluorescence *in situ* hybridisation (FISH)). Long-term survival is most likely in patients who achieve at least a complete cytogenetic response (no Philadelphia chromosome-positive cells detectable in bone marrow).

Initial treatment generally consists of hydroxyurea. This oral cytotoxic drug is effective in reducing the elevated white cell count, but it does not prolong survival. Until recently, most patients were treated with hydroxyurea, busulfan, interferon alfa and/or cytosine arabinoside, with allogeneic haematopoietic stem cell transplant being offered to a younger patient when an HLA-compatible donor is available.

The decision to offer transplantation is generally based upon consideration of the patient's age, phase of the disease and the availability of a suitable donor. Younger patients (under 55) who receive a transplant from an HLA-identical sibling donor during the chronic phase and within a year of diagnosis have a 70% chance of cure. The risks of transplantation are greater in other situations and even in those with the best prognosis the transplant-related mortality is still 5–10%.

Imatinib

The treatment of chronic myeloid leukaemia has recently been revolutionised by the introduction of targeted therapy. Imatinib mesylate is an orally-administered tyrosine kinase inhibitor directed against the bcr-abl fusion protein. It induces complete haematological response and complete cytogenetic response (absence of Philadelphia chromosome) in approximately 75% of newly diagnosed patients.

Despite its early promise, approximately 10% of patients are primarily resistant to imatinib and a further 15–20% may develop resistance after initially responding to the drug.⁴ (Resistance is generally due to point mutations in the bcr-abl kinase region.⁵) Despite these reservations, the advent of molecular therapy means that there is now a distinct possibility that chronic myeloid leukaemia may eventually prove to be a curable condition.

Haematopoietic stem cell transplantation

- Uses multipotent haematopoietic progenitor cells (stem cells) as part of therapy aimed at eliminating underlying disease and restoring normal haematopoietic and immune function
- May be allogeneic (another individual acts as a donor) or autologous (the patient acts as their own source of stem cells)
- Allogeneic transplants may source stem cells from related or unrelated volunteer donors
- Stem cells may be obtained from bone marrow, peripheral blood or umbilical cord blood
- The degree of HLA* identity (match) between the donor and the recipient determines both the choice of donor and the likelihood of adverse outcomes following transplant
- The risks of transplant-related mortality, graft failure, infection and graft vs host disease are lower with transplants from HLA-identical sibling donors.

The question of whether patients should be treated initially with imatinib or transplantation remains unresolved. Many haematologists argue that transplantation remains the only proven cure for chronic myeloid leukaemia and that it should continue to be offered to all younger patients with an HLA-identical sibling donor. Others argue that all patients should have a trial of imatinib and molecular monitoring of their response, with allogeneic haematopoietic stem cell transplantation offered to those who develop disease progression or fail to show a major cytogenetic or a significant molecular response to imatinib.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia is the most common type of leukaemia in the industrialised world, accounting for 40% of all leukaemias in people over 65 years old. Whereas previously many patients presented with lymphadenopathy or symptoms related to bone marrow failure, nowadays over 90% of cases are diagnosed in asymptomatic patients after a blood test is performed for another reason. The median age at presentation is 65–70, but 20–30% of patients are aged below 55 at diagnosis. In most patients the aetiology of chronic lymphocytic leukaemia cannot be established. However, there is an association with some industrial pollutants, and the first-degree relatives of patients with chronic lymphocytic leukaemia are about five times more likely to develop the disorder than the general population.

Chronic lymphocytic leukaemia results from a monoclonal expansion of mature lymphocytes. The malignant clone demonstrates a characteristic phenotype, with cells expressing CD5, CD19, CD20, CD23, light chain restriction and, in cases associated with a poor prognosis, CD38. These findings are sufficiently specific for chronic lymphocytic leukaemia that a bone marrow examination is no longer considered necessary to make a definitive diagnosis.

Chronic lymphocytic leukaemia is generally incurable without allogeneic transplantation. It often progresses slowly, so treatment is generally reserved until there is clear evidence of disease progression, such as progressive bone marrow failure, autoimmune cytopenia, progressive splenomegaly, bulky lymphadenopathy, frequent infections or systemic symptoms. The choice of therapy depends on whether one is aiming for palliation or for complete remission in the hope that this will translate into prolonged survival.

Options for initial therapy include single drug chemotherapy with chlorambucil, cyclophosphamide or the purine analogue, fludarabine. Recent randomised trials have shown that fludarabine leads to higher complete response rates and greater response duration, but not to improved survival when compared with chlorambucil.⁶ These results have led to the increasing use of fludarabine in multidrug regimens.

The most widely used combination includes fludarabine, cyclophosphamide and the anti-CD20 monoclonal antibody, rituximab, given over three days each month for three to six months. Over 90% of patients respond to this regimen, with 70% attaining a complete response, compared to a complete response rate of less than 5% with chlorambucil alone.⁷ Early reports suggest that this may translate into prolonged survival, although this remains to be shown in long-term studies. The major limitation of fludarabine-based regimens is the risk of infection due to the profound immunosuppression associated with such regimens.

There are a number of treatment options available for relapsed or refractory disease including fludarabine, cyclophosphamide and rituximab, cyclophosphamide-vincristine-prednisolone, the same drugs combined with doxorubicin (CHOP), and the monoclonal antibody, alemtuzumab.

Recent studies suggest that allogeneic transplantation with reduced intensity conditioning may offer the best possibility of long-term disease-free survival. However, this is associated with considerable mortality and morbidity and is really only an option for patients aged under 65 years.

Conclusion

Increased understanding of the molecular basis of leukaemia has led to major changes in the way that it is diagnosed, classified and treated. In recent years the development and clinical use of drugs, such as imatinib, and targeted therapies has, in specific patient populations, dramatically improved the chances of disease response and survival. Likewise, advances in transplantation have reduced the early toxicity associated with this procedure and made it an option for more patients. Continuing research into the molecular pathogenesis of leukaemia seems likely to lead to the introduction of new diagnostic techniques and new multidrug therapeutic regimens over the coming years.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

7. Most patients with chronic lymphocytic leukaemia present with the clinical features of bone marrow failure.
8. Chronic myeloid leukaemia is caused by a genetic abnormality.

Book review

Therapeutic Guidelines: Palliative Care. Version 2.

Melbourne: Therapeutic Guidelines Limited; 2005. 369 pages. Price: \$39, students \$30, plus postage

Greg Crawford, Clinical Head of Palliative Care, Lyell McEwin Health Service, Adelaide

The new edition of *Therapeutic Guidelines: Palliative Care* builds on the excellent first edition. This small pocket-sized text is a vital part of the *Therapeutic Guidelines* stable. The published version is very user-friendly and I am looking forward to loading the mini computer version, which is now available, onto my personal organiser.

The *Palliative Care* second version has some changes in format and a tightening of the overall presentation. The order and format of chapters has been streamlined and minor changes only add to the usefulness of this text.

The order of chapters reflects the challenges of caring for people with life-limiting illnesses. There is considerable space given to principles, care of the provider of palliative care, ethical issues and communication. Then follow important guidelines regarding community care and other practical factors. The major symptom groups in order of significance and prevalence are then covered with comprehensive consideration of not only pharmacological therapeutics but all possible interventions.

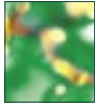
The chapter on Emergencies has moved further up the contents table and many might wonder what is an emergency in

palliative care. The obvious conditions covered were spinal cord compression, superior vena cava obstruction, acute airways obstruction, haemorrhage and acute confusion. The need to recognise these is paramount and then further management should be decided in the context of the clinical situation, the patient, and their wishes – the total picture. As always, relief of distress remains a paramount issue.

A new chapter on intercurrent illnesses has been written. This is a useful addition and explores the interaction of the life-limiting illness and medical comorbidities. The psychological impact of changing long-term medications was dealt with in a clear and logical progression and reminds us of the need to 'negotiate changes to medication over time rather than making sudden sweeping changes'.

The chapter on pain covers this increasingly complex and fascinating area in a clear, logical and approachable manner.

The new version of *Therapeutic Guidelines: Palliative Care* comes with my high recommendation – not only for relatively inexperienced practitioners but also for those more experienced whose primary focus is not end-of-life care. This small book is also a good summary for those of us whose core practice is with people living with a life-limiting illness. I would recommend this text as a useful resource and an accessible update for all clinicians. Good symptom management and the active involvement of the patient and family in care, particularly at the end of life, are core principles for clinicians of all disciplines and experience.



Travelling with medicines

Nicholas Zwar, Professor of General Practice, School of Public Health and Community Medicine, University of New South Wales, and Director, General Practice Unit, Sydney South West Area Health Service, Sydney

Summary

The overseas traveller needs to plan ahead to ensure medicines are available and used properly. This planning needs to take account of relevant legal, customs and Pharmaceutical Benefits Scheme restrictions. Medicines should be transported in their original packaging whenever possible and refrigeration during flight is seldom necessary. The timing of the use of drugs, like insulin, can be difficult when crossing time zones. A health summary including any allergies and a medication list, which includes generic names, is of great assistance to the traveller. Advice should be given about any new medicines that are prescribed or advised specifically for the trip such as drugs for malaria prophylaxis. The traveller may also seek advice about which drugs to carry in a medical kit.

Key words: antimalarials, contraceptives, insulin, thyroxine.

(*Aust Prescr* 2006;29:80–2)

Introduction

In 2004, Australian residents made 4.4 million short-term overseas departures¹ and the number of Australians travelling continues to grow. These travellers include many people with chronic illnesses taking long-term treatment, so the need to travel with drugs is common. This raises questions about supply, packing and storage, documentation and the timing of medicines. There are also issues concerning drugs taken specifically for the trip such as prophylaxis for malaria.

Supply of medicines for travel

People need to ensure that they have sufficient quantities of their regular drugs prescribed and dispensed before travelling. The patient should check the expiry date to make sure the drugs will not expire during the trip.

Drugs subsidised by the Pharmaceutical Benefits Scheme (PBS) can only be taken or sent out of Australia for the personal use of the traveller or someone they are accompanying such as a

child. There are other legal restrictions on the quantity of PBS drugs that a traveller can take or send overseas. The formula for calculating the designated amount is in the providers section of the Medicare Australia website.* Information for the general public about taking PBS medicines overseas is also available from the Medicare Australia website.† The designated amount can be as much as 360 days' supply for some items. Patients should only take with them a quantity that is appropriate for the duration of travel and allows for any unexpected delays in returning to Australia. In some instances patients need to contact the embassy of the countries they are visiting to ensure their medication is legal there. Medicines most often affected by legal restrictions are narcotic analgesics and amphetamines. However, some medicines that may not be scheduled as addictive in Australia can be illegal in other countries. For example, taking medications containing codeine into some countries, such as United Arab Emirates, is illegal.

Problems can arise if travellers need more medicines after the PBS-designated quantity is used. Drugs can be prescribed on a private prescription, supplied by a pharmacist in Australia and sent overseas. However, the Australian Customs Service should be contacted to ensure it is legal to export the medicines concerned and the embassy of the country of destination should also be asked if that importation is legal.

Packing drugs for travel

Travellers should be advised to transport their drugs in their original containers wherever possible. This ensures the drugs are clearly labelled and also reduces the risk of difficulty with customs officials on arrival overseas. To help ensure that the drugs are available when needed the supply should be either carried in hand luggage or divided between hand luggage and checked luggage. It is a good idea to suggest that there is enough medicine in the hand luggage to cover the duration of travel and several days afterwards in case checked bags are delayed.

* http://www.medicareaustralia.gov.au/providers/programs_services/pbs/overseas_drug_diversion/about_oddp.htm#legal

† http://www.medicareaustralia.gov.au/yourhealth/going_overseas/travelling_overseas/taking_pbs_medicine_os.htm (or phone 'Travelling with PBS medicine' enquiry line 1800 500 147)

Medicines storage

Some drugs can be adversely affected by temperature and this creates potential problems during travel, especially if refrigeration is required. As a general rule airlines are not willing to take the responsibility of storing passengers' medicines in aircraft refrigerators. As well as the reluctance of the airlines, there is also the risk that doing so could result in the drugs being lost.

Storage away from heat is necessary for some formulations. These include pessaries and suppositories that are designed to melt at body temperature.

The product information and consumer medicine information for thyroxine were changed in 2004 to state that thyroxine should be stored in a refrigerator between 2 and 8°C. This recommendation has been controversial because of concerns that condensation forming when a refrigerated glass bottle is opened may damage the tablets and affect potency.²

However, the product information and consumer medicine information note that thyroxine can be stored at room temperature (below 25°C) for a maximum of four weeks if refrigeration is not possible, for example during travel. If travel is for longer than four weeks, the patient could take a second unopened bottle of thyroxine and refrigerate this after arrival at their destination.

Insulin remains stable at room temperature for several months³ so refrigeration during travel is not necessary. Packing double the quantity of insulin needed and dividing this between hand luggage and checked luggage has been suggested.⁴ Insulin should be transported in its original packaging and travellers should take a doctor's letter with a health summary, medication list and a statement about the injecting and testing equipment they are carrying. A Medic-Alert bracelet is a worthwhile extra precaution, especially if travelling alone.

Documentation

A health summary including any drug allergies and an up-to-date medication list are very helpful for all travellers with chronic medical problems. As brand names vary from country to country the generic names of the medicines should be included. Medical software programs that allow printing of a patient summary make summaries easier to provide and more legible. If they do not have a doctor's letter, patients can complete a Medicine export declaration form.[†]

Common drug problems during travel

The traveller should be advised to take adequate supplies for all chronic conditions including those that may not have been a recent problem, but which could recur. A good example of this is asthma where exposure to triggers in other countries can lead to a recurrence in someone who has been free of attacks for some time.

Diabetes

The timing of drugs for diabetes during travel is a common medicines management problem. Patients on oral hypoglycaemic drugs should take them as prescribed according to the local time. Those taking insulin should seek advice from their specialist on adjusting the doses if time zone changes are involved. A detailed itinerary of the trip is helpful with departure and arrival times, duration of flights, stopovers and approximate meal and snack times. The patient should carry a supply of rapidly acting carbohydrate such as jelly beans as a precaution against hypoglycaemia.[‡]

Trips with a change of time zones of less than four hours do not usually require an adjustment of insulin dosage. East or west trips with greater time zone changes may require adjustment. One simple regimen which is suggested for people who are familiar with managing their diabetes is to monitor the pre-meal glucometer reading and give an appropriate dose of short-acting insulin. Longer-acting insulin can be added before sleep on the plane on long flights. The traveller then returns to their usual dose the morning after arrival.

Contraception

Travel across time zones can cause confusion about timing of the oral contraceptive pill. Regular dosing is especially important for the progesterone-only pill. The risk of decreased effectiveness arises with flying west where the time between doses is prolonged if based on local time. Travellers taking the oral contraceptive pill can take a second watch and leave this set to the time at home. When adapting to local time on arrival the traveller should err on the side of a shorter dosage interval rather than extending the dosage interval.

The extent to which the risk of travel-related deep vein thrombosis is increased by the combined contraceptive pill is not yet known. In the absence of other risk factors women can be advised to use the standard precautions which include exercises and maintaining hydration. Below-knee compression stockings are an additional precaution. Aspirin has not been shown to be effective at preventing deep vein thrombosis. It is associated with an increased risk of gastrointestinal bleeding so aspirin cannot be currently advised for prophylaxis.

Purchasing drugs overseas

Buying medicines overseas can be problematic due to confusion over variations in brand names and in some countries due to counterfeit drugs. In parts of Asia, Africa and South America 10–50% of prescription drugs may be counterfeit.⁵ This causes problems with efficacy and occasionally with toxicity. If travellers have to purchase medicines overseas they need to check the

[†] Travel and diabetes. Diabetes Australia.

<http://www.diabetesaustralia.com.au> Go to Resources/fact sheets

generic name of the item and if possible get advice from a pharmacist. Buy from a reputable source, not a street market.

Medical kits for travel

Travellers often ask what medicines and first aid supplies should be included in a medical kit for travel in addition to their regular drugs. These kits can be quite extensive depending on the nature of travel and include first aid items such as antiseptic and dressings, illness care items such as analgesics, anti-diarrhoeals and rehydration salts, and preventive care items such as insect repellent, antimalarial drugs, sunscreen and condoms. In a study of British travellers the most frequently used items in travel to developing countries were analgesics, treatments for diarrhoea, antiseptics and sticking plasters. Under-use of insect repellents was noted, and 16% of the travellers in the study used antibiotics during their trip, most commonly for travellers' diarrhoea.⁶

A new prescription may be needed for the prevention or treatment of illnesses associated with travel. The most common examples are drugs for malaria prophylaxis and self-treatment courses of antibiotics for travellers' diarrhoea. Consideration needs to be given to indications, contraindications, possible adverse effects and interactions. Poor compliance with drugs for malaria prophylaxis is common, especially with more complex regimens. Advice is therefore needed to improve compliance and on how else to reduce the risk of infection.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 87)

9. When a patient with insulin-dependent diabetes travels by air, their insulin must be kept in the aircraft's refrigerator.
10. There are no limits on the quantity of Pharmaceutical Benefits Scheme drugs that can be taken out of Australia for personal use.

Dental notes

Prepared by Dr M. McCullough of the Australian Dental Association

Drug treatment of neuropathic pain

The most common cause of intraoral pain in patients presenting to dentists is odontogenic and rarely presents a diagnostic challenge. However, pain in the oral cavity that is not dental or periodontal in origin may be difficult to diagnose and treat.

Neuropathic pain in the orofacial region, such as post-herpetic neuralgia, post-traumatic painful peripheral neuropathy ('phantom tooth pain'), idiopathic trigeminal neuralgia (tic douloureux), or chronic orofacial pain ('atypical odontalgia') can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. The presentation of neuropathic pain in and around the mouth has been extensively reviewed.^{1,2,3}

If neuropathic pain is suspected a thorough clinical evaluation is necessary to assess this type of pain and its mechanism. Dental

treatments that are irreversible and potentially harmful to the underlying dentoalveolar structures must be avoided when the diagnosis is uncertain.

Dentists are often asked to exclude the likelihood of pain of odontogenic origin contributing to neuropathic pain. They need to be aware of the drugs patients may be taking as well as making themselves available to assist in the management of these patients within multidisciplinary pain clinics.

References

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Medicinal mishap

Dosing errors with Donnalix Infant Drops

Prepared by Jeff Robinson, Manager, Victorian Poisons Information Centre, and Noel Cranswick, Director, Australian Paediatric Pharmacology Research Unit, Royal Children's Hospital, Melbourne

Case 1

Parents of a three-month-old boy, weighing 5 kg, phoned the Victorian Poisons Information Centre for advice. The child had just woken up from a big sleep; he was now flushed, cranky and unsettled. Three hours earlier he had been given 5 mL of Donnalix Infant Drops instead of 0.5 mL. The parents were advised to take the child to the nearest hospital.

Case 2

A two-month-old boy, weighing 4 kg, was brought to a hospital emergency department. He had dilated pupils, a dry mouth, a heart rate of 200 beats/minute and was a little sleepy. Ninety minutes earlier, he had been given 2 mL of Donnalix Infant Drops, instead of the correct dose of 0.4 mL. The child required overnight admission for observation.

Case 3

A one-year-old girl, weighing 10 kg, was given three 10 mL doses of Donnalix Infant Drops instead of the correct dose of 1 mL. She presented to hospital with dilated pupils slowly reacting to light, a heart rate of 150 beats/minute, and difficulty feeding. The child required observation, with cardiac monitoring, and supportive care until her symptoms resolved.

Comment

Donnalix Infant Drops contain the anticholinergic compounds hyoscyamine, atropine and hyoscine. The product is used to relieve colic in infants, although evidence supporting its effectiveness is lacking. The drops can be purchased from pharmacies without a prescription. The recommended dose is 0.1 mL/kg of the infant's body weight before troublesome feeds, with a maximum of four doses in 24 hours.

In the last five years, the Victorian Poisons Information Centre has received 26 calls involving a dosing error made by parents or carers administering this product (Table 1). These errors occurred despite clear dosing instructions on the bottle and on the outer packaging and the inclusion of a graduated administration dropper in the pack.

In 22 of these calls, the infant had already been taken to hospital or the caller was advised to take the infant to hospital. Symptoms at the time of the call were noted in seven cases. They included drowsiness, floppiness, facial flushing, tachycardia, dry mouth, dilated pupils and poor feeding.

Toxicity in colicky infants given anticholinergic drugs is well

documented.^{1,2} Neurological manifestations of excessive dosing range from sedation to irritability, agitation, seizures and coma. Features of the anticholinergic syndrome may be seen, such as dry/warm skin, hyperthermia, thirst, dry mouth, dilated pupils, tachycardia, urinary retention, delirium and hallucinations. The range of toxicity is variable and unpredictable. Its effects may be delayed and cyclical. Physostigmine is an antidote for pure anticholinergic toxicity, but this is not without risk and indications for its use are limited.³

Recommendations

Medical, nursing and pharmacy staff need to be aware that dosing errors can occur with Donnalix Infant Drops, particularly giving 10 times the correct dose. Members of the public often assume that because over-the-counter medicines are not regulated by prescription, they are safe, even in overdose.⁴

In view of the potential for toxicity and the absence of a compelling clinical indication we believe Donnalix Infant Drops should be withdrawn from the market. As this is unlikely to happen, parents or carers should be shown the correct dose at the time of purchase. A boxed warning about the importance of measuring the correct dose and a reduction in the 'strength' of the drops would further decrease the risk of mistakes.

Restricting access by rescheduling Donnalix Infant Drops to a 'pharmacist only' or 'prescription only' medicine may further decrease the risk of dosing errors.

Table 1

Dosing errors involving Donnalix Infant Drops

Dosing error	Number of calls
Double dose	3
Two and a half times correct dose	3
Three times correct dose	2
Five times correct dose	3
Seven and a half times correct dose	1
Ten times correct dose	14
Total	26

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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.

Bortezomib

Velcade (Janssen-Cilag)

vials containing 3.5 mg powder for reconstitution

Approved indication: multiple myeloma

Australian Medicines Handbook section 14.3.11

Multiple myeloma is a malignancy of plasma cells. Although modern treatments, such as bone marrow transplant, have improved the prognosis there is no cure and the median survival is 3–5 years. The options for patients whose cancers relapse after chemotherapy or transplantation are limited. Progression of the cancer may be related to dysfunction of an enzyme system (26S proteasome) that normally breaks down cellular proteins. Inhibiting this enzyme disrupts cell homeostasis and can cause apoptosis, particularly in proliferating cells.

Bortezomib is an inhibitor of the proteasome. It is a modified dipeptide related to the amino acids leucine and phenylalanine. Experimentally, bortezomib delays tumour growth in a variety of cancers including multiple myeloma.

A phase II trial recruited 202 people whose myeloma had relapsed and was refractory to therapy. They were given injections of bortezomib twice a week in two-week cycles with one treatment-free week between each cycle. Up to eight cycles were allowed and oral dexamethasone could be added to the regimen if there was a poor response. After a median treatment duration of 3.8 months myeloma protein could not be detected by electrophoresis in 19 patients. Overall 53 patients (27%) had at least a partial response to bortezomib.¹

As high doses of dexamethasone can be used to treat relapsed myeloma it has been compared with bortezomib. The trial randomised 333 patients to eight cycles of intravenous bortezomib and 336 to oral dexamethasone. There was at least a partial response in 38% of the bortezomib group and 18% of the dexamethasone group. The myeloma protein disappeared in 6% of the bortezomib group but less than 1% of the dexamethasone group. This contributed to a higher rate of survival (80% vs 66%) when the patients were followed up after a year.²

Many patients will not complete eight cycles of therapy. In the phase III trial 37% of the patients given bortezomib stopped treatment because of adverse effects.² Common adverse reactions include gastrointestinal upsets, peripheral neuropathy, fever and hypotension. The patient's blood count should be checked before each dose as bortezomib can cause anaemia, neutropenia and thrombocytopenia.

Bortezomib is metabolised by several of the cytochrome P450 enzymes, but there are no drug interaction studies. It should probably not be used in patients with hepatic impairment, and the development of abnormal liver function may require treatment to be stopped.

As our understanding of the molecular biology of multiple myeloma improves new approaches to treatment are likely to emerge. For example, thalidomide can be used in refractory myeloma. Some of the patients in the trials had already been treated with thalidomide, so it seems that bortezomib can improve outcomes after a relapse. The size of the improvement is uncertain as there have been questions about the design of the comparison with dexamethasone³, for example 99% of the dexamethasone group had already been treated with corticosteroids.² Assuming the results are valid, bortezomib only delays progression by about three months. The median time to progression with bortezomib was 189 days compared with 106 days with dexamethasone.² As the price of bortezomib will be much greater, the delay in progression will have a high cost and whether this improves the quality of the patient's remaining life is currently unclear.

manufacturer did not respond to request for data

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Disodium gadoxetate

Primovist (Schering)

pre-filled syringes containing 10 mL

Approved indication: liver imaging

Magnetic resonance imaging (MRI) can be enhanced by the use of contrast agents. Gadoxetate is a gadolinium containing contrast agent which can be used in the detection of focal hepatic lesions.

After intravenous injection gadoxetate concentrates in the liver and kidneys. Uptake into normal hepatocytes is more likely


than into abnormal areas such as metastases. As gadoxetate is eliminated in the bile, as well as in the urine, it may have a role in imaging the biliary system.

One of the clinical trials of gadoxetate involved 131 patients with known or suspected lesions in the liver. These patients had MRI before and 20 minutes after an injection of gadoxetate. Using the contrast agent increased the number of lesions identified by the researchers and by external radiological reviewers. Although the sensitivity of MRI was increased, the improvement was not statistically significant for all the radiologists.¹

In other studies adding gadoxetate has increased the proportion of correctly characterised lesions from 81% to 88%. The combination of precontrast, dynamic and postcontrast MRI correctly characterises 89% of lesions compared to 80% with contrast-enhanced computed tomography (CT).

The main adverse effects of gadoxetate are headache, nausea, vasodilatation, back pain and abdominal pain. Anaphylactoid reactions can occur and gadoxetate may prolong the QT_c interval on the ECG.

Other hepatobiliary contrast agents are available overseas, but the dilemma is whether the advantages of contrast-enhanced MRI are sufficiently superior to MRI and CT to make a difference to the patient's management.

 manufacturer declined to supply data

Reference

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Eflornithine hydrochloride

Vaniqa (Epitan)

11.5% cream in 30 g tubes

Approved indication: facial hair

Australian Medicines Handbook section 8.10

Eflornithine is an inhibitor of ornithine decarboxylase, an enzyme involved in cell proliferation and function. It was first studied in oncology, but was found to be active in trypanosomiasis. The drug's effectiveness in treating African sleeping sickness led to it being called 'the resurrection drug'.¹

Unfortunately, parenteral eflornithine was too expensive for the countries that needed it. Commercial considerations therefore resulted in the manufacturer ceasing production in 1995.¹


During treatment of trypanosomiasis it was noticed that some patients lost their hair. This led to the development of a topical formulation for slowing hair growth, opening up a more lucrative cosmetic market.¹ The Australian indication is for delaying the regrowth of unwanted facial hair, following depilation, in women.

The main clinical trials of eflornithine enrolled women who usually removed their facial hair at least twice a week. Compared to the 201 women randomised to apply the vehicle, the 393 who applied eflornithine twice daily had less hair growth. In the opinion of the treating doctors, after 24 weeks of treatment 32% of the women using eflornithine showed a marked improvement compared with 8% of those applying the vehicle. Secondary endpoints such as feeling 'uncomfortable at social gatherings' or 'uncomfortable in exchanges of affection' all showed that women given eflornithine no longer felt as bothered about facial hair as the women who had used the vehicle. The differences between the groups disappeared after treatment ceased.

Only a few of the women in the trials had polycystic ovary syndrome. Women who were using other treatments for hirsutism were excluded from the trials and published comparative studies are lacking.

Although a small proportion of the dose is absorbed into the systemic circulation, mainly local adverse reactions were reported during the trials. These included burning, stinging, itching, redness and tingling of the skin. Acne was reported in 21% of women using eflornithine or the vehicle and approximately 16% of both groups developed pseudofolliculitis barbae. The effects of long-term continuous use of eflornithine are unknown. Its safety in pregnancy has not been established, and it is contraindicated in severe renal impairment.

While women in developed countries can now access eflornithine to try to improve their appearance, access to eflornithine for sleeping sickness is less certain. Although the manufacturers reached an agreement with the World Health Organization to supply the drug, future production may not be assured.

 manufacturer provided some data

Reference †

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Posaconazole

Noxafil (Schering-Plough)

105 mL glass bottles containing 40 mg/mL suspension

Approved indication: specified fungal infections

Australian Medicines Handbook section 5.2.1

The increase in patients with disorders of the immune system or taking immunosuppressants has led to an increase in fungal infections. The drugs available to treat systemic fungal infections include amphotericin B and the triazole antifungals such as itraconazole and voriconazole.

Like other triazole antifungals, posaconazole inhibits the synthesis of ergosterol. This results in the breakdown of the

fungal cell membrane. *In vitro*, posaconazole is active against species of aspergillus and fusarium. It is also approved for use in chromoblastomycosis, coccidioidomycosis, mycetoma and zygomycosis.

Patients take the suspension twice a day. Doses are taken with meals as food more than doubles the absorption of posaconazole. The half-life is 35 hours so it takes at least a week for concentrations to reach a steady state. Most of the drug is excreted unchanged in the faeces. There is some metabolism, but cytochrome P450 is not extensively involved. Posaconazole does inhibit P450 3A4 so it may reduce the metabolism of drugs such as calcium channel blockers, midazolam, atorvastatin and simvastatin. Drugs which reduce plasma concentrations of posaconazole include phenytoin, rifabutin, H₂ receptor antagonists and, probably, proton pump inhibitors.

Posaconazole has mainly been studied in infections that were resistant to other drugs. Its approval is therefore limited to patients who cannot tolerate other antifungals or have a refractory infection. In a study of fungal infections of the central nervous system, patients were treated with posaconazole for up to a year. Most patients had already been treated with amphotericin. Treatment with posaconazole was successful in 14 of the 29 patients with cryptococcal meningitis and five of the 10 patients with other infections.¹

During the trials of posaconazole the most frequently reported problems were fever, gastrointestinal upsets and headache. Other adverse effects included neutropenia, anorexia, dizziness, fatigue and rash. Posaconazole can alter liver function and may also potentially prolong the QT_c interval in the ECG.

Refractory fungal infections are difficult to treat so there is a need for new antifungal drugs, but already organisms with reduced susceptibility to posaconazole have been identified. There is limited published information about the clinical effectiveness of posaconazole so it is not possible to evaluate if it has any advantage over other antifungals such as voriconazole.

T T manufacturer provided some data

Reference [†]

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Tazarotene

Zorac (EpiPharm)

0.1% and 0.05% cream in 30 g tubes

Approved indication: psoriasis, acne

Australian Medicines Handbook section 8.2.1

Topical treatments are first-line therapy for acne and plaque

psoriasis. The options for acne include the retinoids such as adapalene and tretinoin. Tazarotene is a retinoid which has been available overseas for several years. As tazarotene modulates the proliferation and differentiation of keratinocytes it has been studied in psoriasis and acne.

Early clinical trials compared a gel formulation with applications of inactive vehicle. Tazarotene reduced the severity of psoriasis in 45–63% of lesions depending on the concentration of the gel and whether it was applied once or twice a day. Only 13% of lesions responded to the vehicle.¹ Over 12 weeks the cream formulation produced a clinical improvement in the skin of 49% of patients with facial acne compared with 33% of those given the vehicle.²

The efficacy of a once-daily application of gel was compared with that of twice-daily fluocinonide, a potent topical corticosteroid for psoriasis. After 12 weeks there was no significant difference between the treatments. Patients who responded to tazarotene were less likely to relapse in the 12 weeks after treatment stopped.³

A retrospective study evaluated the effect of topical retinoids in inflammatory facial acne. Clinically significant improvements were judged to have occurred in 36% of the evaluations of patients given tazarotene, 34% of the evaluations of adapalene and in 28% of the evaluations of tretinoin. Only 17% of the evaluations considered that there had been a response to a vehicle.⁴

Tazarotene is a prodrug which is converted to tazarotenic acid. Some of this is absorbed into the systemic circulation then excreted in the urine and faeces. As retinoids are teratogenic, tazarotene should not be used in pregnancy or in women who could become pregnant during treatment.

Common complaints reported in trials of tazarotene include a burning or stinging sensation, itching, irritation, redness and dry skin. Patients should be advised to use sunscreens. Those with acne are likely to develop desquamation. The safety and efficacy of tazarotene have not been established beyond 12 weeks of treatment.

There have been studies of tazarotene in combination regimens, but there do not appear to have been many published comparisons with other treatments. In acne tazarotene is an alternative to the other retinoids and it can probably be considered in psoriasis for patients who have not tolerated or not responded to other topical treatments.

T T manufacturer provided some data

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

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

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

Answers to self-test questions

- | | | | |
|-----------|----------|----------|----------|
| 1. True | 3. True | 5. True | 7. False |
| 2. True | 4. False | 6. False | 8. True |
| 9. False | | | |
| 10. False | | | |

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Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

H. Krum

Australasian Society of Clinical Immunology and Allergy

C. Katelaris

Australian and New Zealand College of Anaesthetists

R. Westhorpe

Australian and New Zealand Society of Nephrology

G. Duggin

Australian Association of Neurologists

F. Vajda

Australian Birth Defects Society

T. Taylor

Australian College of Rural and Remote Medicine

A. Iannuzzi

Australian Dental Association

M. McCullough

Australian Medical Association

J. Gullotta

Australian Pharmaceutical Physicians Association

J.J. Hassall

Australian Postgraduate Federation in Medicine

B. Sweet

Australian Rheumatology Association

J. Bertouch

Australian Society for Geriatric Medicine

R.K. Penhall

Australian Society of Otolaryngology Head and Neck Surgery

E.P. Chapman

Cardiac Society of Australia and New Zealand

J.H.N. Bett

Consumers' Health Forum

C. Newell

Defence Health Service, Australian Defence Force

B. Short

Endocrine Society of Australia

R.L. Prince

Gastroenterological Society of Australia

P. Desmond

Haematology Society of Australia and New Zealand

F. Firkin

High Blood Pressure Research Council of Australia

L.M.H. Wing

Internal Medicine Society of Australia and New Zealand

M. Kennedy

Medical Oncology Group of Australia

S.J. Clarke

National Heart Foundation of Australia

A. Boyden

Pharmaceutical Society of Australia

W. Plunkett

Royal Australasian College of Dental Surgeons

P.J. Sambrook

Royal Australasian College of Physicians

D.J. de Carle (adult division)

C.M. Mellis (paediatric division)

Royal Australasian College of Surgeons

D.M.A. Francis

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

M. Hickey

Royal Australian and New Zealand College of Ophthalmologists

M. Steiner

Royal Australian and New Zealand College of Psychiatrists

R.W. Lyndon

Royal Australian and New Zealand College of Radiologists

P. Carr

Royal Australian College of General Practitioners

J. Gambrill

Royal Australian College of Medical Administrators

L.B. Jellett

Royal College of Pathologists of Australasia

J.M. Potter

Society of Hospital Pharmacists of Australia

C. Alderman

Thoracic Society of Australia and New Zealand

J.P. Seale

Urological Society of Australasia

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