Australian Prescriber
Volume 26
Number 4
2003

EDITORIAL

Statins and muscle damage

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Index words: statins, muscle damage, creatine kinase.

(Aust Prescr 2003;26:74–5)

Muscle damage is an uncommon, but important, adverse reaction to HMG CoA reductase inhibitors ('statins').[1] Patients may experience a range of musculoskeletal symptoms varying from mild aching to severe pain, usually in proximal muscle groups. Muscle stiffness and weakness also occur to a varying degree. The concentration of creatine kinase (CK) in the blood is usually increased.

Mild symptoms, (myalgia) are usually associated with minimal elevation of CK concentrations (3–10 times upper limit of normal). Myalgia occurs in 2–7% of patients treated with statins in randomised clinical trials, but the incidence is similar in placebo-treated patients.

In myopathy, CK concentrations are more than 10 times the upper limit of normal, with or without symptoms. Myopathy occurs in 0.1–0.2% of clinical trials, at a slightly greater rate than in placebo-treated patients.[1]

The most serious type of muscle damage, rhabdomyolysis, occurs only rarely but is important to recognise as it may be fatal.[1] Rhabdomyolysis is associated with CK concentrations more than 40 times the upper limit of normal. The patient often has severe muscle pain, stiffness and weakness, with constitutional symptoms of fever and malaise. Their urine may be dark and of small volume, because of myoglobinuria and impaired renal function.

Stopping the drug is the only specific treatment for muscle damage. The symptoms usually resolve rapidly (within a few days to weeks) after withdrawal of statin therapy.

The mechanism of muscle damage is unknown at this stage. Risk factors include high blood concentrations of statins, increasing age, multisystem disease, hypothyroidism, acute illness, major surgery, low body weight and female gender. Drugs that affect the cytochrome P450 system can increase the concentrations of statins that are metabolised by this enzyme system (all statins but pravastatin).[2] Combination therapy with nicotinic acid and gemfibrozil can also result in muscle damage.

The combination of gemfibrozil and cerivastatin was largely responsible for about 100 deaths from complications of rhabdomyolysis. This led to the withdrawal of cerivastatin from world markets in 2001, and increased the attention given to statin-associated muscle damage.[3] Gemfibrozil inhibits a recently reported pathway of hepatic glucuronidation, which appears to be involved in the metabolism of most statins, particularly cerivastatin.[4]

Recently, histologically-confirmed muscle damage has been found in four patients with normal CK concentrations.[5] Muscle damage was suspected because of weakness and/or severe myalgia, which responded to statin withdrawal and recurred on statin rechallenge. The histochemical changes observed on muscle biopsy suggested a defect in mitochondrial respiratory chain function. These histological changes resolved three months after statin withdrawal in the three patients who had repeat biopsies. As none of the four patients had high concentrations of statins in their blood, they may have had some kind of increased susceptibility to muscle damage with statin therapy. This finding extends previous observations made in Australia.[6]

The prevalence of muscle damage in patients with normal CK concentrations is unknown. The disorder must be seriously considered in any patient taking a statin who complains of muscle aches and pains and/or weakness in spite of normal CK concentrations. A trial of statin withdrawal should be considered.

A plan to manage myopathy in patients on statin therapy has been outlined in the USA.[3] Baseline renal, thyroid and hepatic function tests and CK concentrations are recommended before starting statin therapy. Muscle symptoms should be assessed

In this issue ...

The recent proposal that everyone over 55 years old should take a cocktail of drugs, including a statin, would expose many people to adverse effects. Ian Hamilton-Craig alerts us to the finding that a statin can be causing muscle damage even when a patient's concentrations of creatine kinase are normal.

Damage to cardiac muscle releases troponins into the circulation. Peter Hickman and Julia Potter explain how these troponins can help in the diagnosis of myocardial infarction.

Early diagnosis of childhood deafness is important and several States have introduced screening tests for newborn babies. Harvey Coates and Kim Gifkins discuss the types of screening and some of their limitations.

An accurate diagnosis is essential before subjecting patients to immunotherapy. Richard O'Brien reminds us of some of the safety issues.

after 6–12 weeks and at each follow-up visit. If muscle symptoms occur the CK should be measured. This advice was published before the finding that muscle damage can occur with a normal CK concentration, so the recommendations regarding statin withdrawal may be too conservative.

Controlled trials have shown that statins improve overall mortality and the incidence of all forms of cardiovascular disease in patients at increased risk of these diseases. Muscle damage must be placed in the context of the recognised benefits of statin therapy. Clinicians should be aware of the need for vigilance in the monitoring of symptoms. Patients should be advised to report any symptoms at the earliest stage in order to prevent the rare, but more serious, muscle complications of statin therapy.

In many cases (perhaps the majority), muscle symptoms will prove to be unrelated to statin therapy. In others, elevated CK concentrations may be the result of exercise or minor muscle damage from trauma. Statin withdrawal and rechallenge may also be subject to a pronounced placebo effect. There is also the potential to further reduce compliance if patients were to believe that any muscle ache or pain they experience may be related to statin therapy. These considerations suggest that the management of statin muscle damage will not be straightforward until there is a specific diagnostic test available.

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REFERENCES

1. Hamilton-Craig I. Statin-associated myopathy. Med J Aust 2001;175: 486-9.
2. Martin J, Fay M. Cytochrome P450 drug interactions: are they clinically relevant? Aust Prescr 2001;24:10-2.
3. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002;40:567-72.
4. Prueksaritanont T, Subramanian R, Fang X, Ma B, Qiu Y, Lin JH, et al. Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization. Drug Metab Dispos 2002;30:505-12.
5. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002;137:581-5.
6. England JD, Walsh JC, Stewart P, Boyd I, Rohan A, Halmagyi GM. Mitochondrial myopathy developing on treatment with the HMG CoA reductase inhibitors – simvastatin and pravastatin. Aust N Z J Med 1995;25:374-5.

Conflict of interest: none declared

Letters

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

Preparing tranexamic acid 4.8% mouthwash

Editor, – The beneficial haemostatic effect of tranexamic acid 4.8% mouthwash has been demonstrated in oral anticoagulant treated patients undergoing minor oral surgery.[1,2] However there is no proprietary product readily available to dental practitioners in private practice (Aust Prescr 2002;25:105–6). A practical solution to this problem is the use of Cyclokapron tablets dispersed in water. A crude mouthwash can be prepared by placing a tranexamic acid 500 mg tablet into 10–15 mL of water in a metric measure. The tablet will disperse in approximately 3–5 minutes on standing and quicker with intermittent swirling. Tranexamic acid is readily soluble in water[3], however inactive tablet excipients will still be present after adequate mixing. The resulting slurry has little or no taste. Patients should be instructed to swirl the total preparation including the undissolved residue around the mouth for two minutes and then to expel. This is repeated four times a day for up to seven days.[1,2] Although this method has not been formally validated, sufficient tranexamic acid should be present in the saliva to reduce fibrinolysis.[4]

Unfortunately the Pharmaceutical Benefits Scheme does not subsidise tranexamic acid 500 mg tablets when prescribed by a dental practitioner. However, they are available as a private dental prescription at a cost of around $31 for a broken pack quantity of 20 tablets. For dental practitioners with no access or assistance from a public teaching hospital this approach partly addresses the issue of having ready access to the mouthwash, although it will not be suitable for all patients.

Fotios Ambados
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REFERENCES

1. Sindet-Pedersen S, Ramstrom G, Bernvil S, Blomback M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989;320:840-3.
2. Ramstrom G, Sindet-Pedersen S, Hall G, Blomback M, Alander U. Prevention of postsurgical bleeding in oral surgery using tranexamic acid without dose modification of oral anticoagulants. J Oral Maxillofac Surg 1993;51:1211-6.
3. Windholz M, editor. The Merck index. 10th ed. Rahway, NJ: Merck & Co.; 1983. p. 1368-9.
4. Sindet-Pedersen S. Distribution of tranexamic acid to plasma and saliva after oral administration and mouth rinsing: a pharmacokinetic study. J Clin Pharmacol 1987;27:1005-8.

Asthma delivery devices

Editor, – Thank you for the review of asthma therapy delivery devices (Aust Prescr 2003;26:5–7). This article covered important common sense issues in asthma treatment delivery. As suggested by the author, practical issues of use and patient acceptability dominate the decision between a number of otherwise acceptable drug delivery methods. An additional practical issue, in the experience of many Top End practitioners, is that dry powder devices often do not

stay dry enough to function in tropical humid conditions, particularly if the users are not very careful to keep the cap screwed on tightly. For this reason dry powder inhalers are not recommended in the Central Australian Rural Practitioners Association Standard Treatment Manual[1] for use in the tropical Top End.

Dan Ewald

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Editor

Standard Treatment Manual for Health Workers, 4th edition.

REFERENCE

1. Central Australian Rural Practitioners Association. Standard treatment manual for health workers. 4th ed. Alice Springs: CARPA; 2003.

Tisseel Duo 500

Editor, – I wish to draw your attention to some inaccuracy in the new drug comment about Tisseel Duo 500 (Aust Prescr 2003;26:46).

The article commenced by correctly referring to Tisseel Duo 500 with regard to available sizes and approved indications. It then refers to the composition of the 'kit', referring to vials of thrombin, calcium chloride, fibrinolysis inhibitor etc. This description refers to the lyophilised kit form of Tisseel which required reconstitution. The kit was previously available in Australia under the Special Access Scheme of the Therapeutic Goods Administration, until the registered Tisseel Duo 500 became available. This kit was only viable for four hours following reconstitution. It is no longer available in Australia.

Tisseel Duo 500 is deep frozen fibrin sealant, in a preloaded double syringe delivered with the same Duploject device. It does not require reconstitution, only thawing and warming to 37°C. Once thawed, Tisseel Duo 500 is viable for 48 hours. The thawing process requires very little time once removed from the freezer, significantly less than an autologous cryoprecipitate preparation process.

With regards to viral safety, I can state that the previous formulation of the product has been used for 25 years in 50 countries around the world in over 8 million applications resulting in no reported transmissions of HIV, Hepatitis B or C and prion disease. This is due to the donor screening program, the double steam heat treated processing and PCR testing of the product during the manufacturing process.

There are numerous published articles about fibrin sealants available from our Medical Affairs department.

Peter van Gaalen

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Routine change of intravenous catheters

Editor, – In the article 'Controlling intravascular catheter infections' (Aust Prescr 2003;26:41–3), Table 2 states 'Routinely replace peripheral catheters within 48–72 hours...'. The Centers for Disease Control in the USA found no evidence to support the routine changing of peripheral venous catheters. The 'Guidelines for the prevention of intravascular catheter-related infections' recommend: 'In adults replace catheter and rotate site no more frequently than every 72–96 hours. Replace catheters inserted under emergency basis and insert a new catheter at a different site within 48 hours. In pediatric patients, do not replace peripheral catheters unless clinically indicated.'[1]

Hospital bureaucracies frequently mandate routine changing of peripheral catheters within 72 hours, at the cost of great discomfort to patients and effort by resident medical officers. Given that routine changing of central lines has been shown to be unnecessary, and the daily infection risk quoted for peripheral cannulae is much lower than for central lines, it is also implausible that any benefit from routine changing of peripheral lines has been missed.

It would seem beneficial for *Australian Prescriber* to acquaint its readers with the evidence and discourage them from continuing what seems to be an unnecessary as well as painful custom.

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REFERENCE

1. MMWR 2002 Aug 16;51:711. Appendix B.

Dr Peter Collignon and Dr Robert Horvath, the authors of the article, comment:

The guidelines of the Centers for Disease Control (CDC) do recommend changes of peripheral lines after 72–96 hours rather than our suggested 48–72 hours. Our concern is that the CDC based the guidelines on the incidence of 'phlebitis', not bacteraemia. As phlebitis is thought to be usually due to non-infective causes (e.g. irritation from drugs), we do not believe it is an appropriate surrogate marker for bacteraemia.

If one examines bacteraemia caused by catheters, it becomes clear that there are almost no cases with catheters that are in place for 24 hours or less and sepsis is very uncommon if the catheters are in place for less than 48 hours.[1,2,3] The CDC guidelines still recommend routine replacement at 48 hours for 'emergency cannulas'. This is a vague definition and appears to take in our concerns.

In our experience children do not have peripheral cannulas for prolonged periods. Although there is no reason to believe that intravenous catheter sepsis will be different in children, we are unaware of any authority currently recommending routine replacement of peripheral catheters in children.

The problem with doing studies on peripheral catheter sepsis is the very low incidence of bacteraemia (about one episode for every 3000 catheters).[4] A prospective randomised study would have to be extremely large and is therefore unlikely to be done. However, we believe that the evidence on bacteraemia (rather than phlebitis) strongly suggests that routine replacement of catheters at 48–72 hours will result in lower sepsis rates than replacement at later times.

REFERENCES

1. Smits H, Freedman LR. Prolonged venous catheterization as a cause of sepsis. N Engl J Med 1967:276:1229-33.
2. Collignon PJ, Sorrell TC, Uther JB. Prevention of sepsis associated with the insertion of intravenous cannulae. The experience in a coronary care unit. Med J Aust 1985;142:346-8.
3. Maki DG, Goldman DA, Rhame FS. Infection control in intravenous therapy. Ann Intern Med 1973;79:867-87.
4. Collignon P. Intravascular catheter associated sepsis: a common problem. The Australian study on intravascular catheter associated sepsis. Med J Aust 1994;161:374-8.

Correcting rheumatoid arthritis

Editor, – I wish to point out an error in 'Disease modifying drugs in adult rheumatoid arthritis' (Aust Prescr 2003;26: 36–40). On page 38 the article says sulfasalazine contains acetylsalicylic acid and sulfapyridine. This should be 5-aminosalicylic acid and sulfapyridine.

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Your questions to the PBAC

Folinic acid, the PBAC and the TGA – approval confusion

Editor, – In December 2001 the Pharmaceutical Benefits Advisory Committee (PBAC) approved the listing of oxaliplatin as a pharmaceutical benefit. Oxaliplatin was listed as an authority item for use in metastatic colorectal cancer after failure of fluorouracil-based therapy in patients with a WHO performance status of two or less, to be used in combination with 5-fluorouracil and folinic acid.

Folinic acid is available in Australia in both oral and injectable forms. The indications approved by the Therapeutic Goods Administration (TGA) include megaloblastic anaemia due to folic acid deficiency and reducing the toxicity of folic acid antagonists.

The role of folinic acid in combination with 5-fluorouracil in colorectal disease is well documented. Its use in combination with oxaliplatin and 5-fluorouracil is also well documented. The folinic acid potentiates the antitumour activity of 5-fluorouracil by acting as a coenzyme.[1] However, the use of folinic acid for this indication has not been approved by the TGA.

How can oxaliplatin be approved by the PBAC for combination therapy with folinic acid in metastatic colorectal cancer when the folinic acid does not have an approved indication in this disease? On a separate note, why has the PBAC approved folinic acid in this combination, but not made it available as a pharmaceutical benefit?

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REFERENCE

1. Dorr RT, Von Hoff DD, editors. Cancer chemotherapy handbook. 2nd ed. Norwalk, CT: Appleton & Lange; 1994.

PBAC response:

The PBAC thanks Mr Siderov for drawing this apparent anomaly to its attention. Drugs cannot be listed as pharmaceutical benefits unless the Therapeutic Goods Administration (TGA) has approved the indication. Oxaliplatin has TGA approval for use in the treatment of advanced colorectal cancer, in combination with 5-fluorouracil and folinic acid, and the Pharmaceutical Benefits Scheme (PBS) restriction is consistent with this indication.

Under the Therapeutic Goods Act, the TGA cannot compel a manufacturer to apply for a registered indication, nor can the TGA apply a registered indication to a drug if not requested by the manufacturer. In this case the registration of an indication for combination therapy would need to be sought by the manufacturers of folinic acid, rather than the manufacturers of oxaliplatin. Although use of folinic acid can only be promoted by its sponsor for its approved indications, a medical practitioner is not prevented under the Therapeutic Goods Act from using a product for an unapproved indication.

The PBAC noted that the injectable form of calcium folinate (3 mg/mL) was deleted from the PBS on 1 May 2002 at the request of the sponsor. The Department of Health and Ageing is seeking alternative sources of supply of the injection.

The management of insomnia: an update

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SYNOPSIS

Insomnia is a common symptom but hypnotics should be avoided if possible. Management aims to identify and treat underlying causes, such as psychiatric disorders and medical problems. If symptomatic relief is still required in addition to medical, psychological and social interventions, hypnotics can be considered. Hypnotics should preferably be used intermittently, for less than two to four weeks. The newer non-benzodiazepine hypnotics – zopiclone, zolpidem and zaleplon – are not free of the problems surrounding the use of benzodiazepines.

Index words: benzodiazepines, hypnotics.

(Aust Prescr 2003;26:78–81)

Introduction

Insomnia is a common symptom with up to 25% of Australians reporting trouble getting enough sleep.[1] There are many causes for this perceived inadequacy of sleep, but subjective perceptions do not necessarily mean the patient is not sleeping.

Underlying causes of insomnia

Symptoms associated with insomnia may suggest an underlying medical, surgical, psychological or environmental problem. Treating any underlying problem can help to alleviate the insomnia.

Psychiatric factors

Psychiatric disorders are typically associated with insomnia. Anxiety disorders can cause early insomnia (difficulty in getting to sleep) associated with rumination over particular worries or concerns. With depression, it is typical to have middle insomnia (waking in the early hours of the morning) and late insomnia (waking earlier in the morning than is usual and being unable to get back to sleep). The depressive pattern may also have an associated anxiety disorder so the patient's sleep is disturbed throughout the night. Patients may present with insomnia and only acknowledge their low mood or loss of interest after enquiry.

Middle insomnia is typical with alcohol abuse. The patient goes to sleep in the evening when intoxicated only to wake a few hours later when their blood alcohol concentration drops.

Environmental factors

If a patient's bedroom is too hot, too cold, too noisy, or their bed cramped or uncomfortable, addressing those factors may resolve the problem. A crying baby, or a sick or restless child or other family member may disturb sleep. The assistance of a partner, other relative, or brief period of respite may address the sleeplessness.

Physical factors

Many illnesses including cardiac and respiratory failure and pain syndromes may contribute to insomnia.

Jet lag

Flying across several time zones may also result in insomnia. The therapeutic key is to settle into the new time zone as quickly as possible. This is aided by a regular local sleep-wake cycle and particularly by re-setting sleep rhythms with early morning light and exercise. It is possible to adjust approximately one hour per day, a task which is easier when the sleep cycle is extended rather than shortened. This is quicker following east to west travel than west to east. A similar disturbance may occur when shift workers start and end work cycles. Occasionally, the brief use of a hypnotic may help adaptation to a new sleep pattern. Taking a hypnotic during flight should generally be avoided as immobility may predispose to deep vein thrombosis.

Evaluation

In addition to routine clinical evaluation, it is worth asking in detail about the patient's sleep pattern (see Box 1). Asking the patient to complete a sleep log over a few days is also useful. The log should be completed as each day progresses, as retrospective entries tend to minimise sleep and maximise disturbances. Patients may enter factors you had not considered, but which may be relevant to the sleep disturbance (Fig. 1).

Box 1

Evaluating a patient's sleep

Determine:

- habits and patterns of getting ready to go to bed
- time of going to bed
- time of going to sleep
- time(s) of waking(s)
- time(s) to get back to sleep
- what the patient does when awake in the night
- features (if any) that help the patient settle
- features that tend to add to the patient's disturbance
- any daytime sleeping, times and duration.

A sleep log will usually help this assessment (Fig. 1).

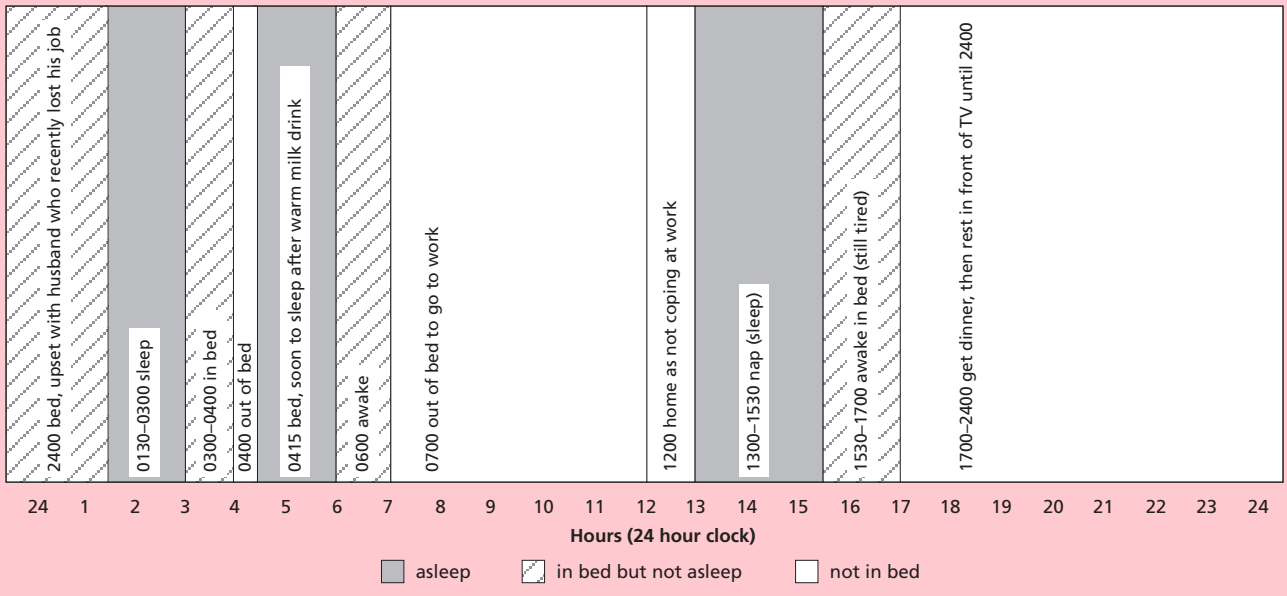
Fig. 1

Sleep log

The patient enters times of going to sleep and when awake, including any daytime naps or sleeps, and any factors that tend to make sleep better or worse, e.g. meals, alcohol. They should also enter the names and times of any medicines taken.

This sleep log helps to establish whether they have early, middle or late insomnia.

Copies of this chart for patient use are available with the electronic version of this article on the *Australian Prescriber* web site www.australianprescriber.com



Sleep hygiene

Sleep hygiene includes a number of social and behavioural interventions to help patients improve their sleep (see Box 2). Cognitive behaviour therapy techniques can also assist some patients.[2,3,4]

Drug treatment of insomnia

General considerations

The prescription of hypnotics should only follow a careful evaluation and consideration of other approaches including psychological interventions such as cognitive behaviour therapy. In general hypnotics should only be prescribed if the duration of use is likely to be less than four weeks, and preferably less than one or two weeks.

Key elements when prescribing are to manage patient expectations of the duration of treatment and likely outcomes, and to have an 'exit' strategy. Explain the likely duration of therapy, when medicines should be used and when they should not be used, common adverse events, and the risks of tolerance, dependency, withdrawal and discontinuation syndromes if use is prolonged.

The exit strategy is a clear plan of change for the patient so that they should not need continued drug treatment. For example, you might expect an antidepressant to have started to work in two to four weeks so that depression-related insomnia should have resolved by that time. Most patients do not need a hypnotic for depression-related insomnia. A few value initial help with sleep, but hypnotics should not be continued once the depression is relieved. Some personal and social crises can

Box 2

Improving your sleep

- Develop a regular pattern of going to bed at about the same time each night, and getting up at about the same time each morning.
- The bedroom should be comfortable and quiet and not the focus of arguments, anger or distress. Avoid clock-watching.
- Substances on which the patient may be dependent, or which cause intoxication or discontinuation syndromes, should be avoided for several hours before bedtime, e.g. caffeine.
- Vigorous exercise, hard work, or activities requiring considerable concentration and arousal should stop some time before going to bed.
- If not sleeping, the patient should either relax in bed and not think about sleep, or get up and stay in a dimly lit room until ready to settle to sleep again.
- Daytime sleeping or naps tend to disrupt night-time sleeping so that although the total hours of sleep are preserved, the patient does not wake refreshed because they have less sleep at night.
- Regardless of the underlying cause, patients may become worried and anxious that the forthcoming night may be disrupted, rather than enjoyed as refreshing sleep. Anxiety management and relaxation techniques may assist in controlling their concerns.

Table 1

Pharmacokinetics of common hypnotics*

Hypnotic	*Time to maximum concentration (hours)*	*Half-life (hours)*
Flunitrazepam	1–2	20–30
Nitrazepam	2 (0.5–5.0)	27 (16–48)
Temazepam capsules (authority PBS)	0.5–1	10 (5–15)
Temazepam tablets (general PBS)	0.5–2	10 (5–15)
Triazolam	1.5±0.7	initial phase 3.4±0.9 terminal phase 7.8±1.5
Zaleplon	1	1
Zolpidem	0.5–3.0	2.4±0.2
Zopiclone	1.75	5.26±0.76

* There is substantial inter-individual variation in the pharmacokinetics of these drugs.

result in the patient becoming so distressed and dysfunctional with insomnia that a few nights assisted sleep helps them reintegrate. They could then be expected to cope with the stresses in their life without the need for ongoing drug treatment. Bereavement would not normally necessitate hypnotics, although they can sometimes be briefly helpful when the bereaved patient is not coping with insomnia.

The hypnotics predominantly used in Australia are benzodiazepines, or non-benzodiazepines acting through benzodiazepine receptors. Other classes of drugs are also used, but are potentially more toxic and would rarely seem to offer any advantage over a benzodiazepine or related drug.

Benzodiazepines

These drugs all have similar actions including sedative-hypnotic, anxiolytic, anticonvulsant, muscle relaxing, and amnesic effects. Although some of the drugs are marketed for different indications, their major differences in practice are brought about by differences in pharmacokinetics.

Half-life (Table 1)

Drugs with longer half-lives may cause appreciable impairment in the morning (on waking). A single dose of temazepam or oxazepam can have actions well into the next day, and nitrazepam and flunitrazepam even more so. There has been a recent campaign to use temazepam tablets rather than capsules (because of the risk of people injecting the contents), however the onset of action and time to maximum effect of temazepam tablets can be slower than one would wish in a hypnotic.

Adverse effects of benzodiazepines

Adverse effects can be anticipated from the normal actions of hypnotics. Excessive or daytime sedation may occur, particularly with drugs that have a longer half-life. The sedative and muscle relaxing activity may combine to increase the risk of ataxia or falls, particularly in the elderly.

The anxiolytic action can be helpful in relieving distress when settling to sleep. However, this can be disadvantageous if it inhibits alertness and responsiveness the following morning.

The anticonvulsant action can result in withdrawal fits if the benzodiazepine is withdrawn abruptly. This risk may increase if a benzodiazepine or related drug is substituted by a sedative antipsychotic or tricyclic antidepressant which is pro-convulsant.

Amnesic effects can result in patients forgetting events soon after taking a dose. They may take extra doses if they forget they have already taken their medication. Some may 'forget' previous cautions about concurrent use of alcohol and anterograde amnesia has been associated with such combined use. Disinhibited behaviour may follow ingestion and hallucinations have been reported, especially at higher doses. Hypnotics, particularly those with a long half-life, can cause cognitive problems the following day.

Newer hypnotics

Zaleplon, zopiclone and zolpidem, although structurally not benzodiazepines, act on the same receptor. While there is a suggestion from animal studies that the new drugs have a more specific hypnotic action, this has not yet been shown in humans. The new drugs are not free of the adverse effects of benzodiazepines and are not necessarily safer medicines. On the contrary, one study suggested that elderly patients taking zolpidem had almost double the risk of hip fracture compared with no medication (adjusted odds ratio 1.95, CI* 1.09–3.51). This risk is greater than that seen with benzodiazepines (1.46, CI 1.21–1.76), antipsychotic medications (1.61, CI 1.29–2.01) and antidepressants (1.46, CI 1.22–1.75).[5]

Zopiclone has a bitter taste as its commonest adverse effect. Zolpidem causes hallucinations in a small proportion of patients, and it should be stopped if these occur. Zaleplon has a short half-life making it useful for sleep-onset insomnia. It may be used during the night if a patient cannot fall asleep as it has less risk of morning sedation. Interestingly, within-night discontinuation effects have not been reported, though one might otherwise expect them given its rapid onset and offset.

Other drugs used as hypnotics

Several other types of drugs are sometimes used as hypnotics, but in general their use is limited by toxicity. These drugs are primarily used for other indications, but as drowsiness is one of their adverse effects they are sometimes prescribed for insomnia.

Sedative antihistamines have prominent anticholinergic effects which can result in confusion, especially in children or the elderly, and should have little or no place in the management of insomnia. They may be effective hypnotics in the short term, but many patients rapidly develop tolerance.

Antidepressants should not be used for insomnia unless the patient also has depression. Tricyclic antidepressants have sedative antihistaminic effects, even at low doses which are sub-therapeutic for depression. They have significant anticholinergic effects leading to confusion, alpha adrenergic blocking effects that can result in marked postural hypotension, and quinidine-like effects with the potential for atrioventricular

* CI confidence interval

block and prolongation of the QT_c interval. Tolerance develops to the sedative effects of tricyclic antidepressants and their potential toxicity generally outweighs their benefit as hypnotics, especially in overdose.

Antipsychotic drugs have been little studied as hypnotics. The toxicity of typical antipsychotics limits their use as hypnotics, while atypical antipsychotics are not suitable and they are only approved for use in schizophrenia.

Stopping long-term hypnotic treatment

By establishing a clear expectation of short-term use when starting treatment with a hypnotic you are more likely to avoid your patient falling into the trap of long-term dependency. If the insomnia persists, it is particularly difficult to stop treatment as the patient fears that stopping the hypnotic will make their insomnia worse.

If it is difficult to stop treatment it is worth reviewing the patient's history, and the possibility of underlying disorders, or dependency on the hypnotic. Reinforcement of sleep hygiene techniques, a gradual process of dose reduction, and intermittent use, with the availability of the hypnotic as 'rescue medication' when needed, may assist the patient in reducing their hypnotic use. Long-term use is particularly an issue for patients who were prescribed hypnotics before problems with this use were recognised. Even if one attempt at discontinuing is unsuccessful, review this regularly as an approach at a different time may have more success. Furthermore, if the patient is actively involved in the process, they can choose a night when they would feel more comfortable about reducing the dose and avoid challenging themselves on a night when they fear sleep will elude them.

There is the occasional patient who does not increase their hypnotic dose, or frequency of use, and remains well on a stable dose, but becomes profoundly dysfunctional if it is ceased. When reviewing such a patient consider dose reduction, or stopping the medicine, as well as the possibility of other illnesses or problems perpetuating the patient's seeming need for a hypnotic.

Summary

Patients should not be given hypnotics when other interventions would be more appropriate. Always address underlying disorders and attend to the patient's sleep hygiene before considering prescribing. Before any hypnotic is prescribed, it is important for the patient to have a clear understanding of the expected outcome and that continued use will be unnecessary. With patients on long-term treatment the aim is to cease hypnotics, not change to a newer drug.

REFERENCES

1. Wilson C, Lack L. Sleeping habits of people living in the Adelaide metropolitan area – a telephone survey. Aust Psychol 1983;18:369-76.
2. Tiller JWG. Cognitive behaviour therapy in medical practice. Aust Prescr 2001;24:33-7.
3. Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia a randomized controlled trial. JAMA 2001;285:1856-64.
4. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. JAMA 1999;281:991-9.
5. Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. J Am Geriatr Soc 2001;49:1685-90.

FURTHER READING

National Prescribing Service patient education material 'Getting a good night's sleep'. http://www.nps.org.au (Go to Topics, Benzodiazepines, Patient education material 'A reduction plan for sleeping tablets and sedatives' page 2)

Professor Tiller has conducted sponsored studies or been a consultant to manufacturers of antidepressants, benzodiazepines, antipsychotics and non-benzodiazepine hypnotics.

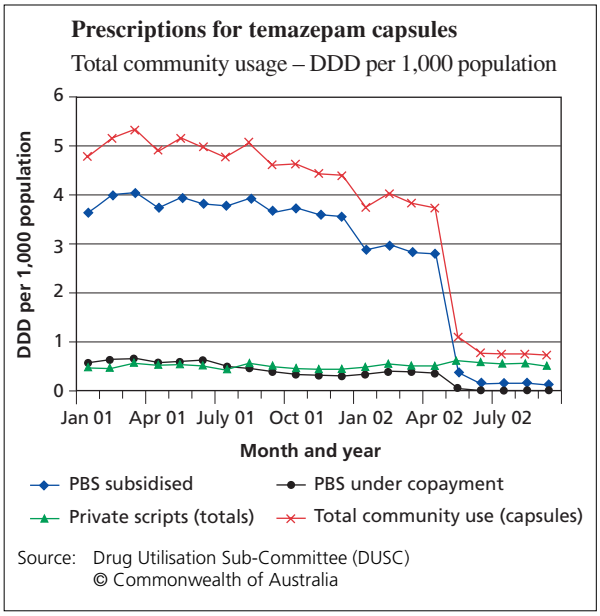
Self-test questions

The following statements are either true or false (answers on page 95)

1. Nitrazepam has a fast onset of action because of its short half-life.
2. Zolpidem may cause more falls in the elderly than benzodiazepines do.

The fall of temazepam capsules

Injecting the contents of a temazepam capsule can cause serious harm. To limit the potential for harm temazepam capsules required an authority prescription from 1 May 2002. This had an immediate effect on the defined daily dose (DDD) per 1000 people.* Although private prescriptions are relatively unchanged, Pharmaceutical Benefits Scheme (PBS) prescriptions have significantly decreased.



* See Birkett D. Monitoring drug use in Australia (Aust Prescr 1993;16:27–9)

DIAGNOSTIC TESTS

Newborn hearing screening

Harvey Coates, Senior Ear, Nose and Throat Surgeon, Princess Margaret Hospital for Children and Clinical Associate Professor, The University of Western Australia, and Kim Gifkins, Speech Pathologist, Telethon Institute for Child Health Research, Perth

SYNOPSIS

Advances in audiological testing equipment and techniques allow accurate hearing screening of the newborn, using either otoacoustic emission screeners or automated auditory brainstem evoked response audiometry. Hearing screening lowers the age of diagnosis of permanent hearing loss. Evidence also indicates that early detection and management of hearing loss leads to improved speech, language and educational outcomes.

In Australia, newborn hearing screening is not widely available. Screening is available to babies 'at risk' of hearing loss, to all babies born in hospitals where the West Australian screening program is implemented, and is either being trialled or developed in other states. Awareness of the benefits and limitations of newborn hearing screening will enable the healthcare professional to support children with a hearing loss, and their families, so that they are able to maximise their potential.

Index words: audiology, deafness.

(Aust Prescr 2003;26:82–4)

Introduction

Hearing screening for congenital sensorineural hearing loss has been called 'the great omission'.[1] The incidence of congenital sensorineural hearing loss in the newborn population is greater than the combined incidence of all the metabolic conditions that we currently screen for with blood tests.[2] The prevalence of congenital bilateral permanent hearing loss is approximately 1 per 1000 live births.[2,3]

In the USA, the Joint Committee on Infant Hearing has recommended that every newborn infant should be screened.[4] Most American states have introduced routine newborn hearing screening, and screening programs are also being implemented in Europe and throughout the UK. However, a review of critical studies on newborn hearing screening could not make a recommendation for or against screening because of insufficient evidence.[5,6]

A review of the evidence for universal newborn hearing screening shows that the technologies used (otoacoustic emission (OAE) and automated auditory brainstem response (AABR) testing) are accurate tests for detecting congenital hearing loss. In Australia, the average age of detection of sensorineural hearing loss remains beyond two years. The age of diagnosis can be reduced by universal screening of the newborn.[6,7]

This is important because early intervention results in significantly better speech and language outcomes than delayed intervention.[8,9] The critical age to commence intervention may be as early as six months.[8]

Newborn hearing screening in Australia

Throughout Australia, to a varying degree, babies 'at risk' are screened for sensorineural hearing loss. Babies who are 'at risk' have one or more of the established risk factors for hearing loss.[4] However, as studies have indicated that approximately 40% of all children ultimately identified with sensorineural hearing loss do not have an established risk factor[7], the efficacy of 'at risk' screening is limited.

The first large-scale newborn hearing screening program in Australia was established in 2000. This program screens all babies born at five of the major birthing hospitals in Perth, usually before they are discharged. To date, over 25 000 babies have been screened and the results for the first 12 708 babies were published recently.[10] In this group, 99% had a pass response in both ears at either the initial or follow-up screen. Only 23 babies were referred for audiologic assessment, with nine babies being diagnosed with bilateral permanent hearing loss. Results suggest that in the well baby population, 2702 babies need to be screened to detect one additional case requiring intervention.

Implementation of universal newborn hearing screening in other states of Australia is either under consideration[11] (Queensland, Northern Territory and Tasmania) or has recently commenced (New South Wales, Victoria, South Australia and the Australian Capital Territory).

Screening technology

Recent technological advances allow the detection of possible hearing loss within the first days of life. The increasing simplicity of operating the equipment enables non-specialist staff to screen for hearing loss. It is difficult to determine the cost of screening due to the high capital costs of establishing a screening program. In Western Australia the cost is approximately $35 per test.

Otoacoustic emission testing

In the healthy cochlea, vibration of the hair cells in response to noise generates acoustic energy, known as otoacoustic

emissions. Otoacoustic emission testing therefore measures the integrity of the inner ear. A lightweight probe is placed in the ear canal and generates wide-band 'clicks' (see Fig. 1). Acoustic energy produced in response to the clicks is detected by a microphone within the probe. Automated OAE screeners display the results of the test as either 'pass' or 'refer', requiring no test interpretation by screening personnel.

The test takes between one and five minutes in ideal conditions, with optimal test techniques. In practice, the average total time for testing, including discussion of the procedure with the parents, settling the baby, performing the test and recording the results, may be between 15 and 20 minutes.

Automated auditory brainstem response testing

This measures not only the integrity of the inner ear, but also the auditory pathway. It can therefore detect the rare condition of auditory neuropathy, in children who are deaf but have normal otoacoustic emissions (because the cochlea is normal).

The stimulus (either clicks or tones) is presented using either earphones or an ear canal probe, and the electrophysiological response from the brainstem is detected by scalp electrodes (see Fig. 2). Automated devices allow screening to be performed by non-specialists. Responses from a large number of stimulus presentations are averaged and the automated screener uses a response algorithm to produce a 'pass' or 'refer' result. The 'pass' level is set at about 35 decibels.

This test takes 15–20 minutes, but once again this time may be longer if a child is restless, and does not include time for discussion and preparation before the test.

Screening protocols

The protocols of established newborn hearing screening programs throughout the world may use OAE only, AABR only, or a combination of technologies. For example, in the West Australian program, in well babies, an OAE test is performed initially, followed by an AABR test if a 'pass' response is not obtained in both ears. Babies who fail the AABR test are followed up and tested again with either OAE or AABR 3–4 weeks later. Children failing the follow-up screen are then referred for full audiological diagnostic testing.[10]

In the neonatal intensive care unit, protocols differ from those in the well baby nursery. Screening may be delayed until the baby is well enough. Although the condition of auditory neuropathy is rare in the well baby population, it can account for approximately 10% of hearing loss in the neonatal intensive care unit so virtually all neonatal intensive care unit screening programs use AABR.

Sensitivity and specificity

Sensitivity and specificity rates are affected by the screening protocol used, the population screened (well babies or neonatal intensive care unit infants), and other test variables. In general, all methods of newborn hearing screening show a screen specificity of greater than 90%. Most of the infants who screen positive for hearing loss are found to have normal hearing on further diagnostic testing.[7] Estimates of sensitivity for OAE range from 80–98% and for AABR from 84–90%.[6,7]

Test limitations

Both the OAE and the AABR screen require a quiet baby and a quiet testing environment. Restlessness can affect the time taken for the test, or may result in the test being discontinued. OAE relies on a functional outer, middle and inner ear, and AABR a functional outer, middle and inner ear, and lower auditory pathway. These screening tests are not designed to detect central hearing impairment (where there is hearing loss secondary to the dysfunction of the pathways from brainstem to the auditory cortex).

As the stimuli for both tests are introduced via the external ear canal, debris in the canal or middle ear fluid can affect the accuracy of the test. In particular, OAE testing may be affected by amniotic fluid in the ear canal when testing is conducted in the first 48 hours following birth. This may account for some false positive results.

Fig. 1

Neonatal hearing screening utilising otoacoustic emission screener

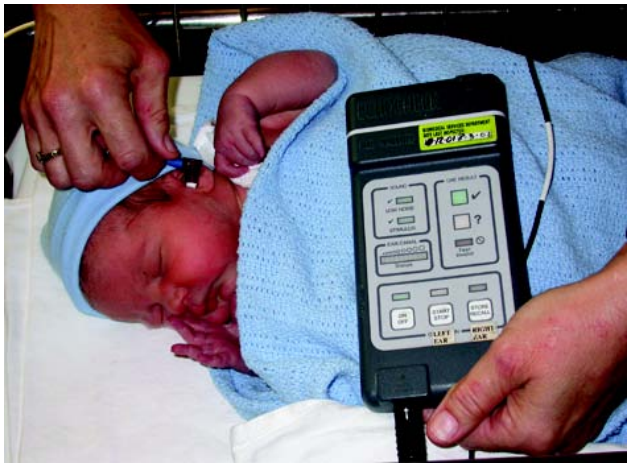


Fig. 2

Neonatal hearing screening utilising automated auditory brainstem response screener

Photographs reproduced with permission from the Public Relations Department, King Edward Memorial Hospital for Women, Perth

Parents' views of screening

Screening is acceptable to parents even if it may result in increased parental anxiety. In the West Australian program screening was well accepted by parents, with only 0.4% refusing screening.[10] Many tests resulting in a 'refer' outcome are ultimately false positives. This potentially can lead to increased levels of anxiety until diagnostic tests are performed, although some mild anxiety may remain even after a normal result.[12] To allay anxiety parents must be provided with accurate information regarding the screening, effective counselling and rapid follow-up.

Follow-up services for hearing loss

It is important that children and families are able to access 'habilitation' and intervention services as soon as possible after the diagnosis of permanent hearing loss. This process usually involves referral to the following specialists:

- ear, nose and throat surgeons
- geneticist
- Australian Hearing (provides audiology services, supplies hearing aids at minimal cost and provides monitoring of the child's hearing throughout childhood)
- early intervention services (in the larger cities, there are education and intervention centres for the hearing impaired, as well as a number of community support groups; in rural areas, a visiting teacher of the deaf service is often available).

The role of the general practitioner

General practitioners may play a role in educating and supporting parents and families about newborn hearing screening, both in the antenatal period and after birth. It is crucial that the general practitioner is kept fully informed of the results of screening. In the West Australian program, the newborn screening results are recorded in the child's personal health record.

The general practitioner has an important role in dealing with the implications of the diagnosis of hearing loss and the ongoing management issues for both the child and the family. Children with a sensorineural hearing loss should be monitored closely for middle ear conditions throughout childhood, so that conductive hearing loss resulting from otitis media does not further compromise hearing levels. Hearing aids may also predispose the child to otitis externa. The general practitioner may also play a role in promoting acceptance of hearing aids, encouraging consistent wearing of aids, and providing information regarding early intervention services.

Neonatal hearing screening will not detect all cases of congenital hearing loss – it only provides an indication of the baby's hearing at the time of the screening. Mild hearing losses and hearing losses outside the main speech frequencies may not be detected. Hearing impairment may develop after the neonatal period[3], and therefore it is crucial for the general practitioner to encourage parents to continue to have their child's hearing checked. The general practitioner should maintain a high index of suspicion if there are manifestations of hearing loss such as speech and language delay. Any parental concerns regarding children's hearing should also be thoroughly investigated.

Conclusion

The technology and expertise for implementation of neonatal hearing screening is available, accurate and acceptable. Australia also has excellent hearing services, including Australian Hearing, cochlear implant technology and early intervention programs. Early identification of children with a hearing loss, so that access to services can be commenced as soon as possible, will enable improved speech, language and educational outcomes.

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ACKNOWLEDGEMENTS

We would like to acknowledge the excellent help of Ms Helen Bailey, Coordinator of the WA Newborn Hearing Screening Program. The support of the WA Department of Health, the Telethon Institute for Child Health Research, King Edward Memorial Hospital, Princess Margaret Hospital for Children, and the Garnett Passe and Rodney Williams Memorial Foundation in the establishment of the WA Newborn Hearing Screening Program is gratefully acknowledged.

REFERENCES

1. Mehl AL, Thomson V. Newborn hearing screening: the great omission. Pediatrics 1998;101:E4.
2. Mehl AL, Thomson V. The Colorado newborn hearing screening project, 1992-1999: On the threshold of effective population-based universal newborn hearing screening. Pediatrics 2002;109:E7.
3. Fortnum HM, Summerfield AQ, Marshall DH, Davis AC, Bamford JM. Prevalence of permanent childhood hearing impairment in the United Kingdom and implications for universal neonatal hearing screening: questionnaire based ascertainment study. Br Med J 2001;323:536-40.
4. Joint Committee on Infant Hearing. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. Am J Audiol 2000;9:9-29.
5. Newborn hearing screening: recommendations and rationale. U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2001. http://www.ahrq.gov/clinic/3rduspstf/newbornscreen/newhearrr.htm
6. Thompson DC, McPhillips H, Davis RL, Lieu TL, Homer CJ, Helfand M. Universal newborn hearing screening: summary of evidence. JAMA 2001;286:2000-10.
7. Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S. A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment. Health Technology Assessment 1997;1. http://www.hta.nhsweb.nhs.uk (cited 2002 Sept 19)
8. Yoshinaga-Itano C, Sedey AL, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. Pediatrics 1998;102:1161-71.
9. Moeller MP. Early intervention and language development in children who are deaf and hard of hearing. Pediatrics 2000;106:E43.
10. Bailey HD, Bower C, Krishnaswamy J, Coates HL. Newborn hearing screening in Western Australia. Med J Aust 2002;177:180-5.
11. Wake MA. Newborn hearing screening: decision time for Australia. Med J Aust 2002;177:172-3.
12. Poulakis Z, Barker M, Wake M. Six month impact of false positives in an Australian infant hearing screening programme. Arch Dis Child 2003;88:20-4.

Patient support organisations

Deafness Forum and Australian Hearing

See page 87

Generics – equal or not?

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SYNOPSIS

Generic products must be bioequivalent to the innovator brand before they can be marketed in Australia. There are no generic formulations of drugs with a narrow therapeutic index as it would be difficult for them to meet the required standard of bioequivalence. In Australia most generic drugs are marketed with a brand name. Some generic brands are manufactured by the same company that produces the innovator brand of the drug. Although generic brands are usually cheaper the proliferation of brands may cause confusion.

Index words: bioequivalence, pharmaceutical industry, drug regulation.

(Aust Prescr 2003;26:85–7)

Introduction

From time to time, controversies and claims arise regarding generic prescribing and generic substitution. For example, a support group for people with epilepsy issued a news release that stated:

- (generic) substitution may impair safety and efficacy of treatment
- (generic) substitution may be dangerous for patients with life-threatening diseases (like epilepsy)
- patients for whom a medication has been substituted should be carefully monitored.

These concerns make it worthwhile to revisit the issues and to try and sort fact from opinion and fiction.

What are generics?

The term 'generic product' is used in different ways. It can mean a product marketed under the drug's non-proprietary approved name, or it can, as is usual in Australia, mean a product marketed under a different brand (proprietary) name. It is sometimes used to mean any product from a company other than the innovator (research-based) manufacturer.

A common use of the term (and that used by the World Health Organization (WHO)), is for a pharmaceutical product that is:

- intended to be interchangeable with the innovator product in an individual patient
- usually manufactured without a licence from the innovator company
- marketed after expiry of patent or other exclusivity rights.

The WHO refers to these products as 'multisource pharmaceutical products'. To be interchangeable such products must be bioequivalent.

Generic prescribing

In Australia writing the non-proprietary (generic) name on a prescription allows the pharmacist to dispense any brand of the drug. The pharmacist does not have to dispense the cheapest brand.

Generic substitution

This policy enables the pharmacist, without reference back to the prescriber, to dispense a different brand of the drug even though the doctor has written a prescription for a particular brand. In Australia, doctors can endorse the prescription to prevent substitution.

Bioequivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

Product quality and bioequivalence data are required before a generic product can be registered in Australia or listed on the Pharmaceutical Benefits Scheme (PBS). The quality data required include purity, stability, good manufacturing practice and quality control. These data are the same as those required for innovator products. It has sometimes been suggested that generic products may contain ratios of enantiomers (optical isomers) that are different from the innovator product. This argument cannot be sustained, as conventional chemical synthesis of the active drug produces a racemic (equal) mixture of the two enantiomers. Data on the enantiomeric ratio of the active substance in a generic product would in any case be required before registration in Australia.

Assessing bioequivalence

Bioequivalence is usually assessed by single dose *in vivo* studies in healthy volunteers. The reference product is usually the innovator product that is marketed in Australia, but for older drugs it may be another generic that is the market leader in Australia. Figure 1 shows a simulation of such a study.

The regulatory limits applied are that the 90% confidence intervals for the ratios (test:reference) of the areas under the drug concentration versus time curves (AUC ratio) and the maximum plasma drug concentrations (C_{max} ratio) must fall between 80% and 125%. (The confidence limits are

Fig. 1

Simulation of the drug concentration versus time curves for two drug products

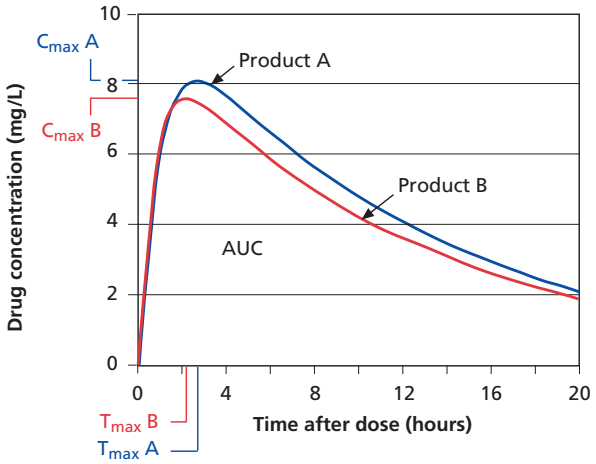
Drug A is the reference product (usually the innovator product) and Drug B is a generic product. The relevant parameters are:

Drug A: C_{max}=8.1 mg/L; T_{max}=2.6 h; $AUC_{0-\infty}$=124.9 mg.h/L

Drug B: C_{max}=7.6 mg/L; T_{max}=2.1 h; $AUC_{0-\infty}$=112.4 mg.h/L

The ratio of areas (generic:reference), and therefore the relative bioavailability, is 0.9

To be accepted as bioequivalent, the 90% confidence intervals for the area ratio would need to fall within the range 0.8–1.25



C_{max} maximum plasma drug concentration

T_{max} time required to achieve a maximal concentration

AUC total area under the plasma drug concentration-time curve

asymmetrical because log transformed data are used in the comparison.) The times to maximum plasma concentration (T_{max}) for the test and reference product should also be similar. These requirements for similarity between the two products are therefore in both the **extent** of absorption (AUC ratio) and the **rate** of absorption (C_{max} and T_{max} ratios). In addition, most regulatory authorities would look at the intersubject variability for the two products and ask questions if there was a marked difference between them. Products satisfying the bioequivalence requirements can reliably be assumed to produce similar clinical effects when used interchangeably in the same patient.

It is sometimes claimed that the 80 to 125% limit means there can be a 45% variation between the new product and the reference product, but this is not really the case. The average ratio (point estimate) is usually reasonably close to 100% and this is the value of maximum likelihood for the comparison. If the average ratio is close to the 80 or 125% regulatory limits then the data would have to be very tight indeed to prevent the 90% confidence intervals falling outside the regulatory boundaries.

Commonly there are a number of generic products linked by a 'chain of inference'. For example, two brands x and y may both have been shown to be bioequivalent to the market leader brand z. Can brands x and y then be considered bioequivalent? They have not been directly compared in a formal bioequivalence study, but in practical terms would be very unlikely to fail if directly compared. The pragmatic decision is taken to consider all brands interchangeable. It would be practically and financially very difficult, and ethically unacceptable, to require each brand to be compared with every other brand in formal human studies.

Special bioequivalence issues

For a drug with a narrow therapeutic index and/or with saturable metabolism it may well be appropriate to require tighter bioequivalence limits for generic products. In fact, there are no generic products in Australia, for example, for digoxin (narrow therapeutic index and established bioavailability problems) or for phenytoin (saturable metabolism, narrow therapeutic index and bioavailability problems). The problems in the early 1970s that focused attention on phenytoin bioavailability occurred when there was a change of excipient (from calcium sulphate to lactose) in the innovator formulation. Another drug with a narrow therapeutic index is warfarin. There are two warfarin brands on the market in Australia, but there has been no formal bioequivalence comparison made of them so they are **not** interchangeable.

Establishing bioequivalence for interchangeable controlled-release products usually requires more extensive data including clinical trial data. However, some of these products are available in Australia (e.g. enteric-coated sodium valproate, sustained-release verapamil and controlled-release diltiazem).

Bioequivalence issues are not confined to generic products. The clinical trial data on which marketing of the innovator product is based are usually obtained with formulations which differ from that ultimately marketed. The requirements for establishing bioequivalence between trial and marketed formulations are similar to those needed when assessing generics. Furthermore, innovator (and generics) manufacturers will frequently change their manufacturing process or site of manufacture and are required to show by appropriate *in vitro* or *in vivo* studies that bioavailability has not changed. The data which link an innovator market formulation back to the clinical trial data are therefore essentially the same as those required to establish interchangeability for generic products.

One valid concern in relation to generics is that individual patients could have idiosyncratic sensitivity to excipients such as colourings that are in the generic but not innovator product. This can occur, but is very rare and is not a problem limited to generics. Changes of excipients in innovator products could cause similar adverse effects.

Generics in Australia

The Therapeutic Goods Administration evaluates all products that are intended to be interchangeable. It assesses them for

quality and bioequivalence with the Australian innovator or market leader product. This usually requires *in vivo* bioequivalence data but, if satisfactorily justified by the sponsor, may be based on *in vitro* dissolution data for drugs with no known bioavailability problems.

Interchangeable products are marked in the Schedule of Pharmaceutical Benefits by a letter (a or b) and brand substitution by the pharmacist is permitted, unless the prescriber has indicated otherwise on the prescription. A brand premium, paid by the patient, is charged if the pharmacist dispenses a brand which costs more than the base-priced brand.

There has recently been a large proliferation in the number of 'generic' brands available through the PBS. This has resulted from the marketing of brands named according to the pharmacy chain selling them (e.g. Chem mart, GenRx, healthsense, Terry White Chemists). They are, in fact, all exactly the same product made by the same manufacturer and just packed and branded (named) differently. This unnecessary proliferation of brands is unfortunate and has the potential to cause confusion, but cannot be prevented under current legislation. A similar twist applies to some of the oral contraceptive products. Some manufacturers have marketed the innovator product under a different brand name as an interchangeable 'generic'. This allows a premium (of the order of $7–9) to be charged for the original 'innovator' product which is then strongly promoted.

Conclusion

There is no evidence in Australia that generic drugs are dangerous and impair the safety and efficacy of treatment. Our regulatory regime is world standard and conforms to requirements in regions such as Europe and the USA. Indeed, the Australian generic and bioequivalence requirements are 'harmonised' to those in Europe. There is also no evidence of systematic problems occurring because of generic availability and substitution. On the other hand, generics are cost-saving and allow the drug and health budgets to be spread further to enable access to new and expensive treatments where these offer cost-effective health outcomes.

FURTHER READING

Birkett DJ. Pharmacokinetics made easy. 2nd ed. Sydney: McGraw-Hill Australia; 2002.

Professor Birkett is now Executive Director, Research and Development at Johnson & Johnson Research Pty Ltd.

Self-test questions

The following statements are either true or false *(answers on page 95)*

3. In Australia, generic drugs must be bioequivalent to the innovator or market-leading brand of the drug.
4. The two brands of warfarin in Australia are not interchangeable.

Patient support organisations

See article on page 82

Deafness Forum

Deafness Forum represents the interests and viewpoints of the deaf and hearing impaired communities of Australia (including those people who have a chronic disorder of the ear and those who are deaf and blind). The Deafness Forum provides information on supporting organisations in local areas, and a range of links on its web site.

Contact

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BRADDON ACT 2612

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Web site: www.deafnessforum.org.au

Australian Hearing

Australian Hearing provides government subsidised hearing care for children and young adults to the age of 21, and pension concession card holders. Subsidised services include hearing assessment, fitting of hearing aids and hearing rehabilitation.

Australian Hearing has over 70 permanent centres. Australian Hearing audiologists also periodically visit community centres, medical centres, local hospitals and other locations. The research arm of Australian Hearing is the National Acoustic Laboratories.

Contact

Phone: 13 17 97
Web site: www.hearing.com.au

ABNORMAL LABORATORY RESULTS

New cardiac markers

Peter E. Hickman, Director of Chemical Pathology, Princess Alexandra Hospital, Brisbane, and Julia M. Potter, Department of Chemical Pathology, Queensland Health Pathology Service, Royal Brisbane Hospital, Herston, Queensland

SYNOPSIS

The use of cardiac troponins in the diagnosis of acute myocardial infarction has changed our understanding of coronary artery disease. Cardiac troponins are slowly released from necrosing myocardium so they are detectable in blood for several days. This prolongs the opportunity for identifying an infarction. Cardiac troponins have therefore significantly reduced the diagnostic role of creatine kinase-MB isoenzyme. Although there is only one assay for cardiac troponin T, confusion can arise because there are different non-standardised laboratory assays for cardiac troponin I. However, the clinically important issue is the detection of troponin rather than its absolute concentration. Of other new markers high sensitivity C-reactive protein may have a role in potential risk stratification, but it is not currently recommended for routine clinical use. In the context of the future diagnosis of other cardiac conditions, the neuroendocrine hormone, B-type natriuretic peptide may have a role in the diagnosis and monitoring of cardiac failure.

Index words: cardiac troponin, creatine kinase-MB isoenzyme, high sensitivity C-reactive protein, B-type natriuretic peptide.

(Aust Prescr 2003;26:88–90)

Introduction

The cardiac troponins have provided an important new insight into the pathophysiology of the acute coronary syndrome and stimulated new approaches to the management of ischaemic heart disease. They have been so significant in defining myocardial injury, that there has been a proposal to redefine acute myocardial infarction, with the presence of measurable cardiac troponin as the central diagnostic feature.[1]

Other markers are also being studied. These include B-type natriuretic peptide, a potential cardiac marker for cardiac failure, and the possible application of high sensitivity C-reactive protein (hs-CRP) as a predictor of future ischaemic heart disease.

Creatine kinase-MB isoenzyme (CK-MB)

The current WHO definition of myocardial infarction requires any two of the following to establish the diagnosis:

- a history consistent with myocardial ischaemia
- characteristic ECG changes
- increased cardiac enzymes.

Creatine kinase (CK) and more particularly its isoenzyme CK-MB still have a formal place in defining myocardial infarction. However the current definition is not a particularly useful one because studies have shown that, as currently defined, patients with myocardial infarction and unstable angina have similar outcomes.[2,3]

Interpretation of CK-MB is problematic, with both false positives and false negatives occurring. While CK-MB is relatively cardiac-specific, even healthy people may have low concentrations of this isoenzyme in their blood. People with chronic myopathies may have high concentrations of CK-MB because it is produced by regenerating skeletal muscle. A high concentration of CK-MB may therefore be unrelated to cardiac disease (false positive).

The half-life of CK-MB in the circulation is relatively short (approximately 12 hours). Samples collected many hours after an infarction may have both a low absolute concentration of CK-MB and a low ratio of CK-MB to total CK (due to the longer half-life of the major isoenzyme, CK-MM). This can give a false negative result.

Some specialists believe that it is no longer appropriate to use CK-MB in the diagnosis of myocardial infarction. It may be more helpful for investigating possible reinfarction, where its short half-life may be useful compared to the longer time that cardiac troponins spend in the circulation.

Cardiac troponin I and cardiac troponin T

The troponins are part of the actomyosin contractile apparatus of muscle cells. Structurally unique forms of troponin T and troponin I are found in cardiac tissue, enabling the development of immunoassays, which recognise only the cardiac forms of these two proteins. In most clinical situations both cardiac troponin I (cTnI) and cardiac troponin T (cTnT) seem to offer similarly useful clinical information.

When a cardiac myocyte dies, CK-MB passes rapidly from the cytoplasm into the circulation and is cleared. In contrast, most of the troponin within the myocyte is found in the structural elements of the cell, so when necrosis occurs there is a steady leaching of troponin into the circulation. Consequently, troponin remains in the circulation for several days after a cardiac event.

Despite extended searching, there is currently no evidence that the cardiac troponins may be produced by tissues other than myocardium. However, the presence of cardiac troponin,

while indicating that cardiac injury has occurred, provides no information as to the mechanism of injury. Cardiac troponin concentrations may rise in conditions unrelated to ischaemic damage such as pericarditis, trauma and sepsis. Such rises provide no information about the likelihood of future ischaemic cardiac disease.

When associated with coronary artery ischaemia even low concentrations of cardiac troponin predict an adverse outcome. This is regardless of whether the other WHO criteria for the formal diagnosis of myocardial infarction are met. The pathophysiological mechanism for these acute coronary syndromes is the presence of an unstable coronary plaque, with release of micro-emboli causing focal myocardial necrosis with release of cardiac troponin. The increased mortality is a reflection of a large thrombus separating from the unstable plaque.[3] This improved understanding of the mechanism of the acute coronary syndrome, has led to a proposal to redefine myocardial infarction, using the presence of a cardiac biochemical marker, with some evidence of coronary artery ischaemia, as the central diagnostic criterion.[1]

Cardiac troponins in patients with renal failure

A small proportion of patients with renal failure undergoing dialysis have detectable concentrations of cTnT. This finding was originally thought to be a false positive test, but careful analysis has shown that these patients do have a worse cardiac prognosis. When one considers that approximately 20% of patients on dialysis die each year and that cardiac disease is the commonest cause of mortality[4], this result is not unexpected. Although there is some increase in cTnI in dialysis patients, this appears to be one area where cTnT is more informative.

Problems with assays for cardiac troponin I

Cardiac troponin I is prone to modification in the circulation. It may be phosphorylated and oxidised and can exist as a complex with either cTnT or cardiac troponin C. This has some clinical relevance, because the different antibodies used in commercial assays may recognise these different molecular forms to varying extents. A major problem with cTnI assays is that the different assays are calibrated with different standards. The same blood sample may give quite different apparent concentrations in different assays. If it is accepted that the presence of **any** cardiac troponin in the presence of coronary artery ischaemia indicates a worse prognosis, then the absolute concentration is less important.

B-type natriuretic peptide

The cardiac natriuretic peptide family of neuro-endocrine hormones has a complex physiological role in modulating blood volume and pressure. This involves natriuresis and diuresis as well as antagonism to the angiotensin-renin system. These peptides are also antimitotic and may modulate cardiac hypertrophy.[5] In the presence of left ventricular dysfunction, with worsening cardiac failure, the concentration of plasma B-type natriuretic peptide (BNP) increases in proportion to the New York Heart Association's (NYHA) classification of severity. However, there are a number of other pathophysiological states in which BNP may be elevated, such as hypertension and cardiac hypertrophy, pulmonary hypertension and renal disease. The most appropriate use of this marker remains to be defined.

As with cTnI, several different assays for BNP or its associated peptides (e.g. NT-proBNP) have been used in the published studies. As these assays are not yet standardised, numerical values from one assay cannot be compared quantitatively with those from another.

C-reactive protein

C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to cytokine release during inflammation. It has long been used in clinical practice to follow systemic inflammation, especially bacterial infection. More recently, epidemiological evidence has shown that basal levels of CRP, in the absence of apparent inflammatory disease (so-called hs-CRP) may be informative in predicting future myocardial or cerebrovascular events.[6]

The value of hs-CRP appears to relate to activity in the atherosclerotic plaque. Amongst the cellular elements of the atherosclerotic plaque are inflammatory cells, which, by releasing interleukin-6, cause secretion of CRP into the circulation. In the Physicians' Health Study, when people in the highest quartile of CRP values were compared to people with the lowest quartile of CRP values, they had a relative risk of future myocardial infarction of 1.9. In the Women's Health Study the relative risk was 4.4.

There are a number of problems in using CRP measurements to predict the likelihood of future cardiovascular events. These are both biological and analytical.

Biological variability in basal CRP concentration is considerable. Even mild, subclinical infections can cause significant increases in CRP concentration that are unrelated to cardiovascular disease. For this reason, no measurements should be made within two weeks of any infection. Even with this precaution, CRP concentrations may vary markedly. Several studies have investigated the variability of the CRP concentration in blood collected repeatedly from individuals over periods of weeks to months. The standard deviation for each individual varies from 30% to 63% of the mean value.[7] Thus it might be highly misleading to contemplate using a single measurement to guide possible therapy. It has been proposed that two separate measurements should be made on each individual, while they are quite well, and at intervals of

Key points

In patients with coronary artery disease:

- the presence of any cardiac troponin indicates a worse prognosis
- CK-MB is no longer the preferred marker in the diagnosis of myocardial infarction
- high sensitivity C-reactive protein and B-type natriuretic peptide are not currently recommended for routine clinical use

more than a week apart. The lowest value is then used to determine which quartile the person is in. Even this approach may be insufficient to correct for the variability.

There are outstanding laboratory problems with use of hs-CRP. Not all assays produce identical results. No laboratory has the resources to determine its own reference ranges, so transportability of results between assays is obviously of great importance in defining the concentrations that relate to the different quartiles of basal CRP concentration. At the present time it appears undesirable to attempt to use hs-CRP in individual risk stratification.

REFERENCES

1. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined – a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959-69.
2. Schroeder JS, Lamb IH, Hu M. Do patients in whom myocardial infarction has been ruled out have a better prognosis after hospitalization than those surviving infarction? N Engl J Med 1980;303:1-5.
3. Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation 2000;102:118-22.
4. Pennell JP. Optimizing medical management of patients with pre-end-stage renal disease. Am J Med 2001;111:559-68.
5. Chen HH, Burnett JC Jr. The natriuretic peptides in heart failure: diagnostic and therapeutic potentials. Proc Assoc Am Physicians 1999;111:406-16.
6. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;103:1813-8.
7. Campbell B, Badrick T, Flatman R, Kanowski D. Limited clinical utility of high-sensitivity plasma C-reactive protein assays. Ann Clin Biochem 2002;39:85-8.

FURTHER READING

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557-65.

Ewald B. B-type natriuretic peptide: a new diagnostic tool for congestive heart failure. Aust Prescr 2003;26:64-5.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

5. Ectopic production of cardiac troponins reduces their usefulness in assessing acute coronary syndromes.
6. Measuring high sensitivity C-reactive protein provides an accurate prediction of an individual's risk of cardiovascular disease.

National Prescribing Service Ltd (NPS) information hotlines

NPS operates two hotlines providing health professionals and the community with information about medicines.

Therapeutic Advice and Information Service (TAIS): 1300 138 677

For general practitioners, pharmacists and other community-based health professionals

The *Therapeutic Advice and Information Service* (TAIS) has been in operation for three years and to date has received more than 15 000 enquiries. The majority of callers were community pharmacists (48%) and general practitioners (35%). The most commonly asked questions were about drug interactions, adverse reactions and therapeutic options.

Information is provided by expert drug information specialists. The service operates Australia-wide, Monday to Friday 9am to 7pm (EST) for the cost of a local call.

Medicines Line: 1300 888 763

For consumers

TAIS is complemented by *Medicines Line,* a medicines information hotline for consumers. *Medicines Line* was launched in September 2002 and receives approximately 1000 calls every month.

Statistics show that most callers are females aged 24–64; 25% of callers ask for information on behalf of a child, partner or parent. Questions often reflect what is being reported in the media at the time and are focused on adverse reactions, interactions, and to a lesser extent the mechanisms of action of medicines. Questions are most commonly related to antidepressants, antihypertensives and complementary medicines.

Information is provided by expert drug information specialists. The service operates Australia-wide, Monday to Friday 9am to 6pm (EST) for the cost of a local call.

Immunotherapy for allergic disorders

Richard M. O'Brien, Department of Medicine, University of Melbourne, Head, Allergy Clinic, Royal Melbourne Hospital, and Head, Clinical Immunology and Allergy, Western Hospital, Footscray, Victoria

SYNOPSIS

Immunotherapy can be an effective and safe treatment for reducing allergic reactivity to a number of inhaled and injected allergens. It can be used for the treatment of problematic respiratory allergic disorders that are not responding well to environmental measures and drug treatment. Immunotherapy for hay fever or asthma is generally given by subcutaneous injection of increasing doses of an extract of the allergen to which the patient is sensitive. Injections should be given by experienced medical practitioners and resuscitation equipment must be readily available. The patient should be under observation for 30 to 45 minutes following each injection.

Index words: desensitisation, injections, rhinitis.

(Aust Prescr 2003;26:91–3)

Introduction

Immunotherapy for allergic disease is the administration of increasing amounts of the specific allergen to which the patient is known to be allergic. It has been used for the treatment of hay fever since 1911. The common allergic disorders treated with immunotherapy are hay fever and asthma. Numerous trials have shown immunotherapy to be effective, although some clinicians have emphasised its potential dangers. Allergen-specific immunotherapy is also used for treatment of bee-venom and wasp hypersensitivity to prevent anaphylactic reactions following stings.

The mechanism of action of immunotherapy has been debated for as long as it has been in use. Early researchers felt that it acted by either reduction in allergen-specific IgE or by induction of 'blocking' IgG antibodies. Whilst both of these serologic changes occur with immunotherapy, they generally do not occur for months or years, well after the beneficial effect of immunotherapy is evident. Furthermore, neither of these alterations in antibody concentrations correlates with the clinical efficacy of the immunotherapy. More recent research indicates that immunotherapy is likely to act by altering T cell reactivity to the specific allergen. This could be considered a form of high-dose tolerance, resulting in a reduction in the release of pro- (allergic) inflammatory cytokines. A reduction in cytokine release would also lead to a decrease in specific IgE, as antibody production is strictly T-cell dependent.

Common allergens

The major perennial allergens include the house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are the major species), pet hair and danders (particularly cat) and mould spore (particularly alternaria and cladosporium). Spore levels do show some seasonal variation in atmospheric concentration, being highest in the summer and autumn but, unlike pollens, significant levels are present throughout the year.

In Australia, and particularly in the southern states, seasonal hay fever and asthma are very common and generally due to grass pollen sensitivity. Clinical allergic disease due to tree and weed pollen sensitivity is certainly important in many areas of Europe (commonly birch and olive) and North America (commonly ragweed) but is less of a problem in Australia.

Indications for allergen-specific immunotherapy

In Australia the major use for allergen-specific immunotherapy is for the treatment of allergic respiratory diseases including hay fever and asthma. It is only one of a range of therapies for these conditions and should not be considered unless allergen avoidance strategies and drug treatments have been implemented and found to be inadequate. These approaches should always be continued even if immunotherapy is commenced.

It is critical to ensure that the allergen for which immunotherapy is being undertaken is relevant to the patient's clinical illness. This is frequently apparent from the correlation of allergen exposure and symptom development but, on occasions, allergen provocation tests may be necessary. Before treatment, the allergen, defined by the presence of specific IgE, must also be confirmed by either skin prick test and/or radioallergosorbent test (RAST).[1]

The use of immunotherapy in the treatment of atopic dermatitis or eczema is controversial. Although it may be beneficial in occasional patients, there is also a risk of significantly aggravating the disease. Eczema frequently coexists in patients with respiratory allergic diseases and, if desensitisation is considered for the respiratory component, the state of their skin disease must be taken into consideration. It is certainly preferable not to commence immunotherapy unless the eczema is well controlled and the skin condition must be closely monitored during treatment.

Immunotherapy is not indicated for the treatment of food allergies and, in fact, a number of trials conducted overseas have been abandoned because of serious anaphylactic events. In general drug allergies are not treated by desensitisation although there are a few situations where this can be beneficial.

In patients who need to continue a medication for which no suitable alternative exists, a form of tolerance can be induced by giving increasing doses of the medication over a relatively short period of time. This form of therapy has been used most successfully for penicillins, but has also been used for a number of other medications including aspirin and allopurinol. The mechanism for the tolerance has not been clearly delineated and is likely to be different for different drugs. Moreover, it is almost certainly not the same as for the more traditional allergen-specific immunotherapy. Furthermore the state of non-responsiveness only lasts as long as the medication is continued.

Efficacy

For seasonal hay fever, immunotherapy is widely considered to be very effective with at least 80% of patients having a significant and prolonged response.[2,3] Perennial hay fever is commonly due to house dust mite sensitivity and properly controlled studies have also shown that immunotherapy is beneficial, although not as much as it is for pollen desensitisation.

Immunotherapy for asthma is somewhat controversial and is certainly not regarded as conventional therapy by all physicians involved in the treatment of patients with asthma. Nevertheless there are a large number of well-powered, randomised, placebo-controlled trials showing beneficial effects. These include statistically significant reductions in symptoms and medication use with improvements in lung function and indices of bronchial hyperreactivity. The Cochrane Database contains a systematic review of immunotherapy for asthma. It includes 54 trials, using a number of different allergens, and shows that the effects were generally beneficial with a highly significant reduction in asthma symptoms and medication use. Immunotherapy also resulted in a significant reduction in allergen-specific bronchial hyperreactivity, with some reduction in non-specific bronchial hyperreactivity as well.[4]

Administration

It is preferable to undertake immunotherapy for only one or a limited number of allergens at a time. In Australia immunotherapy is usually given by subcutaneous injection in the outer upper arm with an increasing dose of the specific allergen to which the patient is sensitive. During the escalation phase of the course the injections are usually given at fortnightly intervals, but anywhere between weekly and every three weeks is as effective. After completion of the course, patients with perennial allergic sensitivity should go on to receive monthly maintenance therapy, again by subcutaneous injections. The optimal duration of the maintenance therapy is uncertain, but a World Health Organization position paper from June 1998 recommended between three and five years.

Opinions vary concerning immunotherapy for grass pollen sensitivity. Allergists practising in southern states of Australia generally advise that patients should receive pre-seasonal courses of immunotherapy during the autumn and winter for three consecutive seasons, without maintenance injections. In more northern states the immunotherapy regimen is usually similar to that for perennial allergens, with a course at any time of the year followed by maintenance injections.

Immunotherapy can also be given by non-parenteral routes, including intranasal, sublingual or oral. The effectiveness of these routes has not been well established and they are not recommended.

Safety

As with all forms of treatment, it is essential that the administration of immunotherapy be as safe as possible. As the patients have high titres of specific IgE and are being given parenteral doses of allergens to which they are sensitive, the risk of a severe systemic reaction always needs to be kept in mind.

In 1986 a report was prepared by the UK Committee on Safety of Medicines because of concern over an increasing frequency of severe reactions including deaths.[5] The report found that serious reactions to immunotherapy occurred at a rate of approximately 1 in 500. A number of problems were identified including poor selection of patients, inadequately trained operators, poorly standardised allergen extracts and lack of readily available resuscitation equipment. The report stipulated that immunotherapy should only be given where full resuscitation equipment was available and that patients should be observed for at least two hours after the injection. Although the waiting time was subsequently reduced to one hour in 1994, the effect of these restrictions was to markedly limit the use of immunotherapy in general practice in the UK.

The peak US body, the American Academy of Allergy, Asthma and Immunology (AAAAI), has reviewed the adverse events following immunotherapy on a number of occasions. One key study reported 24 fatalities associated with immunotherapy over a 25-year period.[6] With rare exceptions, ultimately fatal reactions commenced within 25 minutes of administration of immunotherapy and usually much sooner. The current AAAAI Position Statement recommends a 20-minute waiting period for most patients, extending to 30 minutes for patients at potentially high risk, for example those with asthma or previous systemic reactions. In Australia five deaths were reported to the Adverse Drug Reactions Advisory Committee in a 21-year period. Four of these were in patients with asthma and in each of these a divergence from the recommended protocol had taken place.

The current recommendation from the Australasian Society of Clinical Immunology and Allergy is that the patient should be observed for at least 30 minutes following an immunotherapy injection, increasing to 45 minutes in higher risk patients. Resuscitation equipment must be immediately available and should include an intravenous giving set and fluids, parenteral adrenaline, corticosteroids and antihistamines, an oral airway and equipment for the administration of oxygen. A doctor with experience in administration of immunotherapy and resuscitation should be present at all times. Specialists should

check that these requirements are met before delegating the injections to general practitioners.

Conclusion

Allergen-specific immunotherapy can be a highly effective treatment for allergic respiratory diseases that are responding inadequately to more conventional therapies. Immunotherapy is most effective when given by the subcutaneous route with an increasing dose of the relevant allergen. The administering doctor should have experience in immunotherapy and resuscitation equipment must be readily available. The patient should be under observation for at least 30 minutes following each injection.

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REFERENCES

1. O'Brien RM. Skin prick testing and *in vitro* assays for allergic sensitivity. Aust Prescr 2002;25:91-3.
2. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. Br Med J 1991;302:265-9.
3. Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999;341:468-75.
4. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma (Cochrane Review). In: The Cochrane Library, Issue 2 2003. Oxford: Update Software.
5. Committee on Safety of Medicines. CSM update: Desensitising vaccines. Br Med J 1986;293:948.
6. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol 1987;79:660-77.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 95)

7. Allergen-specific immunotherapy is an effective treatment for patients with food allergy.
8. Allergen-specific immunotherapy can exacerbate eczema.

Book review

Hospital in the home

Michael Montalto. Melbourne: ArtWords Pty Ltd; 2002. 172 pages.

Price $66 (including GST)

Julia Lowe, Director of General Medicine, Department of Endocrinology, John Hunter Hospital, Newcastle, New South Wales

Michael Montalto is the director of the Hospital in the Home at Edgeworth Hospital in Melbourne. It must be recognised that he is an advocate of a certain model of hospital in the home. For reasons that he briefly alludes to in this book, substitution of domestic for hospital care for patients who would otherwise 'require inpatient care by the nature of their medical or social condition', is far more advanced in Victoria than in other parts of Australia. For clinicians from these other areas, his book provides a short introduction to the topic, and a source of references for further reading. As I practise outside Victoria, I found the first two chapters the most interesting. These discuss factors supporting the emergence of alternatives to hospitalisation, the difficulties of organising randomised controlled clinical trials in this area, and organisational models of hospital in the home.

Chapters 3, 4 and 6 outline the frequently asked questions about hospital in the home – general clinical principles, patient selection and management, and the drugs and devices used. I may have missed something, but as a clinician in New South Wales the description of conditions that could be managed at home merely confirmed my suspicion that many of these programs deal with patients who would not be admitted to hospital in other areas. Many general practitioners will manage uncomplicated deep venous thrombosis, pyelonephritis or pneumonia in the community. The Diabetes Education Centre in Newcastle, New South Wales, demonstrated more than 25 years ago that it is not necessary to admit people to hospital to start treatment with insulin, and in Leicester in the UK, even young children have been started on insulin as outpatients, for over forty years. The true advances have been the technological ones that allow long-term intravenous antibiotic therapy of conditions such as septic arthritis and bacterial endocarditis to take place outside the conventional hospital setting.

Chapters 5, 7 and 8 deal with cost, quality and ethical issues. It is always easy to criticise a non-expert writing in these areas, but I thought the chapter on ethics was lightweight and superficial. The final section in this chapter on identifying poor hospital in the home care was interesting, but for those who skim books it would have been better placed in the chapter on quality. I was also surprised that there was no recognition of the major criticism of cost analyses of hospital in the home, namely that while there may be some savings, these are only achieved if hospital in the home is substituted for hospital beds that are then closed. Publicity associated with the publication of the book suggested that hospital in the home was an alternative (less costly) way of meeting the need for increased hospital beds without building more hospitals. I could only find one sentence alluding to this, and those who like me were looking for some discussion of this idea will be disappointed.

These criticisms aside, this is a slim, readable introduction to an important development in health care.

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 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.

Gefitinib

Iressa (AstraZeneca)

250 mg tablets

Approved indication: non-small cell lung cancer

Australian Medicines Handbook section 14.3

Growth factors have an important role in regulating cell proliferation. Abnormalities in the receptors for growth factors can result in cancer development. The epidermal growth factor receptor may be involved in transmitting cellular signals that lead to the progression of lung cancer. These signals can be blocked by inhibiting the enzyme tyrosine kinase.

Gefitinib is a tyrosine kinase inhibitor which can be taken by mouth. It has a bioavailability of 59%, but absorption is not altered by fasting. Gefitinib is metabolised by cytochrome P450 3A4 so it has the potential to interact with drugs that induce, or are metabolised by, this enzyme system. Interactions with itraconazole and rifampicin have been confirmed in volunteers. In clinical trials there have been interactions with metoprolol and possibly warfarin. As most of the drug is eliminated by liver metabolism and, as liver enzymes can increase during treatment, patients should have their liver function checked.

In an early clinical trial gefitinib was given to 71 patients with a variety of cancers that had not responded to other treatment. Although several patients dropped out of the trial, 26 completed at least three months of therapy. Only nine of the 39 patients with non-small cell lung cancer continued treatment for three months. The major dose-limiting toxicities were diarrhoea and rash.[1]

When used as monotherapy for previously-treated patients with locally advanced or metastatic non-small cell lung cancer gefitinib has produced a response in 9–19% of patients. Although treatment relieved some patients' symptoms, the median survival was only 6–8 months. When used in combination with other anticancer drugs in previously untreated patients gefitinib does not improve survival.

Most patients will suffer adverse effects from treatment. These include diarrhoea, rashes and other skin problems, nausea and vomiting. *Australian Prescriber's* sister journal in Japan, Kusuri-no-Check, has been concerned about deaths from gefitinib. Approximately 23 500 people have been treated in Japan, but the drug has been implicated in the deaths of 183.[2] Many of these deaths may have been the result of acute interstitial pneumonia.[3]

Although gefitinib has been marketed before the results of clinical trials have been published, its role in therapy will require further study. Its Australian approval restricts it to patients with locally advanced or metastatic non-small cell lung cancer who have previously received chemotherapy.

REFERENCES

1. Herbst RS, Maddox AM, Rothenberg ML, Small EJ, Rubin EH, Baselga J, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. J Clin Oncol 2002;20:3815-25.
2. Hama R, Sakaguchi K. The gefitinib story. ISDB Newsletter 2003;17:6-9.
3. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137-9.

Voriconazole

Vfend (Pfizer)

50 mg and 200 mg tablets

30 mL glass vials containing 200 mg as lyophilised powder

Approved indication: systemic fungal infections

Australian Medicines Handbook section 5.2.3

The triazole antifungal drugs, such as fluconazole and itraconazole can be used to treat systemic fungal infections. Their fungicidal activity results from the inhibition of ergosterol synthesis in the cell membrane. Voriconazole is a new triazole drug with a broad spectrum of activity. In addition to the treatment of serious fungal infections, voriconazole can be used to prevent infections in patients with febrile neutropenia.

A clinical trial randomised 837 patients with febrile neutropenia to empirical therapy with liposomal amphotericin B or voriconazole. Fungal infections occurred in 21 patients given amphotericin B and in eight patients taking voriconazole. Breakthrough infections were particularly reduced in patients with relapsed leukaemia or an allogenic transplant.[1]

In a study of 277 patients with invasive aspergillosis 29% of those taking voriconazole had died within 12 weeks compared with 42% of those taking amphotericin B. Voriconazole can also be used when fungal infections such as invasive candidiasis do not respond to other antifungal drugs.

A loading dose of voriconazole will produce steady-state concentrations within 24 hours rather than the six days it usually takes with twice-daily doses. The tablets are well absorbed so the loading dose can be given orally. Voriconazole is metabolised in the liver and as this metabolism becomes saturated voriconazole has non-linear pharmacokinetics. There is a lot of variability in the pharmacokinetics of voriconazole, particularly in certain ethnic groups who are poor metabolisers. As the metabolism of voriconazole involves cytochrome P450 2C9, 2C19 and 3A4 there are many potential drug interactions.

Co-administration with drugs such as carbamazepine, ergotamine, pimozide and cisapride is contraindicated.

Hepatic toxicity including fatal liver failure can occur so patients need regular monitoring of liver function. A more common adverse reaction is altered vision. This affects approximately 30% of patients. They may complain of blurring, photophobia or changes in colour vision. Some will develop hallucinations. Rashes are common and some patients have developed Stevens-Johnson syndrome.

Although voriconazole has some significant adverse effects some of these, such as renal dysfunction, occurred less frequently than they did with amphotericin B. There is, however, controversy about whether voriconazole is as effective as amphotericin B. In the study of febrile neutropenia the overall treatment success rate was 26% for voriconazole and 30.6% for liposomal amphotericin B. The American Antiviral Drugs Advisory Committee recommended that the Food and Drug Administration should not approve voriconazole.[2] While there are problems with fluconazole and itraconazole, the role of voriconazole requires further study.

REFERENCES[†]

1. Walsh TJ, Pappas P, Winston DJ, Lazarus HM, Petersen F, Raffalli J, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. N Engl J Med 2002;346:225-34.
2. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever [letter]. N Engl J Med 2002;346:289-90.

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

Correction

New drugs (Aust Prescr 2003;26:46)

There was an error in the comment about fibrin sealant Tisseel Duo 500 (see letter page 76). The components of this new presentation of fibrin sealant are contained in preloaded syringes rather than vials. The product only needs to be thawed out before use, so the preparation time can be reduced by warming. After thawing, the product is viable for up to 48, not four, hours.

Answers to self-test questions

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

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Printed in Australia by
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22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service