Australian Prescriber

CELEBRATING 30 YEARS

VOLUME 28 | NUMBER 1 | AN INDEPENDENT REVIEW | FEBRUARY 2005

CONTENTS

Frequently asked questions about varicella vaccine

Wonie Uahwatanasakul, Paediatric Fellow, Royal Children's Hospital, and Jonathan R. Carapetis, Associate Professor, Department of Paediatrics, University of Melbourne, Infectious Diseases Consultant, Royal Children's Hospital, and Research Fellow, Murdoch Childrens Research Institute, Melbourne

Summary

Each year in Australia severe varicella and zoster infections cause a number of deaths and thousands of hospitalisations. A live attenuated varicella zoster virus vaccine has been available in Australia since 2000. This vaccine is recommended for all non-immune children over 12 months of age and all susceptible adults. There have been theoretical concerns about the vaccine leading to increased cases of zoster and varicella in adults because of a combination of waning vaccine-induced immunity and reduced immunological boosting from exposure to circulating virus. However, clinicians are encouraged to consider its use in all non-immune people apart from immunocompromised patients and pregnant women.

Key words: immunisation, chickenpox, shingles.

(Aust Prescr 2005;28:2–5)

Introduction

Varicella (chickenpox) is a highly contagious disease caused by the varicella zoster virus. Although people of all ages are affected, most cases occur in children under the age of five years. More than 90% of people have been infected by the age of 15 years. Herpes zoster (shingles) is caused by reactivation of latent varicella zoster virus in dorsal root ganglia.

While varicella is usually a mild illness in childhood, there can be serious morbidity and even death resulting from severe varicella, secondary bacterial infections, pneumonitis, encephalitis or myocarditis. Most complications of varicella infection occur in otherwise healthy children, although the relative risk of complication is highest in elderly or immunocompromised patients, pregnant women and their fetuses, and newborn infants.[1,2] In Australia an average of 3.5 people with primary varicella and 11 with herpes zoster died each year between 1980 and 1993. In South Australia and New South Wales, varicella admissions accounted for almost 1200 hospital bed days and zoster admissions for more than 7300 bed days each year.[3]

Who should receive varicella zoster virus vaccine?

Live attenuated varicella zoster virus vaccine (Oka strain) has been available in Australia since 2000. In Australia, vaccination is recommended for everyone over the age of 12 months (including adults) without evidence of prior varicella infection.[4] A single subcutaneous dose should be given to children aged one to 13 years with no clinical history of varicella. The vaccine may be given at any time after 12 months of age. The Australian Standard Vaccination Schedule suggests that a convenient age for administration is 18 months. However, there are currently no other routinely scheduled vaccines for most Australian children at that age, so parents may choose to have their children immunised earlier. For example, a child could receive varicella zoster virus vaccine at the same time as their routine 12 month vaccines or, if parents prefer not to have their child receive four injections at one visit, as a separate immunisation four or more weeks later.

After the 14th birthday, two vaccines should be given at least one month apart to anyone with a negative clinical history of varicella and negative varicella serology. A blood test is recommended in this age group because most adults with a negative clinical history show serological evidence of immunity to varicella zoster virus. This strategy will avoid the expense of the vaccine and the potential (although extremely low) risk of adverse events. An alternative and equally acceptable strategy is to offer vaccine

In this issue…

Welcome to the year in which *Australian Prescriber* celebrates its thirtieth birthday. Many of the problems encountered 30 years ago remain with us. For example, patients are still dying from incorrect doses of potassium. James Reeve and colleagues therefore inform us what can be done to decrease the dangers of intravenous potassium.

Although aspirin has been available for many years, David Newgreen tells us that there is still controversy about aspirin's interaction with alcohol. Antidepressants are also a common cause of adverse events, but Kelsey Hegarty says that many mildly depressed patients can be managed without antidepressants.

to people aged ≥ 14 years with a negative clinical history of varicella without performing serology. There is no evidence that the vaccine is dangerous if given to people who are already immune to varicella. In fact trials are in progress to assess if the boosting effect of varicella zoster virus vaccine has the potential to prevent herpes zoster in older people.[5] Varicella zoster virus vaccine should not be given to immunocompromised patients because of risk of severe reaction, or to pregnant women because of unknown risks to the fetus.

Who pays for the vaccine?

Although varicella zoster virus vaccine is recommended for all children, the federal government does not fund this vaccine. Parents therefore have to pay amounts varying from less than $60 to almost $100 per dose. Potential vaccinees should be advised to shop around for the cheapest price. Many private health insurance 'extras' policies provide partial reimbursement.

How safe is the vaccine?

Since 1995 over 40 million doses have been distributed in the USA.[6] The vaccine has been shown to be safe in healthy children.[7] If reactions occur, they are usually limited to fever or local reactions at the injection site. Skin rash occurs in about 7% of healthy vaccinees, either at the injection site or more generalised, and may be vesicular.[1,8] Rashes caused by the vaccine usually appear approximately three weeks after immunisation. There is a small potential to transmit the vaccine virus at this time, mainly from direct contact with vesicles at the injection site.[1] Vaccinated individuals appear not to be able to transmit the vaccine virus by the respiratory route, and papules (as opposed to vesicles) at the injection site are rarely infectious. If a vesicular rash occurs following varicella zoster virus immunisation, it should be covered with a dressing and clothes if possible, careful handwashing should be encouraged, and the vaccinated individual should avoid contact with immunocompromised people, pregnant women (as much as practical) and be excluded from school only until the lesions have crusted.

> It is not yet clear if the overall rates of disease in adults will increase because of waning protection from immunisation

Varicella zoster virus vaccine can be safely administered at the same time as other vaccines, although, if it is not given simultaneously, it should be given at least four weeks before or after other live vaccines.[4]

There have only been five reports of severe reactions in immunised children and they were later found to be immunocompromised.[6] No one is known to have died as a result of the vaccine virus.

How effective is the vaccine?

Varicella zoster virus vaccine is highly effective in children and adults. A single dose completely protects 85% of immunised children against developing clinical chickenpox. Immunised children who are not fully protected will almost always develop only mild disease if exposed to varicella zoster virus; vaccine effectiveness against moderate or severe disease is 97%.[9] Recently there have been some varicella outbreaks where the effectiveness of the vaccine was lower than expected.[10,11,12,13] Children immunised more than four years previously appeared at increased risk of breakthrough disease in these outbreaks, although almost all cases had mild disease. Despite having mild disease, immunised children with breakthrough disease are contagious and should be subject to the same school exclusion criteria used for other cases of chickenpox.

Can the vaccine be used to prevent chickenpox after someone has been exposed?

The vaccine has been shown to be effective in preventing chickenpox if given within three days of exposure to varicella zoster virus[14], although it may still have some benefit if given up to five days after exposure. Vaccination has also been effective in stopping varicella outbreaks, but in this situation it is recommended that the advice of public health personnel should be sought.[2,15,16] When not effective at preventing disease, post-exposure varicella vaccine may lead to milder disease in vaccinees.

How long does vaccine-induced protection last?

The evidence currently suggests that the vaccine usually remains protective for at least 10 years after immunisation, although the proportion of protected people may decline gradually after the first few years. Protective levels among many children vaccinated in Japan have persisted more than 20 years after vaccination.[9] However, studies into the duration of effectiveness have assessed the vaccine in an environment where wild varicella zoster virus infections and natural boosting of immunity are common. Significant boosting of the varicella immune response has been reported after second injections given 4–6 years after the initial immunisation.[17] However, booster doses are not currently recommended. As the use of varicella zoster virus vaccine increases and exposure to wild-type virus decreases in the community, it is possible that the duration of protection may decrease. Should this prove to be the case, a booster dose of vaccine may be warranted.

Will there be an increased risk of disease in older age groups?

There have been concerns that, by vaccinating children, the burden of disease will be shifted to an older age group who are at greater risk for more severe disease. It is clear that the proportion of cases in older age groups will increase as more

children are immunised. However, it is not yet clear if the overall rates of disease in adults will increase because of waning protection from immunisation and reduced boosting from exposure to circulating varicella zoster virus.

A study in the USA five years after the introduction of the vaccine highlighted that cases of varicella declined in both children and susceptible adults, and hospitalisations for complicated varicella also substantially declined.[18] Although this observation is reassuring, the effect of immunisation on the epidemiology of varicella zoster virus infections in the community will require ongoing surveillance.

What effect will the vaccine have on the future risk of herpes zoster?

Immunological boosting from circulating varicella zoster virus may protect adults from developing shingles. There is concern that this boosting will not occur as the proportion of children being vaccinated increases resulting in a short- to medium-term increase in cases of herpes zoster in adults. This effect has not yet been seen in the USA, although further surveillance will be required. There appears to be a reduced incidence of herpes zoster among immunised people, although the long-term risk is not yet known.

How should the vaccine be stored?

There are two varicella zoster virus vaccines available in Australia: Varilrix (GlaxoSmithKline) and Varivax Refrigerated (CSL/Merck Sharp and Dohme). The two vaccines are equally effective. Both vaccines come in lyophilised preparations which require protection from light and should be stored at 2–8°C (or frozen). Varilrix can be stored for up to two years, and Varivax Refrigerated for up to 18 months from the date of manufacture. The diluents for each vaccine should not be frozen; they can be stored in the refrigerator or at ambient temperatures. Both vaccines should be used promptly after reconstitution: within 90 minutes for Varilrix or within 30 minutes for Varivax Refrigerated.[4]

Conclusion: who should have the vaccine?

Although there are theoretical concerns that varicella zoster virus vaccine may alter the epidemiology of varicella zoster virus infections in the community, data from the USA where varicella immunisation has been routine since the mid-1990s suggest that the vaccine has had a positive impact.

Susceptible adults at high risk of exposure (for example healthcare workers, women prior to pregnancy, parents of young children, childcare workers and teachers) and all susceptible household contacts of immunosuppressed people should be given priority, but all healthy susceptible people over 12 months of age can be offered the vaccine.

References

1. Vazquez M. Varicella zoster virus infections in children after the introduction of live attenuated varicella vaccine. Curr Opin Pediatr 2004;16:80-4.
2. Litt J, Burgess M. Varicella and varicella vaccination. An update. Aust Fam Physician 2003;32:583-7.
3. Chant KG, Sullivan EA, Burgess MA, Ferson MJ, Forrest JM, Baird LM, et al. Varicella-zoster virus infection in Australia [published erratum appears in Aust N Z J Public Health 1998;22:630]. Aust N Z J Public Health 1998;22:413-8.
4. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003. http://www.immunise.health.gov.au/handbook.htm [cited 2005 Jan 10]
5. Levin MJ, Smith JG, Kaufhold RM, Barber D, Hayward AR, Chan CY, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis 2003;188:1336-44.
6. Gershon AA. Varicella vaccine: rare serious problems – but the benefits still outweigh the risks. J Infect Dis 2003;188:945-7.
7. Black S, Shinefield H, Ray P, Lewis E, Hansen J, Schwalbe J, et al. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. Pediatr Infect Dis J 1999;18:1041-6.
8. White CJ, Kuter BJ, Hildebrand CS, Isganitis KL, Matthews H, Miller WJ, et al. Varicella vaccine (VARIVAX) in healthy children and adolescents: results from clinical trials, 1987 to 1989. Pediatrics 1991;87:604-10.
9. Vazquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. N Engl J Med 2001;344:955-60.
10. Lee BR, Feaver SL, Miller CA, Hedberg CW, Ehresmann KR. An elementary school outbreak of varicella attributed to vaccine failure: policy implications. J Infect Dis 2004; 190:477-83.
11. Centers for Disease Control and Prevention (CDC). Outbreak of varicella among vaccinated children – Michigan, 2003. MMWR 2004;53:389-92.
12. Tugwell BD, Lee LE, Gillette H, Lorber EM, Hedberg K, Cieslak PR. Chickenpox outbreak in a highly vaccinated school population. Pediatrics 2004;113:455-9.
13. Galil K, Lee B, Strine T, Carraher C, Baughman AL, Eaton M, et al. Outbreak of varicella at a day-care center despite vaccination. N Engl J Med 2002;347:1909-15.
14. Asano Y, Nakayama H, Yazaki T, Kato R, Hirose S. Protection against varicella in family contacts by immediate inoculation with live varicella vaccine. Pediatrics 1977;59:3-7.
15. Ferson MJ. Varicella vaccine in post-exposure prophylaxis. Commun Dis Intell 2001;25:13-5.
16. Prevention of varicella. Update recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999;48(RR06):1-5.

17. Kuter B, Matthews H, Shinefield H, Black S, Dennehy P, Watson B, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. Pediatr Infect Dis J 2004;23:132-7.
18. Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA 2002;287:606-11.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

1. A skin rash may occur three weeks after an injection of varicella zoster virus vaccine.
2. Adults who request vaccination against varicella zoster virus are recommended to first have a blood test to check their immunity to the virus.

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.

Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis

Editor, – Professor McColl is to be congratulated for his admirable review of TNF-targeted antibodies (Aust Prescr 2004;27:43–6). These protein therapies may still need to be used as synergists with well-tried drugs such as methotrexate. They are very expensive and a real burden to both the Pharmaceutical Benefits Scheme (PBS) and to rheumatologists, who must provide much supportive data justifying the patient's need. Some of the criteria for their use may be suspect.[1]

Two of these antibodies can bind cell-bound TNF, perhaps inducing apoptosis of the TNF-producing cells. In the long term, this may compromise natural defences against comorbidities, for example tumours, tuberculosis. (The third drug (etanercept) binds TNF after release from the cells.)

There are much cheaper drugs for controlling TNF production such as thalidomide and oxpentifylline (pentoxifylline).[2] Thalidomide may be in the 'too-hard basket', but oxpentifylline has been used for more than 30 years to treat poor circulation.[3] Oxpentifylline is a proven alternative to steroids for controlling granulomatous inflammation in Hansen's disease.[4,5] So its safety is not an issue. Its short half-life[3] permits rapid suspension of use should compromising situations such as infections arise. For optimal efficacy in treating chronic inflammation oxpentifylline may have to be used synergistically.[6] One month's supply (400 mg tds) costs approximately $80 in Australia.

You will not read much about company-sponsored trials as the drug is out of patent and regulatory agencies do not favour drug combinations. The big question is whether support can be found for clinical trials of non-protein TNF-blockers. Positive outcomes might be much reduced costs to the PBS and widening the availability of TNF inhibition therapy.

Michael Whitehouse
Therapeutics Research Unit
Department of Medicine
Princess Alexandra Hospital
Woolloongabba, Qld

References

1. Lu CY, Day RO, Williams KM. Lack of evidence for an association between rheumatoid factor status and clinical response in patients with rheumatoid arthritis treated with TNF alpha inhibitors. Intern Med J 2004;34:S104.
2. Strieter RM, Remick DG, Ward PA, Spengler RN, Lynch JP, Larrick J, et al. Cellular and molecular regulation of tumor necrosis factor-alpha production by pentoxifylline. Biochem Biophys Res Commun 1988;155:1230-6.
3. Ward A, Clissold SP. Pentoxifylline. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy. Drugs 1987;34:50-97.
4. Nery JA, Perisse AR, Sales AM, Vieira LM, Souza RV, Sampaio EP, et al. The use of pentoxifylline in the treatment of type 2 reactional episodes in leprosy. Indian J Lepr 2000;72:457-67.
5. Sampaio EP, Moraes MO, Nery JA, Santos AR, Matos HC, Sarno EN. Pentoxifylline decreases in vivo and in vitro tumor necrosis factor-alpha (TNF-alpha) production in lepromatous leprosy patients with erythema nodosum leprosum (ENL). Clin Exp Immunol 1998;111:300-8.
6. Whitehouse MW. (Point of view) Anti-TNF-α therapy for chronic inflammation: reconsidering pentoxifylline as an alternative to therapeutic protein drugs. Inflammopharmacology 2004;12:223-7.

Professor G. McColl, the author of the article, comments:

I agree that the presence or absence of rheumatoid factor in patients treated with TNF inhibitors may not alter the likelihood of them responding. Studies subsequent to those used for the submission to the Australian Pharmaceutical Benefits Advisory Committee have shown that rheumatoid factor may not be a response-modifier, but further analysis of this information is required. I also agree about the increase of infectious risk when using TNF inhibitors and all clinicians using these agents must remain vigilant with regard to this risk.

Oxpentifylline and thalidomide do have anti-TNF effects, but the magnitude of their biological effect in rheumatoid arthritis appears modest, and certainly less than the TNF inhibitors described in my review, even when used in combination with methotrexate.[1,2,3,4] Complications of thalidomide, especially neuropathy, also limit its clinical applicability in rheumatoid arthritis. The final comment about testing medications not protected by patent is reasonable and clearly work in this area will have to be investigator-driven and supported by institutions such as the National Health and Medical Research Council or the National Institutes of Health.

References

1. Dubost JJ, Soubrier M, Ristori JM, Beaujon G, Oualid T, Bussiere JL, Sauvezie B. An open study of the anti-TNF alpha agent pentoxifylline in the treatment of rheumatoid arthritis. Rev Rhum Engl Ed 1997;64:789-93.
2. Huizinga TW, Dijkmans BA, van der Velde EA, van de Pouw Kraan TC, Verweij CL, Breedveld FC. An open study of pentoxyfylline and thalidomide as adjuvant therapy in the treatment of rheumatoid arthritis. Ann Rheum Dis 1996;55:833-6.
3. Scoville CD. Pilot study using the combination of methotrexate and thalidomide in the treatment of rheumatoid arthritis. Clin Exp Rheumatol 2001;19:360-1.
4. Gutiérrez-Rodríguez O, Starusta-Bacal P, Gutiérrez-Montes O. Treatment of refractory rheumatoid arthritis: the thalidomide experience. J Rheumatol 1989;16:158-63.

Dispensing practices and labelling of drugs

Editor, – As a consumer of various prescription drugs I am concerned at the dispensing practices of some pharmacists with regard to exterior packaging of jars containing drugs.

For example, one of the drugs I regularly take is methotrexate which is packed into a small plastic jar, which is then packed inside a box. The extra packaging (that is, the box) is usually discarded and the jar containing the tablets is kept in the cabinet. What concerns me is that the pharmacist's label with the doctor's instructions for use is too often placed on the exterior box!

These are not blister packs, but jars within boxes. Other drugs I take that are dispensed in the same manner are leflunomide and calcium folinate. How many other drugs are dispensed in this manner?

Can you understand my concern regarding the possible mismanagement of drugs when labels are not present on jars? Is this standard practice for dispensing, or do the guidelines need to be reviewed?

Vivienne McCullagh
Kellyville, NSW

Ms Kerry Deans, Chief Executive Officer, Pharmaceutical Society of Australia, comments:

Pharmacists are required by State legislation to place dispensing labels on medicine containers which are usually understood to be the primary container. There are exceptions on some types of medicines, but I do not believe these are relevant in this case.

As you would be aware, there is also much other mandatory information (e.g. trade name, active ingredient name, dose form, strength, quantity, expiry date, warning statements and other regulatory requirements) that the manufacturer must provide on the original label on the container of prescription medicines.

There is a general expectation that pharmacists should not obscure any vital information on the manufacturer's label when affixing the pharmacy dispensing label. At times this presents a challenge, particularly with small containers, and pharmacists may opt to 'flag' the label (where part of the label is folded back onto itself) or place the label on the outer box or packaging.

In such cases it would be reasonable to expect the pharmacist to provide verbal reinforcement of the key messages as well as perhaps an explanation of why the dispensing label has not been placed on the primary container.

In some instances it may also be beneficial if the patient was able to communicate their preference to assist with safe and appropriate administration and quality use of medicines.

Changes to the shelf-life of thyroxine

Editor, – In June 2003 the Therapeutic Goods Administration (TGA) instructed Sigma Pharmaceuticals to reduce the shelf-lives of Oroxine and Eutroxsig – the Australian brands of thyroxine – from 24 months to 12 months (with refrigeration). This was in light of evidence that their potency was reduced at the end of their shelf-life. Sigma, following consultation with the TGA, has been able to extend the shelf-life of these products to 18 months (with refrigeration), with a maximum unrefrigerated period of 4 weeks (below 25°C).

While Thyroid Australia understands and appreciates the TGA's efforts to ensure the potency of thyroxine for the entirety of its shelf-life, we view the change to refrigeration as a retrograde step in the treatment of hypothyroidism in Australia.

We are concerned that this change could have a negative impact on compliance. In addition, it seems Australia is the only country where thyroxine tablets require refrigeration. In many countries the shelf-life unrefrigerated is much longer than 18 months. This leads Thyroid Australia to question the TGA's approach to remedying potency issues with thyroxine. Addressing the matter by introducing refrigeration places the burden on patients.

Due to thyroxine, hypothyroidism is a readily treatable condition. It enables affected individuals to lead very close to normal lives. This change moves hypothyroidism from a condition that can be easily lived with, to a condition that impinges upon everyday life. In particular, it places limits on travel and spontaneity. We hope that refrigeration is only an interim measure until a more viable long-term solution is found.

Gail Pascoe
President, Thyroid Australia
Melbourne

Dr Leonie Hunt, Assistant Secretary, Drug Safety & Evaluation Branch, Therapeutic Goods Administration, comments:

The Therapeutic Goods Administration has been working with the manufacturer and sponsors of thyroxine tablets to review the potency of the tablets throughout their shelf-life. There have been a number of consumer complaints about apparent lack of potency of thyroxine tablets over time. It is apparent that these tablets do not maintain their full potency if stored at room temperature.

For this reason it has been considered necessary to change recommended storage conditions of the tablets so they are now recommended to be stored in the refrigerator. It is essential that there be no significant variability in the potency of tablets either within any one bottle of tablets or between successive bottles of tablets. Refrigerated storage will assist in this endeavour.

The shelf-life of a medicine in any country will depend on a number of factors including the manufacturing within that country, room temperature conditions and factors related to the final formulation sold in the market place. What is important is that the shelf-life and storage conditions chosen for a market place result in the brands in that market place having reliable stability and potency over time.

Editorial note:
Sigma Pharmaceuticals, the manufacturer of thyroxine tablets, did not wish to add to the discussion.

Off-label prescribing

Editor, – Roger Goucke calls for *Australian Prescriber* to clarify the situation with regard to off-label prescribing (Aust Prescr 2004;27:82–3). NSW Therapeutic Advisory Group (NSW TAG)* has recently released a discussion paper to guide clinicians, policy makers and funders of health care in systematically evaluating the appropriateness of medicines proposed for off-label use.

In calling for clarification, Dr Goucke focuses his concerns on the legal issues associated with off-label use of medicines. Neither the Therapeutic Goods Administration in Australia nor the Food and Drug Administration in the USA[1] regulate the use (including administration) of a medicine once it has been supplied by a product sponsor. Therefore off-label use by a practitioner (who was not a sponsor of the medicine) does not appear to be in breach of the *Therapeutic Goods Act 1989* (Commonwealth) or the US Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040. Although this has not been tested in an Australian court, it has been tested in US courts and found not to breach US legislation.[2]

In addition to legal issues, however, clinical and ethical issues, including patient consent, also need to be considered in any decision to prescribe medicines off-label. The NSW TAG Discussion Paper highlights these issues and provides a systematic approach to addressing them. The paper may be accessed on NSW TAG's web site www.nswtag.org.au

* NSW TAG is an independent, incorporated association of clinical pharmacologists, pharmacists and clinicians committed to promoting quality use of medicines in public hospitals and the wider community.

Maria Kelly
Executive Officer
New South Wales Therapeutic Advisory Group (NSW TAG)

Madlen Gazarian
Senior Lecturer, School of Women's and Children's Health
University of New South Wales
Paediatric Clinical Pharmacologist and Rheumatologist
Sydney Children's Hospital, Randwick

John McPhee
Legal Academic
Honorary Associate and Honorary Senior Lecturer
Centre for Values, Ethics and Law in Medicine
University of Sydney

References

1. Blum RS. Legal considerations in off-label medication prescribing. Arch Intern Med 2002;162:1777-9.
2. Buckman Co. v. Plaintiffs' Legal Committee. 531 U.S. 341 (2001).

Management of mild depression in general practice: is self-help the solution?

Kelsey Hegarty, Director of Postgraduate Programs, Department of General Practice, University of Melbourne, Melbourne

Summary

Mild depression is a common but often hidden problem in patients attending general practitioners. Current evidence is unclear about whether these patients need to be identified. The best management strategy is also unclear. There are very few data from general practice studies to guide us, however there seems to be no evidence to support the use of antidepressants in mild depression. Psychological strategies, St John's wort and self-help strategies may be of assistance to patients with mild depression. An approach that allows people to ventilate their concerns and have them validated, combined with self-help strategies, such as cognitive behaviour therapy programs or exercise programs, may be of most assistance to mildly depressed patients.

Key words: antidepressants, cognitive behaviour therapy, counselling.

(Aust Prescr 2005;28:8–10)

Introduction

Depression is a large cause of disability in Australia. It is mainly managed in general practice, but current guidelines for treatment are generally based upon data that have not been collected in general practice.[1] Despite much national effort to implement management guidelines and the availability of effective treatments, around half the patients experiencing depression are unlikely to be diagnosed as 'depressed' by their general practitioner. About 40% of the group that do receive treatment will experience persistent or relapsing depression.[2] General practitioners seem least likely to miss patients with severe and persistent episodes of major depression, where antidepressant pharmacotherapy should be considered as part of their treatment.

The cases general practitioners miss seem more likely to be towards the mild end of the spectrum. Minor depression is a major factor underlying the use of general practitioners' services.[3] Is it a problem that minor depression is missed or not treated by general practitioners?

What is mild or minor depression?

The depression seen in general practice often coexists with physical conditions. It has a fluctuating course and usually is of shorter duration and meets fewer of the diagnostic criteria for major depression than the depression seen in psychiatric clinics. Distinguishing between the different types of depression is often very difficult and the DSM IV classification system[4] is not useful for many general practitioners.

Mild or minor depression often overlaps with dysthymia and mild major depression. However, general practitioners tend not to use these definitions and, like their patients, see depression as mild, moderate or severe. Both general practitioners and their patients view depressed mood as being in response to the patients' social situation, life events or chronic physical illness. They may not make the distinction between emotional distress and depression occurring in the absence of an external precipitant.

What is the natural history of mild or minor depression?

Major depression occurs in about 5% of patients attending general practice and minor depression is thought to be two to three times more common.[5] Many studies only enrol patients with major depression who are taking, or willing to take, antidepressant medication. This excludes the large group of patients who are seen in primary care. As a result, little is known about the natural history of mild or minor depression in the primary care setting.[2]

General practitioners who initially miss depression, particularly in patients who present with somatic symptoms, often diagnose it at subsequent visits. However, in one study 14% of the patients who were initially missed remained significantly depressed three years later.[6] There is no evidence that routine screening for depression would necessarily result in a better outcome for these patients.[7]

How should mild depression be treated?

The management of any patient who is depressed should include:

- discussion with the patient about the nature of depression and its course
- discussion about treatment options and likelihood of response to treatment

- reassurance as to the effectiveness of treatment – this is important in combating the feelings of hopelessness and in maintaining treatment adherence
- consideration of specific psychological strategies, for example cognitive behaviour therapy, interpersonal therapy, problem solving therapy (Table 1).

In clinical practice, psychological strategies are generally used to help patients with mild depression and may be considered as first-line treatment. The main non-pharmacological treatment used by general practitioners is still supportive counselling.

Counselling at a basic level involves active listening, allowing patients to tell their story over a series of visits and to be listened to in a way that enables them to reflect on the path that they could take to recovery. Active listening is an interactive, engaging process whereby the listener focuses attention on the person and attempts to understand and interpret the non-verbal and verbal messages. The listener then uses verbal and non-verbal techniques to communicate that they have heard and understood the message. This requires attending, following, directing and reflecting skills. However, there has been no published randomised controlled trial involving general practitioners using active listening techniques for patients with minor depression.

The Australian Government has introduced initiatives, which include incentives for general practitioners to undertake further mental health training in the belief that this will improve their management of depression. This training has particularly encouraged the use of focused psychological strategies which have some evidence to support them, for example cognitive behaviour therapy and problem solving therapy.[8]

A systematic review comparing brief psychological therapy (cognitive behaviour therapy or interpersonal therapy) with usual care for patients with major depression included six primary care studies.[8] Overall, patients were more likely to experience remission of the depression in the psychological therapy group, although there have been no published studies examining cognitive behaviour therapy or interpersonal therapy in patients with minor depression or dysthymia.

Some small randomised studies have looked at problem solving therapy and shown that it may be as effective as antidepressants for moderate depression. However, there are very limited efficacy data on patients in general practice with mild depression.

St John's wort

St John's wort, also known as *Hypericum perforatum*, is one of the many herbal remedies readily available over the counter to the general public in Australia. There is growing evidence that St John's wort can effectively treat mild to moderate forms of depression in the short term, although there are no long-term efficacy and safety data available on its use. St John's wort has been well tolerated in trials, with fewer adverse effects being reported than with antidepressant drugs, although it does have the potential for a variety of drug interactions.[9] The potential interactions with commonly used medications have considerable implications for general practitioners, regardless of whether they would actively encourage their patients to use St John's wort. The Therapeutic Goods Administration in Australia has issued an 'Information sheet for health care professionals' to outline the potential risks.[10]

Table 1

Specific psychological strategies

Type of therapy	Method used
Cognitive behaviour therapy	Uses structured approaches to modify thoughts and behaviours Challenges automatic negative thoughts and irrational beliefs, and encourages the development of constructive responses
Interpersonal therapy	Focuses on current interpersonal experiences Improves quality of relationships
Problem solving therapy	Identifies significant problems Generates practical and achievable solutions Evaluates the preferred solutions

For minor depression, there are insufficient research data to support the efficacy of 'newer antidepressants'

Antidepressant use

The use of antidepressant drugs has increased dramatically over the last decade, in response to greater awarenesss by general practitioners and patients and the availability of selective serotonin reuptake inhibitors. Much of this prescribing may be to primary care patients with minor depression. This is despite the fact that for minor depression, there are insufficient research data to support the efficacy of 'newer antidepressants' such as selective serotonin reuptake inhibitors and there is no good evidence that tricylic antidepressants work.[11] Even for mild major depression, psychological strategies using cognitive behaviour therapy or problem solving techniques have similar efficacy to antidepressants. For dysthymia or chronic mild major depression there is evidence that tricyclic antidepressants and selective serotonin reuptake inhibitors are as effective as each other.

If the patient is presenting with either a recurrent episode of major depression or an initial episode with moderate to severe

depression or with psychotic features, then psychological therapy is not first-line. Antidepressants may similarly be indicated for people who are not responding to psychological therapy.

Self-help

In Australia, it is very difficult for depressed patients to find accessible, affordable and timely counselling by psychologists or psychiatrists. Many general practitioners have recommended self-help books and more recently the internet to help their patients. What is the evidence that this is of any use? Recent systematic reviews have found that bibliotherapy (self-help books and leaflets)[12] and computerised cognitive behaviour therapy programs[13,14] can assist patients with depression and/or anxiety over and above usual care. For mild depression, it may be that access to these resources could be the cheapest and most effective management strategy that general practitioners can use. Exercise has also been shown to be of assistance in improving mood and in one study it lowered relapse rates compared to antidepressants for patients with persistent depression.[12]

Conclusion

Mild or minor depression is very commonly managed by general practitioners, and the majority of patients probably get better by themselves or with a supportive 'waiting' approach. In a small proportion of patients, the depression becomes chronic and disabling.

All of the management strategies have been studied in patients with major depression, mostly in secondary or tertiary care settings. There is no evidence to support the use of antidepressants in general practice patients who do not meet the criteria for major depression or dysthymia. There are limited data from primary care settings on the usefulness of psychological strategies, St John's wort and self-help strategies.

Supported self-help programs based on cognitive behaviour therapy and exercise programs may be the most appropriate strategies to use with patients experiencing mild depression. Listening carefully to patients' stories can be an intervention by itself and will allow the many social factors (work, relationship, family) and other factors (abuse, illness, alcohol) that interact with depression to emerge. Patients who are not improving should be reassessed as they may be becoming more depressed and may require the addition of drug treatment.

References

1. Hickie IB. Primary care psychiatry is not specialist psychiatry in general practice. Med J Aust 1999;170:171-3.
2. van Weel-Baumgarten EM, Schers H, van den Bosch WJ, van den Hoogen H, Zitman FG. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. J Fam Pract 2000;49:1113-20.
3. Simon GE. Long-term prognosis of depression in primary care. Bull World Health Organ 2000;78:439-45.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
5. Mitchell PB. Managing depression in a community setting. Med J Aust 1997;167:383-8.
6. Kessler D, Bennewith O, Lewis G, Sharp D. Detection of depression and anxiety in primary care: follow up study. Br Med J 2002;325:1016-7.
7. Gilbody SM, House AO, Sheldon TA. Routinely administered questionnaires for depression and anxiety: systematic review. Br Med J 2001;322:406-9.
8. Bower P, Rowland N, Hardy R. The clinical effectiveness of counselling in primary care: a systematic review and meta-analysis. Psychol Med 2003;33:203-15.
9. Linde K, Mulrow CD. St John's wort for depression (Cochrane Review). In: The Cochrane Library, Issue 4, 2004. Chichester, UK: John Wiley & Sons, Ltd.
10. St John's wort: information sheet for health care professionals. http://www.tga.gov.au/docs/html/info.htm [cited 2005 Jan 10]
11. MacGillivray S, Arroll B, Hatcher S, Ogston S, Reid I, Sullivan F, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. Br Med J 2003;326:1014.
12. Jorm AF, Christensen H, Griffiths KM, Rodgers B. Effectiveness of complementary and self-help treatments for depression. Med J Aust 2002;176 Suppl:S84-S96.
13. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. Br Med J 2004;328:265.
14. Proudfoot J, Goldberg D, Mann A, Everitt B, Marks I, Gray JA. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depresssion in general practice. Psychol Med 2003;33:217-27.

Further reading

Burns D. Feeling good: the new mood therapy. New York: William Morrow; 1980.

Lewinsohn PM, Munoz RF, Youngren MA, Zeiss AM. Control your depression. Englewood Cliffs, NJ: Prentice-Hall; 1986.

Blue Pages: information on depression. http://bluepages.anu.edu.au [cited 2005 Jan 10]

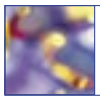
The MoodGYM training program: delivering cognitive behaviour therapy for preventing depression. http://moodgym.anu.edu.au [cited 2005 Jan 10]

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

3. Clinical trials show that antidepressant drugs are the most effective treatment for minor depression in general practice.
4. Screening for depression in general practice improves the outcomes for patients.



Diagnostic tests

Diagnosing dementia: mental status testing and beyond

Catherine E. Meade, Senior Clinical Neuropsychologist, St Vincent's Hospital, Melbourne, and Stephen C. Bowden, Honorary Head of Neuropsychology, St Vincent's Hospital, and Associate Professor, School of Behavioural Science, The University of Melbourne, Melbourne

Summary

The rising prevalence of dementia in Australia means that general practitioners will have an increasingly important role in the timely and accurate assessment of this condition. Two tools that are commonly used for assessing dementia are the Mini-Mental State Examination and the Alzheimer's Disease Assessment Scale (Cognitive sub-scale). The utility of these tools is maximised by the inclusion of information from other relevant sources, such as the patient's carers, and from clinical evaluation of the patient. These tests are not as complete as neuropsychological assessments. Referring patients for a more detailed assessment is appropriate when the diagnosis of dementia is in doubt.

Key words: Alzheimer's disease, Alzheimer's disease assessment scale, mini-mental state examination.

(Aust Prescr 2005;28:11–13)

Introduction

The requirement that patients with Alzheimer's disease must be assessed before drugs such as donepezil can be supplied through the Pharmaceutical Benefits Scheme (PBS) has focused attention on psychological testing of cognitive status. As the prevalence of neurodegenerative conditions is increasing, early accurate diagnosis is important so that patients can be treated promptly or referred for further assessment as required. General practitioners can play a vital role in this assessment.

Assessment tools

Despite the many advances in our understanding of Alzheimer's disease, primary diagnosis still relies on the identification of cognitive decline.

The most widely used cognitive assessment tool in primary care settings is the Mini-Mental State Examination (MMSE, see www.minimental.com). It provides a brief evaluation of the cognitive domains affected in Alzheimer's disease, including orientation, registration, attention, recall, language and constructional praxis.[1] Patients' scores range from 0 to 30, with low scores indicating greater cognitive impairment. Scores less than 24 are conventionally interpreted as evidence of a dementing illness.

Another instrument, which has gained more attention after it was used in antidementia drug trials, is the Alzheimer's Disease Assessment Scale – Cognitive sub-scale (ADAS–Cog).[2] The primary cognitive functions sampled are similar to those of the MMSE, including components of memory, language and praxis. This test takes about 30 minutes. The ADAS–Cog is scored from 0 to 70, but in contrast to the MMSE, higher scores indicate greater cognitive impairment.

Although testing is required before antidementia drugs can be supplied through the PBS (see box) the availability of ADAS–Cog kits is now limited. The manufacturer of one of the antidementia drugs, which originally distributed the kits in Australia, is no longer doing so. Patients may therefore need to be referred to a neuropsychologist or other professional who is familiar with using the ADAS–Cog in the context of broader psychological assessment.

Problems with brief cognitive tests

Any brief screen or assessment of a complex behaviour such as cognition has limitations.

Authority prescriptions

The Pharmaceutical Benefits Scheme requires that the diagnosis of dementia must be confirmed by a specialist if donepezil, galantamine or rivastigmine is prescribed. Applications for authority prescriptions must state the result of the baseline MMSE and, if this score is at least 25 points, the application must also include the result of the baseline ADAS–Cog. After six months repeat prescriptions will only be approved if the MMSE score has increased by two points, or, in cases where the baseline MMSE is at least 25 points, the ADAS–Cog has decreased by at least four points.

Despite its widespread clinical use, and like all brief dementia-screening tests, the MMSE has been criticised[3] for:

- being insensitive to patients with mild cognitive impairment
- lacking diagnostic specificity
- not taking into account levels of education, premorbid ability, and other patient variables such as visual problems or poor command of English.

Dementia may be missed in some patients, and other patients without dementia may be misclassified. A normal score on the MMSE does not necessarily exclude a brain abnormality or dementia.

There is also some uncertainty about the clinical relevance of changes in MMSE scores, owing to relatively high measurement error. This limits the ability of the MMSE to document change in individual patients over time. Clinical studies have shown wide variability in the way the average MMSE score changes over time. In view of problems with accuracy and reproducibility, the MMSE may be of limited value in tracking change in patients with Alzheimer's disease who are followed up for less than three years.[3] Even in patients followed up for four years or more, 16% of patients with an initial diagnosis of probable Alzheimer's disease showed no meaningful decline in MMSE scores.[3,4]

The ADAS–Cog shares many of the limitations reported for the MMSE. Scores on the ADAS–Cog are also variable. For example, in the original clinical study of the scale, 27 patients with Alzheimer's disease and 28 normal elderly people were rated then re-tested 12 months later. The range of scores corresponding to one standard deviation from the mean in the Alzheimer's disease group was 0 to 31 at baseline, and 0 to 38 at 12 months, demonstrating wide variability in scores. Perhaps not surprisingly given this variability, only eight of the patients with Alzheimer's disease showed a significant increase in the severity of their dysfunction after 12 months.[2]

The need for more information

The limitations of the tests in indexing change highlight the importance of referring patients with suspected Alzheimer's disease for specialist psychological assessment. Comprehensive psychological assessment is necessarily a time-consuming process. It is not possible to capture a reliable sample of behaviour in a few minutes, particularly in anxious elderly patients. Thorough cognitive assessment may be more valuable in terms of diagnosis and long-term outcome. It may also provide important information about other confounding cognitive, mood or personality changes. Additional allied health assessments, for example by an occupational therapist, can provide useful information regarding functional capacities.

Supporting information

General practitioners can improve the sensitivity of clinical assessment by looking for other evidence of symptoms or evidence of functional change in everyday life. This evidence may come from the patients or other informants, such as carers.

Questionnaires completed by informants can be a helpful adjunct to cognitive assessment. They can quantify information about aspects of memory and broader intellectual function in everyday life. Informant accounts are not without limitations, including the complicating effect of the emotional state of the patient and of the informant, and the relationship between the patient and informant. However, research[4,5] on clinical and community samples of elderly participants suggested that using informant questionnaires and cognitive screening together yields more information and provides better sensitivity than either tool used alone. For example, compared to clinical diagnosis of dementia, the MMSE has a sensitivity of 0.75 and a specificity of 0.82. Combining the MMSE with the Informant Questionnaire on Cognitive Decline in the Elderly[6] increased sensitivity to 0.92 with a specificity of 0.78.[5]

Memory symptoms reported by patients may have some predictive validity if they are developing dementia.[7] However, the patient's affect has a strong influence on self-report of cognitive impairment. This can confound how they report their symptoms and needs to be carefully addressed. Signs of a mood disorder with or without cognitive symptoms therefore warrant treatment or referral for further assessment. In patients already taking psychoactive medication, the potential benefit of withdrawal of medication for a better appreciation of current cognitive status needs to be weighed against potential difficulties with ongoing management of mood.

Where to get help

Accurate and thorough clinical examination of patients with memory disturbance, incorporating a range of psychological investigations, is relatively time-consuming and expensive. The inherent time and cost pressures of primary care settings expose patients to the risk that dementia will be missed or misclassified by brief screening tests. Memory clinics at major hospitals may be a helpful referral point to assist primary care providers. Alternatively neuropsychological services may be accessed through private providers or the Australian Psychological Society referral service*.

For other helpful resources related to assessment and management of patients with Alzheimer's disease, general practitioners can refer to Alzheimer's Australia (www.alzheimers.org.au).

* Telephone (03) 8662 3300 or 1800 333 497

References

1. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
2. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356-64.

3. Clark CM, Sheppard L, Fillenbaum GG, Galasko D, Morris JC, Koss E, et al. Variability in annual mini-mental state examination score in patients with probable Alzheimer disease: a clinical perspective of data from the consortium to establish a registry for Alzheimer's disease. Arch Neurol 1999;56:857-62.
4. Mackinnon A, Mulligan R. Combining cognitive testing and informant report to increase accuracy for dementia. Am J Psychiatry 1998;155:1529-35.
5. Mackinnon A, Khalilian A, Jorm AF, Korten AE, Christensen H, Mulligan R. Improving screening accuracy for dementia in a community sample by augmenting cognitive testing with informant report. J Clin Epidemiol 2003;56:358-66.
6. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19:1015-22.
7. Jorm AF, Christensen H, Korten AE, Jacomb PA, Henderson AS. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. Psychol Med 2001;31:441-9.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 23)

5. A high score in the Mini-Mental State Examination means the patient has probable dementia.
6. Memory is affected by mood.

Website review

Media Doctor website

www.mediadoctor.org.au

Mary Hemming, Chief Executive Officer, Therapeutic Guidelines, Melbourne

The reporting of new medical treatment in the lay media usually leaves much to be desired. So it is pleasing to see a website dedicated to improving the accuracy of such reporting.

The team behind Media Doctor consists of a group of academics and clinicians from the Newcastle Institute of Public Health. They have an interest in promoting better and more accurate reporting in the area of medical treatments.

Media Doctor reviews current news items about medical treatments, assesses their quality using a standardised rating scale, including criteria such as novelty of treatment, treatment options, disease mongering, evidence, and a quantification of benefits, harms and costs of treatment. The site presents reviews of good and bad examples of reports, the hope being that these independent and objective critiques will improve journalistic practices in reporting new medications and treatments.

Recently reviewed articles are listed on the home page and from each of the headings both the original article and the related review can be accessed. The site can be searched for articles by news source, intervention type, disease or specific words.

The site loads quickly, is easily navigable and each topic is clearly presented. However, there are several design elements that could be addressed that would improve the overall readability. For example, on the home page it would be more intuitive for the overview of the site to be displayed on the left hand side of the page, with the list of recent topics on the right, or even on a separate page. Also, it is jarring for major headings to be in a smaller font than lower level headings. Finally, the menu headings are a bit too cryptic to indicate content – a 'tooltip' window that appears when you hover your mouse over each menu option would resolve the problem.

The information that this website offers is extremely useful, but the burning question is – how is it being publicised? Ensuring target groups, especially senior editorial staff, are aware of the site is the only way for it to have an impact, but it is unclear from the site whether or how it is promoted.

This is an important initiative, but it needs significant public exposure if it is to achieve its aim.

PBAC questions: update

In the December issue of *Australian Prescriber* (Aust Prescr 2004;27:155) readers asked the Pharmaceutical Benefits Advisory Committee (PBAC) about the restriction on prescribing narcotic analgesics for chronic pain. The PBAC has now relaxed the requirements for authority prescriptions for increased maximum quantities and repeats of some narcotic analgesics.

High-risk medication alert: intravenous potassium chloride

James F. Reeve, Project Pharmacist, and Yvonne M. Allinson, Executive Director, The Society of Hospital Pharmacists of Australia; and Adele Stevens, Assistant Director (retired), Management Group, Australian Council for Safety and Quality in Health Care

Summary

Patients have died in hospitals both in Australia and overseas after being mistakenly injected with potassium chloride instead of normal saline. In an effort to reduce the risks associated with the use of intravenous potassium chloride, the Australian Council for Safety and Quality in Health Care has issued a high-risk medication alert for intravenous potassium chloride. This alert contains recommendations for prescribing, storage, preparation and administration of intravenous potassium chloride.

Key words: adverse effects.

(Aust Prescr 2005;28:14–16)

Case 1

An elderly patient was admitted to hospital for investigation of weight loss and anaemia. The patient had a history of chronic renal failure and hypertension with underlying coronary disease. X-rays disclosed deteriorating cardiac failure.

As part of the investigation a colonoscopy was performed, but a perforation occurred necessitating a sigmoid colectomy. In the intensive care unit the patient developed cardiac complications with rapid atrial fibrillation and hypotension. The potassium concentration was 3.6 mmol/L (normal range 3.5–5.0 mmol/L) and was suspected as the cause of the atrial fibrillation. A dose of 2 g of potassium chloride was prescribed. This was administered as an intravenous infusion over a period of less than 10 minutes. The patient suffered a cardiac arrest and died. The inquest found that the rapid infusion of potassium chloride caused the cardiac arrest, which led to the death of the patient.[1]

Case 2

An elderly patient was admitted to hospital for terminal care. The patient was receiving total parenteral nutrition via a Hickman (Cook) intravenous catheter. This was flushed with heparinised saline three times per week. Instead of saline, two ampoules of potassium chloride were inadvertently selected and used to flush the catheter. Before the flushing was completed, a nurse observed that the patient 'clutched her chest and rolled her eyes'. The patient immediately had a cardiac arrest and died.

The coroner's investigation found that routine procedures for checking of the correct drug against the medication chart were not followed.[1]

Comment

The risks associated with intravenous potassium chloride are well known. If it is injected too rapidly or in too high a dose, it may cause cardiac arrest within minutes. The effect of hyperkalaemia on the heart is complex – virtually any arrhythmia may be observed.[2]

The true incidence of potassium-related fatalities and incidents is unknown. Fatal intravenous injection of potassium produces no specific anatomic changes and subtle, if any, findings at autopsy.[3] A search of the national Australian database of coronial findings (the National Coroners Information System) containing data from all States and Territories from January 2001 found no fatalities associated with potassium chloride. A more detailed keyword search was possible within the Victorian case management system. This uncovered five fatalities associated

Recommendations from Safety and Quality Council medication alert: intravenous potassium chloride can be fatal if given inappropriately [5]

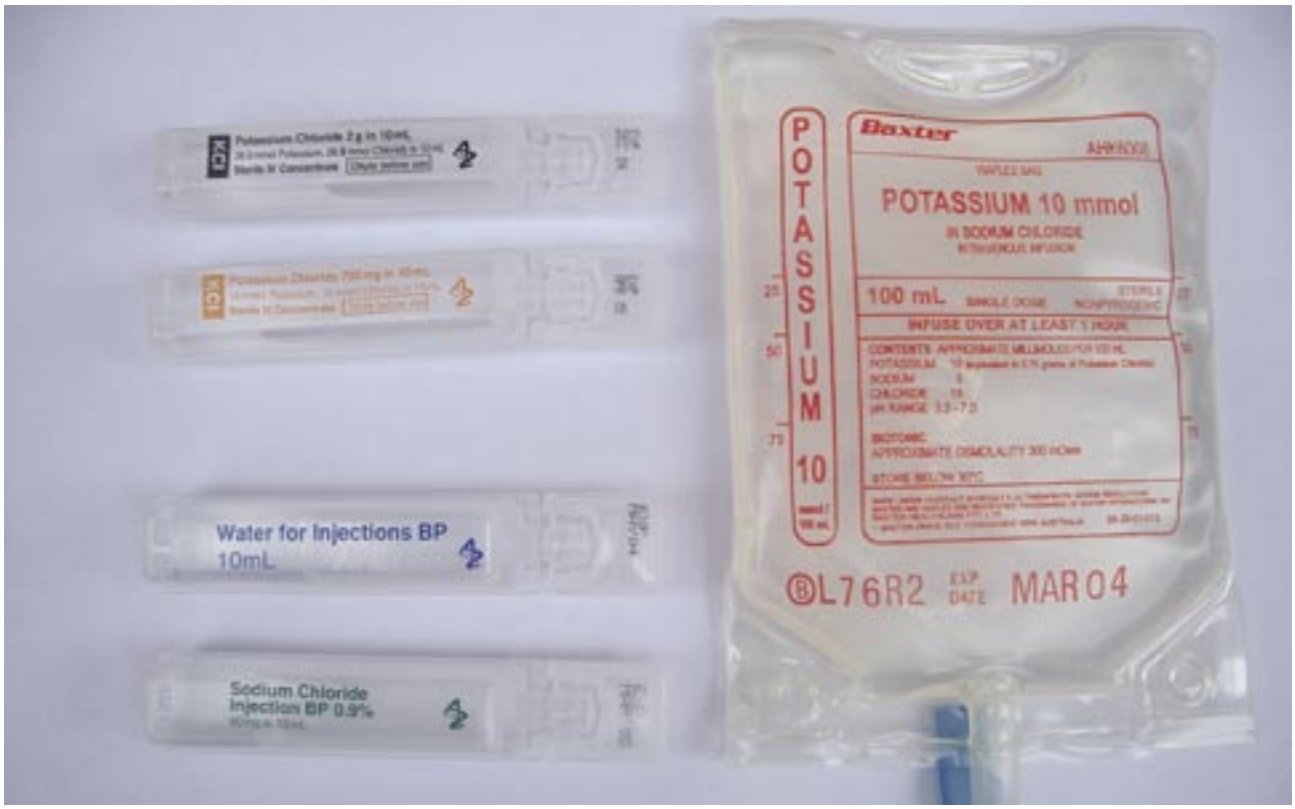
1. **REMOVE AMPOULES OF POTASSIUM CHLORIDE FROM WARD STOCK AND REPLACE WITH PREMIXED SOLUTIONS.**

   Due to the risk associated with intravenous potassium chloride, ampoules of potassium chloride SHOULD NOT be kept as a stock item in wards.
2. In critical areas where high concentrations and doses of potassium chloride are necessary, do a risk assessment to determine whether it is appropriate to keep the ampoules as a stock item and develop a protocol for safe preparation and use.
3. Assess the storage of potassium chloride ampoules and premixed solutions to ensure they are stored separately and are readily identifiable from preparations with similar packaging.

The recommendations also apply to ampoules of potassium phosphate or other concentrated potassium salts.

Fig. 1

Ampoules of potassium chloride have been confused with other ampoules (and administered by mistake)



Picture provided by J. Reeve

On left, 10 mL ampoules containing, from the top:

- Potassium chloride 2 g
- Potassium chloride 750 mg
- Water for injections
- Sodium chloride 0.9%

On right:

- Minibag of 750 mg potassium chloride in 100 mL sodium

with potassium chloride between 1992 and 1997 and an open case from July 2003. The Australian Incident Monitoring System (AIMS) and AIMS Anaesthetic databases contain details of more than 30 intravenous potassium chloride-related incidents (no fatalities).[4]

Medication incidents associated with intravenous potassium chloride tend to occur due to inadvertent selection and administration of an ampoule of potassium chloride in place of another drug with similar appearance (Fig. 1), or due to an error in preparation or administration.

Prevention

Analysis of incidents associated with intravenous potassium chloride have led patient safety organisations in the USA, Canada, the UK and Australia to recommend a simple way to prevent these tragic deaths – 'replace concentrated ampoules with large-volume premixed solutions in general ward areas in acute care facilities'.[4]

In areas where ampoules of concentrated solution need to be retained, it is recommended that they are stored separately and are readily identifiable from preparations with similar packaging. Overseas and in Australia, manufacturers are taking steps to reduce the problem by colour-coding and/or changing the shape of potassium chloride ampoules.

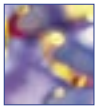
The Australian Council for Safety and Quality in Health Care has issued a high-risk medication alert for intravenous potassium chloride (see box for recommendations).[5] The alert covers prescribing, storage, preparation and administration of intravenous potassium chloride. The alert, and tools to action the recommendations in the alert, is available at www.safetyandquality.org

References

1. Case reports supplied courtesy of the Monash University National Centre for Coronial Information (MUNCCI). Available from the authors on request.
2. Rardon DF, Fisch C. Electrolytes and the heart. In: Schlant RC, Alexander RW, editors. Hurst's The heart. 8th ed. New York: McGraw-Hill; 1994. Ch. 37, p. 759-74.

3. Wetherton AR, Corey TS, Buchino JJ, Burrows AM. Fatal intravenous injection of potassium in hospitalized patients. Am J Forensic Med Pathol 2003;24:128-31.
4. The Society of Hospital Pharmacists of Australia. High-risk medication alert project report. Melbourne: The Society of Hospital Pharmacists of Australia; 2003.
5. Australian Council for Safety and Quality in Health Care. Medication alert: intravenous potassium chloride. Canberra: Australian Council for Safety and Quality in Health Care; 2003. http://www.safetyandquality.org [cited 2005 Jan 10]

Conflict of interest: none declared



Bowel preparation

Richard Sarre, Colorectal surgeon, Adelaide

Summary

Colonoscopy and radiological investigations of the large bowel require the bowel to be cleared of faeces. In addition to dietary restriction, patients are usually given a laxative, orally or rectally. Osmotic laxatives containing sodium phosphate are highly effective, but can cause severe electrolyte disturbances. Polyethylene glycol is an osmotic laxative which is less likely to cause this problem. It is given in an iso-osmotic solution, but patients have to drink several litres of fluid. Stimulant laxatives such as bisacodyl and sodium picosulfate are easy to use, but can also cause electrolyte disturbances.

Key words: laxatives, colonoscopy.

(Aust Prescr 2005;28:16–17)

Introduction

Complete cleaning of the large bowel is essential for colonoscopy and radiological investigation of the colon (barium enema and more recently CT colonography). Bowel preparation has also traditionally been used prior to colonic surgery although the evidence for its benefit is scanty.[1] Investigation for colonic disease is common nowadays so referring doctors should have an understanding of the cleaning products used (see box), their effects, adverse effects and contraindications.

General principles

All bowel preparation regimens require exclusion of high residue foods for at least 48 hours and a diet of clear fluids only for 24 hours before the examination. This will require adjustment of insulin and oral hypoglycaemic medications in patients with diabetes. Although some regimens require patients to drink a lot of fluid, overenthusiastic intake of water can induce hyponatraemia. Patients on diuretic therapy are especially at risk. Fluids free of non-absorbed sugars should be used to reduce the possibility of explosive gas mixtures within the colon.

If possible, medications that may aggravate constipation should be ceased (for example opiates, anticholinergics, antidiarrhoeals and iron supplements). Iron compounds tend to stick to the wall of the colon obscuring the view at colonoscopy and also inhibiting coating with barium during barium enema. Iron should ideally be stopped a week prior to the examination. It should be noted that oral medications taken at the same time as the bowel preparation may be poorly or incompletely absorbed (for example oral contraceptives, antihypertensives).

Examples of some of the products available for bowel preparation

Phosphate preparations	Fleet phospho-soda buffered saline mixture
	Fleet ready-to-use enema
	Phosphoprep
Polyethylene preparations (with electrolytes)	ColonLYTELY
	Glycoprep
Diphenylmethanes	
bisacodyl	Bisalax
	Durolax
	Fleet laxative preparations
sodium picosulfate (often combined with other laxatives)	Durolax SP
	Picolax
Magnesium preparations (combined with other laxatives)	Picoprep

Sodium phosphate

Phosphate preparations are commonly used orally and rectally to empty the bowel. They are highly effective and well tolerated. The mechanism of action is largely osmotic – increased fluid retention in the intestine causes distension which in turn promotes peristalsis and evacuation of the colon. When sodium phosphate is given orally, diarrhoea occurs within 0.5–4 hours while a bowel action occurs within 10–15 minutes after rectal administration. An adequate oral intake of water is essential.

Phosphate preparations have the potential to cause electrolyte disturbances[2] including serious hyperphosphataemia and hypocalcaemia; deaths have been reported. Sodium phosphate must therefore be avoided in patients with impaired renal function and used with great care in the presence of congestive cardiac failure because of the potential large fluid shifts. The frail, elderly and the very young are particularly at risk of fluid and electrolyte complications and alternative preparations should be used.

Polyethylene glycol

Polyethylene glycol comes mixed with a balanced electrolyte (iso-osmotic) solution and is consumed in a large volume (3–4 litres) of water. This preparation is often poorly tolerated because the patient has to drink a large volume of salty tasting fluid. As polyethylene glycol is a high molecular weight carbohydrate it holds water in the gastrointestinal tract. The volume and balanced electrolyte solution reduces the fluid shifts seen with the other osmotic and stimulant laxatives. There is not the same requirement to consume extra clear fluids and there is considerably less risk of dehydration or electrolyte disturbances. Although it is undoubtedly safer than phosphate preparations, polyethylene glycol can cause nausea, bloating and abdominal pain and may not be tolerated readily. It works within 1–4 hours.

Diphenylmethanes (bisacodyl, sodium picosulfate)

These drugs are hydrolysed by bacteria in the colon to bis (para-hydroxyphenyl)pyridyl-2-methane. This is a locally acting laxative that is minimally absorbed from the gastrointestinal tract. As it is released in the colon, it stimulates peristalsis and promotes water and electrolyte accumulation within the colon. Given orally the effect occurs 6–12 hours after ingestion. If bisacodyl is given as a suppository it is effective within 15–30 minutes. As these stimulant laxatives are easy to administer and have few adverse effects they are commonly used in conjunction with other products (for example magnesium sulphate). Adequate fluids to replace the diarrhoeal losses are essential as electrolyte disturbances can occur.[3]

Magnesium sulfate

Magnesium is a well-known traditional laxative which increases water in the gastrointestinal tract and stimulates peristalsis. A combination of magnesium sulfate and sodium picosulfate is a commonly prescribed oral bowel preparation, presented in two sachets. The contents of each sachet are mixed in a glass of water and taken approximately four hours apart. A laxative effect usually starts within 3–4 hours, but it is important to maintain an adequate oral intake of clear fluids during this time. The combination is relatively contraindicated in the presence of congestive cardiac failure and impaired renal function where the potential for dehydration and dangerous hypermagnesaemia exists.

Conclusion

In controlled trials, phosphate preparations have consistently scored better than polyethylene glycol preparations for patient acceptability and compliance as well as cleanliness of the bowel at colonoscopy.[4] However, because of the potential for large fluid shifts and electrolyte disturbances, phosphate preparations are contraindicated in frail and elderly patients, children and those with cardiac failure or renal impairment.

Products containing diphenylmethane provide ease of administration. They have a lower risk of severe electrolyte disturbances than phosphate preparations, but they are relatively contraindicated in the presence of renal impairment and cardiac failure.

Phosphate preparations provide ease of administration and excellent bowel cleansing. They can be used in the majority of patients. In the presence of impaired renal function, congestive cardiac failure, and with elderly or very young patients, polyethylene glycol solutions are preferred.

References

1. Zmora O, Pikarsky AJ, Wexner SD. Bowel preparation for colorectal surgery. Dis Colon Rectum 2001;44:1537-49.
2. ADRAC. Electrolyte disturbances with oral phosphate bowel preparations. Aust Adv Drug React Bull 1997;16:2.
3. ADRAC. Electrolyte disturbances with sodium picosulfate bowel cleansing products. Aust Adv Drug React Bull 2002;21:1.
4. Young CJ, Simpson RR, King DW, Lubowski DZ. Oral sodium phosphate solution is a superior colonoscopy preparation to polyethylene glycol with bisacodyl. Dis Colon Rectum 2000;43:1568-71.

Conflict of interest: none declared

Should consumers be warned about aspirin, alcohol and gastric bleeding?

David B. Newgreen, Pharmacist, Melbourne, and member, Therapeutic Goods Administration's Medicines Evaluation Committee

Summary

The risk of gastrointestinal bleeding is increased in people who regularly take high doses of aspirin and consume more than three alcoholic drinks a day, but it may also be increased in drinkers who take low-dose aspirin. The intensively competitive non-prescription analgesic market is sensitive to the presence or absence of cautionary and advisory statements, irrespective of the particular analgesic. Australian health authorities have decided against introducing a requirement for aspirin products to have labels advising people who consume more than certain amounts of alcohol to seek medical advice before taking aspirin. The mandatory imposition of such a label is controversial.

Key words: analgesics, over-the-counter medicines.

(Aust Prescr 2005;28:18–19)

Introduction

In 2002, the Therapeutic Goods Administration asked the Medicines Evaluation Committee to update its 1998 review on non-prescription analgesics*. One of the terms of reference was to consider the need for the labels on Australian packages of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) to have the same mandatory statement as in the USA. This statement reads: 'If you consume three or more alcoholic drinks every day, ask your doctor whether you should take [name of drug] or other pain relievers/fever reducers. [Name of drug] may cause stomach bleeding.'

The gastrointestinal effects of aspirin

Salicylates may cause epigastric distress, nausea and vomiting. Gastric ulceration and haemorrhage may also occur. High doses of salicylates can exacerbate the symptoms of peptic ulcer such as heartburn and dyspepsia. Gastric bleeding induced by the salicylates is usually painless and at the recommended dose of over-the-counter aspirin, the blood loss is usually of little significance.

* www.tga.gov.au/docs/html/analgesics.htm [cited 2005 Jan 10]

The gastrointestinal effects of alcohol

Alcohol can cause gastric inflammation and bleeding. A large controlled study in the USA showed that the relative risk of major gastric and duodenal bleeding in non-predisposed individuals was 6.3 when at least 35 standard drinks were consumed weekly.[1] It is important to note that there are differences from country to country in the mass of ethanol in a 'standard drink'. In Australia it is 10 g, but in the USA it is 14 g.

Aspirin with alcohol

The clinical significance of using alcohol and aspirin together is uncertain. Complicating factors in studies include:

- the doses selected for each
- the duration of the study
- the proximity of dosing with each substance
- whether other drugs are taken
- whether the participants are healthy volunteers or people with a history of gastrointestinal disorders.

Epidemiological studies have their own shortcomings, such as the participants' candour about their alcohol consumption and their recollections of analgesic use.[2]

A major epidemiological case-control study based on data collected in the USA and Sweden sought to evaluate whether the deleterious effects of aspirin and other NSAIDs were increased among drinkers.[3] The relative risk of acute upper gastrointestinal bleeding was 2.8 times higher for people who consumed at least 21 drinks per week, than for people who consumed less than one drink per week. The relative risk for all current drinkers increased to 7.0 if they were taking more than 325 mg aspirin at least every other day.

A careful analysis of this study agreed that the relative risk of gastrointestinal bleeding due to aspirin, along with an increasing baseline risk with increasing alcohol intake, is consistent with a rising incidence of gastrointestinal bleeding in aspirin users who are heavy drinkers.[4] The data supporting an additive effect of aspirin and alcohol on the risks of gastrointestinal bleeding are controversial because:

- the relative risk of taking aspirin did not consistently increase with increasing alcohol use for occasional or regular takers of aspirin or for different doses of aspirin
- while the non-drinking controls had a relative risk of bleeding that was increased from baseline by taking NSAIDs, it did not differ statistically from the risk in patients who combine aspirin and alcohol

- irrespective of the dose, kind or frequency of NSAIDs taken, no significant difference was reported to exist overall between NSAID users who described any current drinking, those who were ex-drinkers, and those who never drank.

There is no proof that mild to moderate alcohol use significantly increases the risk of upper gastrointestinal bleeding in patients taking aspirin, especially if the aspirin is taken only as needed. However, people who consumed **at least** 3–5 drinks daily and who regularly took more than 325 mg of aspirin did have a high risk of bleeding.

Commercial considerations

The Medicines Evaluation Committee, while acknowledging the evidence, did not recommend an alcohol warning on labels of aspirin products. A similar warning which appears on US labels of paracetamol with 'liver damage' replacing 'stomach bleeding' was also rejected for Australia. The issue is whether, in order to maintain a degree of commercial parity in the highly competitive over-the-counter analgesic market, both paracetamol and aspirin/NSAIDs should have an alcohol statement (for different reasons) or neither should have it. Anything that will encourage product differentiation can operate to favour one product or, on the other hand, disadvantage its competitor by invidious comparison. Media advertisements that use the term 'gentle to the stomach' for paracetamol suggest, by innuendo, that other over-the-counter analgesics might be less than gentle. However, for most people, the use of over-the-counter doses of aspirin, ibuprofen or paracetamol carries little risk. The regulatory authorities therefore decided not to interfere in the market by imposing mandatory warning labels.

What do clinicians do?

At-risk patients need to be identified. Patients may understate their consumption of alcohol and not think that aspirin and other over-the-counter NSAIDs can cause problems. The clinician may need to alert patients to the risks of all medicines, not just those obtained on prescription. Heavy drinkers who regularly take aspirin are at particular risk of gastrointestinal bleeding.

References

1. Kelly JP, Kaufman DW, Koff RS, Laszlo A, Wiholm BE, Shapiro S. Alcohol consumption and the risk of major upper gastrointestinal bleeding. Am J Gastroenterol 1995;90: 1058-64.
2. Rees WD, Turnberg LA. Reappraisal of the effects of aspirin on the stomach. Lancet 1980;23:410-3.
3. Kaufman DW, Kelly JP, Wiholm BE, Laszlo A, Sheehan JE, Koff RS, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. Am J Gastroenterol 1999;94:3189-96.
4. Pfau PR, Lichtenstein GR. NSAIDs and alcohol: never the twain shall mix? Am J Gastroenterol 1999;94:3098-101.

Further reading

Dart RC. The use and effect of analgesics in patients who regularly drink alcohol. Am J Manag Care 2001;7(19 Suppl):S597-601.

Conflict of interest: none declared

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Articaine hydrochloride with adrenaline

Septanest, Deltazine, Bucanest (Specialites Septodont)

1.7 mL glass cartridges containing 4% articaine and 1 in 100 000 adrenaline

Approved indication: dental anaesthesia

Australian Medicines Handbook section 2.4

Articaine is a local anaesthetic that has been approved overseas for several years. Like other amide anaesthetics, articaine blocks nerve conduction when it is infiltrated around a nerve. This action is prolonged by combining the drug with a vasoconstrictor such as adrenaline.

The combination of articaine and adrenaline can be used for local or regional anaesthesia for dental procedures. Anaesthesia begins within six minutes and lasts for an hour. The half-life of articaine is approximately 1.8 hours. It is metabolised and then mainly excreted in the urine.

Articaine 4% with adrenaline was compared with lignocaine 2% with adrenaline in three double-blind trials. The drugs were given as submucosal infiltrations or nerve blocks before dental procedures. There were no significant differences, on a visual analogue pain scale, between the anaesthesia achieved by the 882 patients given articaine and the 443 given lignocaine.[1]

Approximately one patient in five reported an adverse event after dental anaesthesia. The most common complaint in both groups was postoperative pain, followed by headaches and facial swelling. Although the incidence was less than 1%, paraesthesia and hypoesthesia affected more of the patients treated with articaine. Although some patients developed changes in pulse and blood pressure these could have been related to anxiety

about the injection and the procedure.[2] As with other local anaesthetics it is important that the drug is not injected into a blood vessel. The dental surgery should have resuscitation equipment in case of cardiovascular collapse or convulsions. Although the immunogenic potential of articaine is probably low, it is contraindicated in patients with an allergy to sodium metabisulfite as the formulation includes this antioxidant.

Widespread use of articaine has allowed rare adverse effects to emerge. For example, there may be paralysis of the ocular muscles after posterior, superior alveolar injections of articaine.[3] Although the efficacy of articaine appears to equal that of lignocaine, there does not seem to be a compelling clinical reason for Australian dentists to change their choice of local anaesthetic.

References *

1. Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: a new amide local anesthetic. JADA 2000;131:635-42.
2. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. JADA 2001;132:177-85.
3. Penarrocha-Diago M, Sanchis-Bielsa JM. Ophthalmologic complications after interoral local anesthesia with articaine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:21-4.

Efalizumab

Raptiva (Serono)

vials containing 125 mg lyopholised powder for reconstitution

Approved indication: psoriasis

Australian Medicines Handbook section 8.6.1

The recognition of psoriasis as an autoimmune disorder has prompted research into the role of T-lymphocytes. The activation of these lymphocytes involves leukocyte-function associated antigen type 1 (LFA-1). By binding to LFA-1 efalizumab reduces inflammation by inhibiting the adhesion of T-lymphocytes to other cells.

Efalizumab is a monoclonal antibody produced by genetic engineering. Although it is produced using Chinese hamster ovary cells, the molecule is humanised. Efalizumab has to be given by weekly subcutaneous injections.

A placebo-controlled trial of efalizumab enrolled 556 patients with chronic plaque psoriasis covering at least 10% of their bodies. After 12 weeks 27% of the patients given efalizumab (1 mg/kg) had at least a 75% improvement in their psoriasis area and severity index (PASI). Only 4% of the patients given a placebo had a similar response.[1]

Another placebo-controlled trial treated 597 patients weekly for 12 weeks then re-randomised patients who had responded to efalizumab to continue treatment for another 12 weeks, reduce to fortnightly injections, or switch to placebo. Patients whose PASI had not improved were re-randomised to take a higher dose or a placebo for another 12 weeks. After the first 12 weeks there was a 75% improvement in the PASI in 5% of the patients given weekly injections of placebo. This outcome was achieved by 22% of the patients given efalizumab 1 mg/kg and 28% of those given 2 mg/kg. The improvement was sustained in most of the patients who responded and were re-randomised to continue treatment. The response was only maintained by 20% of the responders who were switched to a placebo. Only 13% of the patients who did not initially respond achieved a PASI improvement of 75% when treated with a higher dose.[2] Although a dose of at least 2 mg/kg was used in the patients who continued treatment after 12 weeks, the recommended weekly dose in Australia is 1 mg/kg with a maximum single dose of 200 mg.

As efalizumab affects the immune system there is a potential for serious adverse effects such as malignancy and lymphoproliferative disorders. Patients should have their blood counts checked as lymphocytosis and thrombocytopenia can occur. Flu-like symptoms such as headache, fever and chills are significantly more common with efalizumab than with placebo. As adverse reactions may be more frequent early in treatment an initial dose of 0.7 mg/kg is recommended. Efalizumab is potentially immunogenic. Approximately 8% of patients will have an allergic reaction and some will develop anti-efalizumab antibodies. Information about the long-term safety of efalizumab is limited, but there is a risk of the psoriasis getting worse if the drug is stopped abruptly.

In Europe efalizumab is restricted to patients who have failed to respond to treatments such as cyclosporin, methotrexate or phototherapy. This restriction does not apply in Australia, but there is a need to investigate if efalizumab is more effective than other systemic therapies for chronic plaque psoriasis.

References *

1. Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis. JAMA 2003;290: 3073-80.
2. Efalizumab Study Group. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med 2003;349:2004-13.

Fosamprenavir calcium

Telzir (GlaxoSmithKline)

700 mg tablets

225 mL bottles containing 50 mg/mL suspension

Approved indication: HIV infection

Australian Medicines Handbook section 5.4.3

Amprenavir is a protease inhibitor that can be used in combination with other drugs to treat patients infected with HIV.[1] It can be given with ritonavir as their interaction

significantly increases the plasma concentration of amprenavir (see New drugs, Aust Prescr 2002;25:44-7).

Fosamprenavir has been developed to try and overcome some of the pharmacological disadvantages of amprenavir, such as low solubility. It is a prodrug which is rapidly converted to amprenavir during absorption. Fosamprenavir can also be given with low dose ritonavir to increase the concentration of amprenavir.

Fosamprenavir was compared with nelfinavir in a study of patients who had not previously received antiretroviral drugs. Each group of patients also received abacavir and lamivudine. After 48 weeks 66% of the 166 patients given fosamprenavir and 51% of the 83 patients given nelfinavir had less than 400 copies of viral RNA/mL. The median increase in CD_4 cell counts was 201 cells/mm^3 in the fosamprenavir group and 216 cells/mm^3 in the nelfinavir group.[2]

Another study enrolled 315 patients who had previously been treated with protease inhibitors. This compared regimens of fosamprenavir and ritonavir to a regimen of lopinavir and ritonavir. After 48 weeks 58% of the patients taking fosamprenavir twice daily had less than 400 copies of viral RNA/mL. However, 61% of the patients taking lopinavir with ritonavir had the same response. It is therefore uncertain that the fosamprenavir regimens are as effective as lopinavir with ritonavir.

The adverse effects and interactions of fosamprenavir are the same as those of amprenavir. Gastrointestinal symptoms and skin rashes are common. As fosamprenavir is metabolised by P450 3A4 it must not be prescribed with drugs such as ergot derivatives, midazolam or triazolam. Fosamprenavir can also interact with complementary medicines such as St John's wort.

Although the pharmacology of fosamprenavir may be an advance on amprenavir, there is currently no evidence to show this will improve the clinical outcomes for patients. Fosamprenavir is only approved for use in combination with ritonavir.

References *

1. Palmer C. HIV treatments and highly active antiretroviral therapy. Aust Prescr 2003;26:59-61.
2. Rodriguez-French A, Boghossian J, Gray GE, Nadler JP, Quinones AR, Sepulveda GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naïve HIV-1-infected patients. J Acquir Immune Defic Syndr 2004;35:22-32.

Ketotifen hydrogen fumarate

Zaditen (Novartis)

250 microgram/mL in 5 mL bottles

Approved indication: seasonal allergic conjunctivitis

Australian Medicines Handbook section 11.3

Ketotifen is an antihistamine which has been available overseas for many years. In addition to antagonising the H_1 histamine receptors, ketotifen stabilises mast cells to prevent the release of inflammatory mediators.

Patients instil ketotifen eye drops two or three times a day. It is unclear how much of the drug is absorbed, but a therapeutic effect begins within a few minutes.

An Australian study compared ketotifen with placebo and levocabastine for one month. Although only half of the 109 patients given ketotifen responded, this was higher than the 41% response in the levocabastine group and significantly better than the 33% response in the placebo group.[1]

Olopatadine is another antihistamine which stabilises mast cells. Some comparisons favour olopatadine[2] while others favour ketotifen.[3] There appear to be no published comparisons of ketotifen and ophthalmic non-steroidal anti-inflammatory drugs.

The main adverse events in trials of ketotifen were conjunctival injection, headaches and rhinitis. Patients may also complain of burning or stinging in their eyes.

Although the mast cell stabilisers cromoglycate and lodoxamide can be used to prevent allergic conjunctivitis, they have to be given for a few weeks in advance of exposure to the allergen. Ketotifen is more suited to be one of the options for the short-term treatment of patients with symptoms of seasonal allergic conjunctivitis.

References *

1. Kidd M, McKenzie SH, Steven I, Cooper C, Lanz R. Australian Ketotifen Study Group. Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. Br J Ophthalmol 2003;87:1206-11.
2. Aguilar AJ. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. Acta Ophthalmol Scand 2000;78:52-5.
3. Ganz M, Koll E, Gausche J, Detjen P, Orfan N. Ketotifen fumarate and olopatadine hydrochloride in the treatment of allergic conjunctivitis: a real-world comparison of efficacy and ocular comfort. Adv Ther 2003;20:79-91.

Pemetrexed disodium

Alimta (Eli Lilly)

vials containing 500 mg powder for reconstitution

Approved indications: lung cancer, mesothelioma

Australian Medicines Handbook section 14.3

Pemetrexed disodium is an antifolate anticancer drug. It inhibits folate-dependent enzymes and inside cells it is converted to a metabolite which is a more potent inhibitor. Inhibiting the enzymes decreases the synthesis of nucleic acids and therefore reduces cell replication.

Although the use of chemotherapy for non-small cell lung cancer is increasing[1], the prognosis remains grim. Pemetrexed

has therefore been studied in patients with metastatic or locally advanced disease which has progressed despite previous chemotherapy. In a phase II study 79 patients were given an infusion of pemetrexed every 21 days. One patient had a complete response and six had partial responses. Although most of the responses occurred in patients who had not been previously treated with platinum-based chemotherapy, they did not live longer. Their median survival was four months, while patients who had already been treated with platinum-based chemotherapy had a median survival of 6.4 months.[2] The Australian approval of pemetrexed is limited to patients who have previously received platinum-based chemotherapy.

A phase III study randomised 283 patients with advanced non-small cell lung cancer to receive pemetrexed and 288 to receive docetaxel. The overall response rate was about 9% for both drugs, but pemetrexed appeared to be less toxic. The median survival time for each treatment group was approximately eight months.[3]

Pemetrexed has also been studied in patients with malignant pleural mesothelioma. As only a minority of patients can be treated with surgical resection, there is interest in assessing if chemotherapy has any benefits. In a trial involving 448 patients, pemetrexed and cisplatin were compared with cisplatin alone. As judged by computed tomography, there was a response to treatment in 16.7% of the patients given cisplatin and 41.3% of those given cisplatin and pemetrexed. The median survival with the combination was 12.1 months compared with 9.3 months for cisplatin alone.[4]

Like many anticancer drugs pemetrexed can cause serious adverse reactions, particularly myelosuppression. During the mesothelioma study there were several deaths at the start of the trial. Thereafter, all the patients enrolling in the study were given supplements of folic acid and vitamin B_{12} to try and reduce the toxicity of pemetrexed. Despite supplements, the combination of cisplatin and pemetrexed will cause neutropenia and leucopenia in 55–60% of patients, so there is a risk of infections and febrile neutropenia. Anaemia and thrombocytopenia are also common, so regular blood tests are needed to check if the patients are still fit for treatment. Although adverse reactions are less frequent when pemetrexed is used alone, supplements are still required. As skin rashes are very common, patients also require premedication with dexamethasone. Non-steroidal anti-inflammatory drugs should not be used with pemetrexed, particularly if renal function is impaired.

While pemetrexed has comparable efficacy to other drugs, such as docetaxel, its benefit to the patient dying of non-small cell lung cancer is less clear. Its effect on quality of life in the phase II study is difficult to interpret, partly because the median number of treatment cycles was only two.[2] There was no significant difference between pemetrexed and docetaxel in the quality of life analysis of the phase III study.[3]

Although pemetrexed and cisplatin had an overall advantage in mesothelioma, the choice of cisplatin for the single blind comparative study can be questioned: cisplatin may be an ineffective comparator. In addition, the survival advantage of combination treatment was only of borderline statistical significance ($p = 0.051$) in patients who followed the recommended regimen of cisplatin and pemetrexed with supplements of vitamin B_{12} and folic acid.[4]

References *

1. Boyer MJ. Drug therapy of lung cancer. Aust Prescr 2003;26:103-5.
2. Smit EF, Mattson K, von Pawel J, Manegold C, Clarke S, Postmus PE. Alimta (pemetrexed disodium) as second-line treatment of non-small-cell lung cancer. Ann Oncol 2003;14:455-60.
3. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
4. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.

Ropinirole hydrochloride

Repreve (GlaxoSmithKline)

0.25 mg, 0.5 mg and 2 mg film-coated tablets

Approved indication: restless legs syndrome

Australian Medicines Handbook section 16.2

Patients with restless legs syndrome are distressed by an irresistible urge to move their legs. They may also complain of crawling or burning sensations in their lower limbs. The symptoms are worst at night. In most cases there is no obvious cause, but patients may get relief with self-help techniques such as relaxation exercises.

As restless legs syndrome involves motor restlessness it follows that drugs for Parkinson's disease could have some effect. As levodopa can make the problem worse, there has been interest in dopamine agonists such as bromocriptine and pergolide. Ropinirole is a dopamine agonist which binds to the D_2, D_3 and D_4 receptors and has been used to treat Parkinson's disease. In a crossover study of 22 patients with restless legs syndrome, ropinirole produced more relief than placebo. The main difference between ropinirole and placebo was 12 points on a rating scale of 0–40 points.[1] Larger studies show that after 12 weeks of treatment ropinirole will reduce a patient's score by 11 points while a placebo will reduce it by approximately 8.5 points.

If a patient's restless legs are so frequent and distressing that drug treatment is required then ropinirole can be considered.

It is taken once a day before bedtime and the dose is gradually increased over several weeks according to the patient's response.

The tablets are rapidly absorbed, but first-pass metabolism reduces the bioavailability to 46%. Ropinirole is metabolised in the liver and there is a potential for interactions with drugs, such as theophylline, ciprofloxacin and fluvoxamine, that are metabolised by or inhibit cytochrome P450 1A2. The drug has a half-life of six hours with most of the metabolites being excreted in the urine.

As dopamine receptors are not confined to the central nervous system, some of the adverse effects of ropinirole can be predicted. For example, peripheral dopaminergic effects can cause hypotension. Ropinirole should therefore be used cautiously in patients with cardiovascular disease. Nausea is the most frequent adverse reaction, affecting up to 38% of patients. Ropinirole can cause fatigue and some patients may suddenly fall asleep. Patients with somnolence are advised not to drive or operate machinery. Other adverse effects include dizziness, vomiting and nervousness.

Although some of the benefits of ropinirole could possibly be related to making people sleepy, it seems to have an advantage over placebo. There appear to be no direct comparisons of ropinirole with other dopamine agonists.

Reference

1. Adler CH, Hauser RA, Sethi K, Caviness JN, Marlor L, Anderson WM, et al. Ropinirole for restless legs syndrome. Neurology 2004;62:1405-7.

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

Answers to self-test questions

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

www.australianprescriber.com

Australian Prescriber is available on the internet in full text, free of charge. Go to **New issue email alert** to be sent an email each time a new issue goes online.

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list, contact the *Australian Prescriber* Mailing Service

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* website on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

☐ Change my address

☐ My reference number is .....

☐ Send me all the available back issues

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist, etc.)

Postal: *Australian Prescriber* Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 3407

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6282 6755
Facsimile: (02) 6282 6855
Postal: The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
AUSTRALIA
Email: info@australianprescriber.com
Website: www.australianprescriber.com

Australian Prescriber

Address correspondence to:
The Editor
Australian Prescriber
Suite 3, 2 Phipps Close
DEAKIN ACT 2600
Telephone (02) 6282 6755

Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica. The views expressed in this journal are not necessarily those of the Editorial Executive Committee or the Advisory Editorial Panel.

Typesetting
Barnes Desktopping and Design

Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service Ltd, an independent, non-profit organisation funded by the Australian Department of Health and Ageing

NPS
National Prescribing Service Limited

INTERNATIONAL SOCIETY OF DRUG BULLETINS

Print Post Approved PP349181/00151 • ISSN 0312-8008