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CONTENTS

Editorial

What now for Alzheimer's disease? An epidemiological evaluation of the AD2000 trial

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Key words: donepezil, dementia.

(Aust Prescr 2005;28:134–5)

In recent years, acetylcholinesterase inhibitors have been approved for the treatment of Alzheimer's disease. This has been mainly on the strength of many randomised placebo-controlled trials showing a statistically significant improvement in cognitive, functional and behavioural scores mainly at 12 and 24 weeks.[1,2,3] The questions now are whether this statistical difference translates into a clinically meaningful difference and whether treatment is cost-effective. The AD2000 trial[4] sheds light on this question.

This placebo-controlled trial of donepezil was not sponsored by a drug company. The trial has many strengths as it:

- is the only trial to look at end points beyond one year
- focuses primarily on clinical end points such as time to institutionalisation or progression to disability
- includes measures of caregiver burden (as a secondary outcome)
- enrolled a broader spectrum of patients than those typically included in trials sponsored by drug companies.

In this issue…

Knowledge about new drugs is usually limited to the experience of the carefully selected patients who participated in the clinical trials. A drug which satisfies short-term criteria of safety and efficacy may be less effective in the long term. The editorial by John Attia and Peter Schofield suggests that any benefits of donepezil may not be sustained, while Jeffrey Post and Mark Kelly say that cardiovascular diseasemay be emerging as a long-term adverse effect of antiretroviral therapy.

To improve our knowledge of drug safety it is important to report adverse events, particularly to new drugs. Kerri Mackay explains what happens to your reports of adverse reactions.

Amiodarone is a drug with many possible adverse reactions. Terry Campbell therefore advises on how to minimise the risk of serious adverse effects.

The drawbacks of the trial were that recruitment was slower and smaller than planned (566 versus 3000 patients). It had a complex design (multiple treatment phases and washout periods) and a large withdrawal rate. This makes a true intention-to-treat analysis difficult, however, the overall effect of these factors is to bias away from the null, that is to overstate the effect size. With this caveat in mind, the results show:

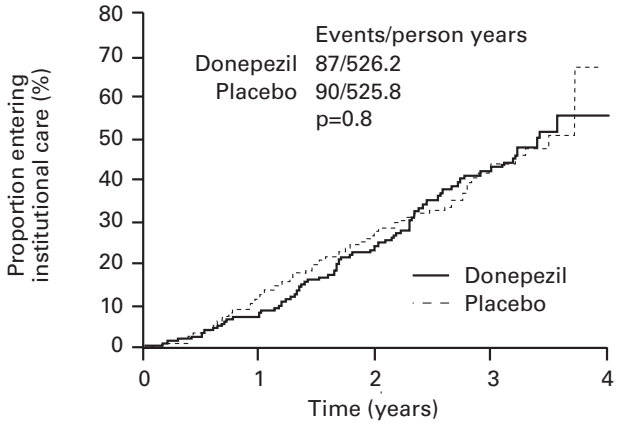
- A difference in the 30-point mini-mental state examination of 0.8 points (95% CI 0.5–1.2*) between the treatment and placebo groups at two years. This is about half the treatment effect previously seen at one year in other trials (1.8 points, 95% CI 0.5–3.2).
- No difference in institutionalisation (RR=0.97†, 95% CI 0.72–1.3) over 114 weeks. This conflicts with a previous drug company-sponsored trial indicating a significant delay in nursing home placement of about 21 months.[5] However, the sponsored trial was a non-randomised, open-label study with large potential for selection bias. The survival curves for AD2000 seem to indicate some gap at one year (Fig. 1), a potential 2–3 month delay in institutionalisation. This is consistent with many studies showing a 2–3 month delay in symptomatic progression, however this is not sustained and the overall rates at two years are similar.
- No difference in progression to disability (RR=1.02, 95% CI 0.72–1.45) over 114 weeks.
- There was a statistical difference in the functional score (as measured on the Bristol activities of daily living scale, BADLS) of about 1 point, out of a total of 60. Like the statistical difference in the mini-mental state examination, this difference was present by 24 weeks, but there was no further divergence (or convergence) of the curves with continued treatment. Neither of these score differences met previous, externally set criteria for clinical significance.
- There was no difference in behavioural and psychological symptoms as measured by the neuropsychiatric inventory.

* CI confidence interval

† RR relative risk

Fig. 1

Entry to institutional care



Number at risk

Donepezil	282	212	134	57	1
Placebo	283	209	135	60	0

Reprinted with permission from Elsevier (The Lancet 2004;363:2105-15)[4]

- Importantly, there was no significant difference in the carer's psychological morbidity score as measured by the General Health Questionnaire (GHQ-30). Treatment made no significant difference to the amount of time the caregiver had to spend with the patient.
- The mean annual cost per patient resident in the community was higher in the donepezil group than placebo by £500 (approx. A$1180). This increased cost was mainly due to the donepezil group requiring more hospital and home visits.

So what can we say in summary? This trial once again highlights the importance of independent trials that enrol a representative patient population. Previous work shows that industry-sponsored studies tend to have more favourable results than non-industry studies.[6,7] This may be a consequence of inclusion and exclusion criteria that are very tightly defined and implemented. After the initial wave of favourable, mainly company-sponsored, results using cognitive and behavioural scales, AD2000 suggests that these changes in scores do not translate into clinically important or cost-effective changes. It is also evident that most of the relative improvement in scores occurs in the first six months. Prolonged use does not continue to improve scores, although it is unclear whether this is needed to maintain the benefit or if stopping will accelerate the patient's decline.

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Dr Schofield has received honoraria from Pfizer for lectures and consultancy.

Note

While this article was under review, another study looking at the effect of donepezil and vitamin E on cognitive impairment was published with three-year outcomes (Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-88). The results of this study are very similar to those of the AD2000 trial, that is, although there may be some mild protective effect at one year, this is not sustained at longer time points.

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.

Smoking cessation

Editor, – It was with considerable disappointment that I read J. Litt's contribution 'What's new in smoking cessation?' (Aust Prescr 2005;28:73–5). Nothing the author reviewed was new. The only truly new development in the field of smoking cessation has been the anti-nicotine vaccine. This did not seem to get a mention in the article at all. A lot of experimental research in animals has been published since 2002 and a review of current progress has recently been published.[1]

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Reference

1. Cerny T. Anti-nicotine vaccination: where are we? Recent Results Cancer Res 2005;166:167-75.

Dr John Litt, the author of the article, comments:

Nicotine is the main addictive agent in cigarettes.[1] A nicotine vaccine offers an additional therapeutic option to reduce the likelihood of relapse in smokers who have recently quit. Its role in assisting cessation or preventing the development of nicotine addiction remains speculative.[2]

Animal models have shown proof of concept.[3] Specifically, vaccination with a nicotine conjugate vaccine in mice produces antibodies that prevent nicotine crossing the blood-brain barrier. The vaccine also prevents the nicotine stimulation of dopamine release in the nucleus acumbens. This pathway is the postulated pleasure/reward pathway associated with various addictions, including nicotine. Blocking significant nicotine uptake in the brain reduces the rapid gratification effect and interrupts the subsequent reward provided by smoking. The process is not compromised by concomitant nicotine administration, suggesting that the vaccine may have a role in cessation.

The first phase I study was only published in July 2005.[4] After being immunised with a nicotine vaccine conjugated with bacteriophage Qb virus-like particles, 32 volunteers had significant increases in nicotine-specific IgM and IgG titres at 7 and 14 days respectively. Local reactions including erythema, local swelling and tenderness were common (88–100%) and a variable number (13–38%) experienced flu-like symptoms 2–12 hours post-injection.

A phase II trial is currently underway to assess vaccine efficacy. This and subsequent phase II studies will need to address a number of unknowns. For example, it is possible that the smoker may be able to alter their inhalation of nicotine and overcome the relative blockade of nicotine uptake into the brain.[5] How many boosters are required? What is the duration of immunity? What longer-term adverse effects are there? Most investigators agree that the anti-nicotine vaccine, if shown to be efficacious, will only provide an adjunct to counselling and other strategies, for example referral to an active callback program offered by state Quitlines.[2,5] A vaccine is unlikely to assist the patient in overcoming the habit of smoking or provide a coping strategy for dealing with negative emotions.

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Upper gastrointestinal haemorrhage

Editor, – In the article 'Management of acute bleeding in the upper gastrointestinal tract' (Aust Prescr 2005;28:62–6), the authors say that an infusion of a high-dose proton pump inhibitor for 72 hours is recommended and they give the dosing recommendation for omeprazole.[1] Recently, AstraZeneca has discontinued the intravenous preparation of omeprazole, replacing it with esomeprazole. Consequently, we wish to comment on the choice of proton pump inhibitor now that omeprazole is unavailable.

Almost all clinical trials evaluating continuous infusion in acute gastrointestinal bleeding have used omeprazole. The efficacy of other proton pump inhibitors in equivalent doses is unproven. There are no published trials directly comparing, for example, intravenous omeprazole and pantoprazole for nonvariceal acute upper gastrointestinal bleeding. There is a study of healthy people, uninfected by *Helicobacter pylori*, which compared intravenous esomeprazole 40 mg with

pantoprazole 40 mg once daily. It showed that esomeprazole provides faster and more pronounced control of intragastric acidity.[2] We are unaware of any published studies on the use of continuous infusion of esomeprazole.

Esomeprazole is the S-enantiomer of omeprazole and has the same pharmacological activity.[3] The major difference between the enantiomers is in their pharmacokinetics. After equivalent doses, esomeprazole reaches higher plasma concentrations.[4] The manufacturer has provided unpublished data based on a study in healthy volunteers comparing the effects of various regimens of esomeprazole on maintaining intragastric pH > 4 and pH > 6. The results showed that intravenous esomeprazole 80 mg when given as an initial bolus dose over 30 minutes, followed by a continuous infusion of 8 mg/hr, maintained intragastric pH > 4 and pH > 6 for longer during a 24-hour period than other dosages.

Given the limited data that are available, we are recommending esomeprazole when continuous infusions are necessary, until further evidence becomes available. The dosage for esomeprazole should follow those suggested for continuous infusions of omeprazole, with an initial 80 mg dose given over 30 minutes, followed by continuous infusion of 8 mg/hr (at a concentration of 0.4 mg/mL) over 72 hours.[5]

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Professor R.J. Fraser, one of the authors of the article, comments:

As mentioned in our article, the current standard for pharmacological treatment for non-variceal upper gastrointestinal haemorrhage is intravenous omeprazole or equivalent. Omeprazole has been the proton pump inhibitor studied in the majority of published clinical trials, but a small number have involved other drugs.[1] Esomeprazole, which will soon replace omeprazole, obviously fulfils the criteria of equivalence, but it is unlikely to be the only drug to do so. Esomeprazole is an enantiomer, with theoretical benefits in terms of metabolism, but to date this has not been shown to provide significant overall benefits compared to racemic preparations.

Many clinicians believe the benefits in gastrointestinal haemorrhage result from a class effect, with the rise in intraluminal pH and resultant clot stability the key to improved outcome. The exact parameters that determine clot stability and the speed with which these need to be attained are unknown. The unpublished data reporting superior acid control in healthy volunteers are likely to have limited relevance to patient therapy. Although drug potency and the speed of acid suppression are clearly important, using these unpublished data to infer benefit in patient management is unjustified. More data are required in patients before making definite recommendations. For economic reasons, and in the absence of comparative randomised clinical trials in patients with gastrointestinal haemorrhage, clinicians frequently prescribe alternatives to omeprazole. Until such trials are done, the selection of proton pump inhibitor will continue to be a balance between cost, potential benefits and ease of administration in the face of incomplete evidence.

Reference

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Biochemical tests in pregnancy

Editor, – In addition to the tests mentioned in the article 'Abnormal laboratory results: Biochemical tests in pregnancy' (Aust Prescr 2005;28:98-101), there are several other tests where the changes in the normal ranges during pregnancy are of clinical importance.

- Serum bicarbonate falls by approximately 4 mmol/L to compensate for the respiratory alkalosis which results from elevated progesterone concentrations stimulating respiratory drive.[1]
- Serum vitamin B_{12} falls in 25% of pregnant women such that a value of greater than 100 pmol/L should be

regarded as normal for pregnancy. In the absence of folate deficiency serum homocysteine is of value in establishing true B_{12} deficiency in pregnancy.[2,3]

- Erythrocyte sedimentation rate rises significantly (often up to 100 mm/hour).[4]
- White cell count rises due to neutrophil leucocytosis.[5]
- D-dimer becomes elevated in second and third trimesters.[6]
- Free protein S concentrations fall significantly.[7]
- Creatine kinase (MB subfraction) rises after vaginal delivery.[8]
- Serum troponin may be elevated in pre-eclampsia making diagnosis of myocardial ischaemia problematic if mothers develop pulmonary oedema.[9]
- Plasma renin activity and serum aldosterone rise masking detection of primary aldosteronism as a cause of pre-gestational hypertension in pregnancy.[10]

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Dr H.A. Tran, author of the article, comments:

Dr Morton's comments on other laboratory parameters that change during pregnancy are very much appreciated. The article aimed to highlight biochemical changes in common tests without being overly exhaustive. Generally speaking, pregnancy is a volume retentive, prothrombotic and nutritionally challenged state which results in all the corresponding changes described.

The hypervolaemic state is the result of an activated renin-angiotensin system with markedly elevated aldosterone concentrations and plasma renin activity. The normal physiological control of this system however remains intact, distinguishing it from primary hyperaldosteronism during pregnancy.[1]

The prothrombotic state is highlighted by the elevated d-dimer concentrations and reduced free protein S concentrations. The latter is the result of elevated protein binding capacity which is typical of pregnancy. Similarly, elevated transcobalamin and haptocorrin concentrations contribute to the reduction in cobalamin concentrations[2] although preferential fetal transfer during pregnancy also adds to the problem, particularly in vegans. It is probably more cost-effective to replenish B_{12} storage empirically for the duration rather than relying on homocysteine concentrations to diagnose B_{12} deficiency. Erythrocyte sedimentation rate, by way of physiological anaemia during pregnancy, is expected to be elevated but usually not to 100 mm/hour. The mean peak ranges from 50–70 mm/hour depending on the gestational age.[3] Thus, where it exceeds 100 mm/hour it is important that active inflammation or infection is excluded. Similarly, while white cell count can rise up to 15–16 x 10^6/mL, the majority often do not exceed the non-pregnant reference range.[4]

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Ciprofloxacin and fever

Editor, – Adverse drug reactions are a common problem in medical practice and can present in a variety of ways. Fever is not an uncommon manifestation and may confuse the prescriber.

We have recently seen three cases involving patients who were taking ciprofloxacin for febrile illnesses. While their conditions improved the patients remained febrile until they stopped the ciprofloxacin. We remind readers that fever is one of the more common adverse reactions reported with ciprofloxacin.

Mujibur Rahman
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Dental dizziness

Editor, – I refer to the article 'Dealing with dizziness' (Aust Prescr 2005;28:94–7). I wish to recount a personal experience where, following dental treatment during which my head and neck were held in a rotated position for some time, I suffered an acute, but fortunately brief episode of severe dizziness and recall feeling 'queer' when given the all clear to sit up. Two days later I was confined to bed for 36 hours with an acute episode from which I recovered completely. Subsequent doppler studies revealed no evidence of compromised cerebral circulation. Is it possible that unusual posturing of one's head during dental therapy could be another cause of an acute episode of dizziness?

Judy Rice
Pharmacist
Adelaide

Dr Mark Paine, the author of the article, comments:

The scenario is very suggestive of benign paroxysmal positional vertigo. The positioning of the patient during the dental treatment is very similar to the Hallpike positioning manoeuvre. While a bout of positional vertigo is usually brief, there may be after-effects causing persisting low grade dizziness which may last hours to days. To be certain about this diagnosis, it is essential to examine the patient during the episode.

Dr M. McCullough, Australian Dental Association, comments:

An acute feeling of dizziness following prolonged dental treatment is not uncommon in dental practice. Sudden changes in blood pressure following postural changes after prolonged periods in a supine dental chair may be responsible. Usually, if patient and dentist are aware of this possibility, then treatment procedures can be kept to shorter duration, with rest breaks during the procedure.

Postural hypotension is unlikely to explain the episode occurring two days after the dental procedure. Possible explanations to consider include tooth extraction and subsequent haemorrhage with breakdown of haemostasis, infection and acute dental pain causing decreased nutrition or hydration.

'Statins' and muscle symptoms

Editor, – With 12 years of 'statins' under my personal belt I feel able to comment on the medicinal mishap 'Statins and muscle symptoms' (Aust Prescr 2005;28:102), particularly the checklist of muscle symptoms. My observations over many years since I first recognised the connection between my muscle pains and simvastatin, and briefly atorvastatin, lead me to assert that the pain:

- is severe enough to wake you up
- tends to be nocturnal, within 2–8 hours of the last dose, unless the statin is taken in the morning
- is quickly and surprisingly easily relieved by a few contractions of the muscle concerned, or a walk to the bathroom – the ensuite may not be far enough
- recurs in the same area of muscle, which is tender to touch and also on contraction
- is never symmetrical – my right vastus lateralis was originally involved, and lately my left deltoid muscle.

Earlier I could control the symptoms by leaving out my daily dose of 10 mg on two days per week, but relief (that is unbroken sleep) sometimes took 24 hours. I tested this response perhaps dozens of times.

The insouciance of an overseas trip three months ago led me to taking a tablet **every** day. The result was persistent pain and weakness in the same muscle, and ultimately wasting, to the point where I was unable to step up with the right leg – a drastic disability in Europe.

After stopping the drug for two months, my thigh is nearly back to normal, but I can still feel the affected area. My lipids are not optimal now, but creatine kinase seems unaffected.

There seems little prospect of these adverse effects being reported to the Adverse Drug Reactions Advisory Committee because both my general practitioner and cardiologist attributed them (not so definitely of late) to my old age. I graduated in medicine 54 years ago. Having experienced both, I find old age much easier to take, so far, than the adverse effects I have experienced with the statins.

Peter J. Stobie
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Showing the blue card: reporting adverse reactions

Kerri Mackay, Acting Director, Adverse Drug Reactions Unit, Therapeutic Goods Administration, Canberra

Summary

The primary function of an adverse reaction reporting system is to identify harmful effects associated with the use of medicines. Since 1964 the Australian system has contributed to the early recognition of many drug-related problems. Reports of suspected adverse drug reactions are sent to the Adverse Drug Reactions Unit of the Therapeutic Goods Administration by healthcare professionals, pharmaceutical companies and consumers. The reports are reviewed, coded and entered into a database before being analysed for patterns of adverse events. Selected reports are forwarded to the Adverse Drug Reactions Advisory Committee which can recommend actions ranging from no action to the withdrawal of a drug from the market. An important role of the Committee is to inform healthcare professionals about the adverse effects which emerge from their reports.

Key words: hyoscine, drug regulation.

(Aust Prescr 2005;28:140–2)

Introduction

In Australia, healthcare professionals, pharmaceutical companies and consumers can report suspected adverse drug reactions to the Adverse Drug Reactions Advisory Committee (ADRAC). Healthcare professionals usually submit reports on the 'blue card' which accompanies the Australian Adverse Drug Reactions Bulletin and the Schedule of Pharmaceutical Benefits. Reports can also be made by letter, fax or electronically to http://www.tga.gov.au/problem/index.htm#medicines

Constant review of reports

Suspected adverse drug reactions are generally reviewed within three working days by staff in the Adverse Drug Reactions Unit of the Therapeutic Goods Administration. Selected reports are further reviewed by the independent medical experts of ADRAC.

Reports are searched for signals that may indicate safety issues. Individual reports are reviewed and the proportional reporting ratio calculated for each reaction. This is the proportion of a specified reaction or group of reactions for a drug compared with the proportion for that reaction or group of reactions for all drugs in the database.[1]

Health professionals should not defer making a report because a suspected association between an adverse event and a medicine has not previously been noted or seems tenuous. This would limit the ability of the system to detect new associations. We are particularly interested in reports concerning newly marketed medicines because the safety information for these compounds is usually limited. We are also interested in reports concerning older medicines. The adverse event profile for these medicines may seem well-established, but new reactions, changes in the frequency of known adverse reactions, interactions or problems with generic forms of a medicine may occur and should be recognised to allow appropriate action to be taken. All reports are gratefully acknowledged.

Reports can be made by letter, fax or electronically

Analysis of aggregated reports

Reports are analysed for a possible causal relationship between an adverse event and a medicine. For signal detection, a cluster of reports is usually required, depending on the seriousness of the event and the information reported. International reports including literature reports are also considered in these analyses. Examples of the value of this type of analysis are shown in Boxes 1 and 2.

Over 200 000 reports have been received since the scheme commenced in 1964. In 2004, 9823 reports were received. Australia is a founding member of the WHO Collaborative Program for International Drug Monitoring and regularly contributes data to this program.

The most publicised recent contribution of the Australian spontaneous reporting system to the safety of medicines was the detection of an association between Travacalm and anticholinergic syndrome. Over a period of a few days in December 2002 and January 2003 reports were received of patients developing symptoms such as hallucinations, ataxia and visual disturbance after taking Travacalm, a motion sickness preventative containing hyoscine hydrobromide.

Box 1

Australian reports contributing to the early global recognition of a drug-related problem *

- Travacalm and anticholinergic syndrome
- Cerivastatin and rhabdomyolysis
- The 'Triple Whammy' – acute renal failure due to the combination of ACE inhibitor, diuretic and non-steroidal anti-inflammatory drug
- Tiaprofenic acid and cystitis
- Flucloxacillin and hepatitis
- Amoxycillin with potassium clavulanate and hepatitis
- Bismuth subgallate and neurotoxicity
- Mianserin and agranulocytosis
- Mebhydrolin and agranulocytosis
- Glucomannan and oesophageal obstruction
- Oxolamine citrate and hallucinations
- Coumarin and hepatitis
- Phenylpropanolamine and hypertension

* most recent first
(references available on request)

Box 2

Australian reports giving early notice of a drug-related problem in Australia *

- Pergolide and cardiac valvulopathy
- Atypical antipsychotics and hyperglycaemia
- Diptheria, tetanus, acellular pertussis vaccine and extensive limb swelling
- Leflunomide and pancytopenia and pulmonary toxicity
- Interactions with St John's wort
- Zanamivir and respiratory disorders
- Hypersensitivity reactions with echinacea
- Interferon and depression
- Ondansetron and chest pain
- Nefazodone and hepatic dysfunction and visual disturbances
- Isotretinoin and depression
- Ticlopidine and thrombotic thrombocytopenic purpura
- Kombucha tea and liver dysfunction
- Alendronate and oesophageal disorders
- Vigabatrin and visual field defects
- Clozapine, olanzapine and neuroleptic malignant syndrome
- Fluoroquinolones and Achilles tendinitis
- Selective serotonin reuptake inhibitors and withdrawal reaction, particularly in neonates
- Moclobemide and hypertension
- Cisapride and cardiac arrhythmias
- Minocycline and liver dysfunction
- ACE inhibitors and angioedema
- Cefaclor and serum sickness-like reactions
- Royal jelly and bronchospasm
- Clozapine and constipation
- Clozapine and myocarditis

* most recent first
(references available on request)

Prompt investigation by the Therapeutic Goods Administration Laboratories revealed that some individual tablets contained seven times the amount of hyoscine hydrobromide stated on the label.

Strengths of spontaneous reporting

Spontaneous reporting systems are most valuable for identifying potential medication-induced adverse events when they are rare events unlikely to be associated with other causes.[2] The Australian voluntary reporting system differs from some overseas systems in that it accepts reports from consumers as well as from healthcare professionals and pharmaceutical companies. This is particularly important for over-the-counter and complementary medicines as the consumer may not have consulted a healthcare professional about the suspected reaction.

Limitations of spontaneous reporting

Voluntary reporting systems have limitations and are complementary to other postmarketing safety assessment methods such as cohort and case-control studies. Spontaneous reporting systems generally do not allow for quantification of risk. Under-reporting of adverse events is likely and submission of reports is possible only when a potential connection between an adverse event and a specific medication is suspected.

Recognition and reporting are least likely to occur when adverse events happen after prolonged treatment with a drug, when the condition reported is common in the community (for example hypertension) or it has other plausible aetiologies (for example diabetes).[2] An association between those types of adverse event and a medicine is more likely to be detected in case-control or cohort studies. In Australia we are not usually able to determine the total amount of a medication consumed. The voluntary reporting systems therefore cannot calculate the prevalence of adverse reactions.

Communication

The primary function of Australia's voluntary reporting system is to identify the risk of harm from drugs. Following from this

the nature and extent of the risk must be communicated. The Australian Adverse Drug Reactions Bulletin is the main vehicle for communication of these risks. The Bulletin is distributed with *Australian Prescriber* to approximately 60 000 healthcare professionals and is also available online.* The database belongs to all Australians and anyone in Australia can contribute or request information. Currently searches can be requested via email to adrac@health.gov.au. An online facility for searching aggregated data is under development.

* http://www.tga.gov.au/adr/aadrb.htm

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Conflict of interest: none declared

Report adverse drug reactions

Blue card

Fax: 02 6232 8392

Online at www.tga.gov.au/problem/index.htm#medicines

Dental notes

Prepared by Dr M. McCullough of the Australian Dental Association

Reporting adverse reactions

A large section of the public regularly visit their dentist, often much more frequently than they visit other health professionals. Dentists may well be in a unique position to be able to assess potential adverse reactions to the medication that we prescribe and that prescribed by our medical colleagues.

The Australian system of spontaneous reporting relies on both the public and health care professionals to have a high level of suspicion and to report potential adverse reactions. Such was the case with the recently observed association between the use of bisphosphonates and avascular necrosis of the jaw.[1] It is incumbent on dentists to be vigilant with regard to potential adverse reactions and be willing participants in the reporting of these events. Reactions can be reported to the Adverse Drug Reactions Advisory Committee using the blue card enclosed with this issue of *Australian Prescriber*.

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Medication overuse headache

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Summary

Medication overuse headache is common, affecting at least 1% of the population. It is responsible for the majority of recurrent daily headache and the majority of referrals to headache specialists. A high index of suspicion is warranted especially as there are no specific diagnostic tests. Withdrawal of the inciting medication(s) is the only effective treatment. With large numbers of affected patients and a duration that commonly exceeds 10 years, it is likely that both the economic and psychosocial costs of medication overuse headache are high.

Key words: analgesia, migraine.

(Aust Prescr 2005;28:143–5)

Introduction

Patients commonly take analgesics for headaches. However, chronic use of analgesics for headache can cause headache as a withdrawal phenomenon. Epidemiological data suggest that 4% of the population misuse pain medication, and that a minimum 1% of the general population in Europe, North America and Asia suffer from medication overuse headache.[1]

Classification

In the most recent headache classification (International Classification of Headache Disorders: ICHD-II)[2] medication overuse headache is subdivided according to the drugs involved, such as ergotamine, triptans, opioids, minor analgesics and combination medications. Confusion can arise because these headaches have previously been classified by reference to the preceding headache (transformed migraine, evolved migraine, chronic migraine, status migrainosus), the temporal pattern of the headache (chronic daily headache), the postulated mechanism (analgesia rebound headache) and the likely cause (drug-induced headache, painkiller headache).

It is important that headaches due to overuse of medication are distinguished from those which are caused directly by medication, such as nitrates and related compounds. Although medication overuse headache is associated with tolerance and drug use to prevent withdrawal symptoms, it can usually be distinguished from drug dependency. Patients are less likely to have cravings or to escalate the quantity of drugs they take. Their lives are unlikely to be significantly disrupted by drug-seeking behaviour.

Risk factors

Those 'at risk' for medication overuse headache are patients with frequent migraine or tension-type headache. Patients taking analgesia for other reasons (for example, arthritis) are only at risk of developing medication overuse headache if they also have a history of headaches. Some (particularly migraine) headache is familial and likely to have genetic determinants, so it is possible that medication overuse headache patients may also have some genetic predisposition to the condition.

In a cohort of patients with newly diagnosed migraine, a prospective study documented the development of medication overuse headache in more than 9% of the patients within 12 months.[3] Interestingly, recent data suggest that 'triptans' (serotonin agonists, such as sumatriptan) produce medication overuse headache more quickly, and at a lower frequency of use than either ergotamine or simple analgesics like aspirin or paracetamol.[4] It is believed that analgesics compounded with other substances, such as caffeine, codeine or barbiturates, are more likely to produce the syndrome of medication overuse headache. In the case of caffeine, withdrawal causes tiredness, lowered alertness and poor concentration, providing an incentive to ingest more caffeine, along with the associated analgesic.

Diagnosis

A typical patient is a 30–60-year-old female, with a history of more than a decade of migraine or tension-type headache. There may be a family history of headache and the presentation is often complicated by emotional distress. However, medication overuse headache is certainly not restricted to patients with this profile. It may affect patients from childhood to old age and may arise from apparently infrequent (three times weekly) or relatively short-term treatment. Medication overuse headache is estimated to be responsible for 30% of chronic daily headache, and accounts for 10–60% of patients attending specialist headache clinics. A high index of suspicion is therefore appropriate for any patient presenting with frequent headache.

There are no useful diagnostic tests for medication overuse headache. The history is by far the most important item of information. A critical aspect of the history is the temporal course of the headache, with transformation from intermittent pain or headache to continuous, or frequent (at least second-daily) headache.

The characteristics of medication overuse headache are not uniform.[4] The headache may vary in severity, type and location. In the case of patients with triptan-induced medication overuse headache, the headaches have similar characteristics to the migraines for which treatment was initiated, but may occur on a daily basis. Medication overuse headache developing after a history of tension-type headache is often described as a generalised, dull ache. Ergot-induced medication overuse headache is more likely to have a throbbing component.

Patients who fear headache pain and take prophylactic analgesia are likely to be at higher risk of developing medication overuse headache. A variety of constitutional and dysphoric symptoms may accompany or precede the development of medication overuse headache.

Medication overuse headache is not associated with focal or lateralising neurological symptoms. However, patients with a history of migraine who develop medication overuse headache may experience an aura before the headache emerges. Between episodes neurological examination should be normal. If the patient's symptoms have been stable over months or years, there is no indication for neurological investigation or imaging. Abnormalities on brain imaging are most likely to be incidental. However, atypical features, and particularly fixed abnormal neurological signs, should prompt consideration of the wider differential diagnosis of headache. Such signs include, but are not restricted to, ptosis, pupillary asymmetry, papilloedema, lateralised weakness or sensory disturbance, asymmetrical tendon reflexes and cerebellar inco-ordination. In contrast, signs of migraine aura typically evolve and resolve over 20–30 minutes prior to the development of the headache, and are much less significant.

Pathophysiology

At least some of the characteristics of medication overuse headache may be understood by considering the mechanism of action. Triptans are agonists at serotonin 5-HT_{1B} and 5-HT_{1D} receptors. These receptors are rapidly downregulated following drug exposure (within 24–96 hours). By contrast, aspirin and non-steroidal anti-inflammatory medications act on the enzymes cyclo-oxygenase 1 and 2. These enzymes are also downregulated following drug exposure, but much more slowly. Triptan usage therefore results in tachyphylaxis (less effect for the same dosage) more quickly, at a lower frequency of use, and at a lower dosage than other non-narcotic analgesics. Receptor and enzyme downregulation in structures responsible for the transmission and reception of nociceptive input creates increased sensitivity to such input, resulting in a lowered threshold for pain perception.

Management

The essential treatment of medication overuse headache is withdrawal of the offending medication, but in most cases that is easier said than done. Some patients find it very difficult to accept that the medication they use to treat their headaches is actually making their situation worse. Drug withdrawal can be undertaken by general practitioners with patients who are motivated and overuse triptans or other single drugs, excluding barbiturates, benzodiazepines or opioids. However, if the patient has failed a trial of outpatient withdrawal, overuses barbiturates, benzodiazepines, opioids or multiple drugs, and particularly if there is significant anxiety or depression complicating the presentation, inpatient withdrawal or specialist consultation should be considered (see box).

Prophylactic medication can be commenced before drug withdrawal. Migraine prophylactics and other previously ineffective drugs can become effective following drug withdrawal. This information can be used to encourage reluctant patients (particularly those who argue 'only drug X is effective in my case').

The withdrawal from triptans will be complete for almost all patients after four days so additional medication is usually not required. However, after four days only a minority of patients overusing standard analgesics will have completed withdrawal. Response in this group may be gradual. In some cases it may take three months before there is a two-thirds reduction in headache frequency. It may be six months before the patient has six consecutive days free of headache. To assist in the transition period, other drugs can be used. In hospital, some specialists use intravenous lignocaine[5], although risks include cardiac dysrhythmia and seizures. In the short term, steroid therapy[6], and over the medium term naproxen, may diminish withdrawal headache.

For patients overusing compound analgesics or ergot compounds, withdrawal symptoms may also include nausea and vomiting, as well as tachycardia and hypotension. These symptoms may require additional treatment with intravenous fluids, antiemetics and vasoactive drugs such as clonidine or propranolol.

Management hints

- Triptans, ergot and non-opioid medications can be ceased abruptly
- Non-steroidal anti-inflammatory drugs may be used for withdrawal headache (e.g. naproxen 500 mg twice a day)
- Prophylactic drugs in migraine may be commenced prior to triptan or ergot withdrawal (e.g. propranolol 10–40 mg thrice a day)
- Tricyclic antidepressants can be a useful 'prophylactic' drug to cover withdrawal of treatment for tension-type headaches (e.g. amitriptyline 10–25 mg at night)
- Benzodiazepines, barbiturates and opioids may require dose reduction prior to withdrawal (particularly if high doses have been used for years)

Relapse

Following successful withdrawal of the overused medication, migraine prophylaxis, careful assessment of precipitants, counselling, a headache management plan and clear limits on the use of analgesia may all be required in order to prevent relapse. Studies suggest that following withdrawal of the offending drug, medication overuse headache will relapse in approximately 40% of patients. This relapse is most likely to occur in the first 12 months following withdrawal. Patients with a prior history of tension-type headache are three times more likely to relapse than those with migraine precursor headaches. Those overusing analgesics (especially combination) are more likely to relapse than those using triptans or ergot (these may not be independent observations as patients with tension-type headache are less likely to be using triptans and ergot than patients with migraine).

Although supporting evidence is limited, behavioural interventions may help prevent headaches. Examples include relaxation therapy, stress management, meditation, regular aerobic exercise, or movement disciplines such as t'ai chi or yoga. Specific recommendations need to be mindful of patient preference and likely compliance, as well as local availability.

Conclusion

The prevalence of medication overuse headache is high and the condition is usually present for a long time before it is recognised and treated. Consider medication overuse headache as a possible cause in all patients with daily or second-daily headache, particularly among those with a prior history of migraine or tension-type headache. Medication must be withdrawn to treat the condition. A comprehensive management plan should be implemented to prevent relapse.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 159)

1. Patients who complain of daily headaches with no obvious cause may have medication overuse headache.
2. The aura of migraine can occur in medication overuse headache.

New developments in antiretroviral therapy for HIV infection

Jeffrey J. Post, Department of Infectious Diseases and Albion Street Centre, Prince of Wales Hospital, Randwick and School of Medical Sciences, University of New South Wales, Sydney; and Mark D. Kelly, AIDS Medical Unit, and School of Medicine, University of Queensland, Brisbane

Summary

Health professionals need to be aware of the current approach to the treatment of HIV infection as more Australians are living with HIV/AIDS. Approximately half of these patients are taking combination antiretroviral therapy. These regimens have a wide range of adverse effects and interactions. The prevalence of HIV infection is expected to increase, not only because the incidence is increasing, but also because effective antiretroviral therapy is prolonging survival. People living with HIV/AIDS are increasingly likely to seek care from doctors without a special interest in HIV because of increasing comorbidities including cardiovascular disease.

Key words: cardiovascular disease, drug interactions.

(Aust Prescr 2005;28:146–9)

Introduction

Treatment with a combination of antiretroviral drugs prevents the progression of human immunodeficiency virus (HIV) disease by inhibiting viral replication.[1] It also stops the associated immunological deterioration associated with the depletion of CD4 lymphocytes. Effective inhibition of HIV replication may even restore the patient's immune system.

Principles of management

Combination antiretroviral therapy is indicated in patients with symptomatic HIV infection as it reduces the risk of disease progression. The decision to treat asymptomatic patients is made by balancing the benefits and harms of therapy. Current guidelines recommend starting antiretroviral therapy when the risk of disease progression is significant. Treatment is recommended once the CD4 lymphocyte count is below 350/microlitre, but before it falls to 200/microlitre, when there is a significant risk of the development of the acquired immune deficiency syndrome (AIDS). Starting treatment at a lower CD4 count is associated with an impaired immunological response to therapy. The Australasian Society for HIV Medicine has developed locally relevant antiretroviral therapy guidelines* that adapt the detailed guidelines of the US Department of Human Services and Health.

Combination therapy

Treatment usually starts with two nucleoside(tide) analogue reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or a 'ritonavir-boosted' protease inhibitor. Ritonavir is a protease inhibitor that also inhibits the cytochrome P450 enzyme system. This inhibits the metabolism of other protease inhibitors, boosting their concentrations. By favourably altering the pharmacokinetics, a low dose of ritonavir enables less frequent dosing of other protease inhibitors.

Since the last review of antiretroviral therapy in *Australian Prescriber*[1] several new drugs have been approved, including one drug (enfuvirtide) with a new target of action (see Fig. 1 and Tables 1 and 2). The availability of new drugs provides options in the management of patients who have exhausted existing treatment options due to either drug toxicity or resistance. Therapy with three nucleoside/tide reverse transcriptase inhibitors in combination has now been shown to be inferior and this approach is not recommended. Similarly, despite the potency of the individual drugs, certain combinations (such as tenofovir with didanosine and efavirenz or nevirapine) are associated with a significant risk of treatment failure and the development of significant drug resistance and cross resistance to many other antiretroviral drugs. Where possible, it is important that clinicians prescribe the specific combinations that have been studied in clinical trials.*

Some combination formulations are now available. As well as reducing the number of pills patients have to take, most combinations can now be taken twice or even once daily. Adherence to twice-daily doses is better than to thrice-daily doses, although adherence to twice-daily and once-daily doses appears equivalent.

Many HIV-infected women are now contemplating pregnancy given the improved prognosis of HIV infection and the increased capacity to prevent mother-to-child transmission of HIV infection. There is increasing experience regarding the safety of antiretroviral drugs in pregnancy. However, efavirenz is a proven teratogen.

* http://www.ashm.org.au

Fig. 1

Simplified lifecycle of HIV showing sites of action of new drugs

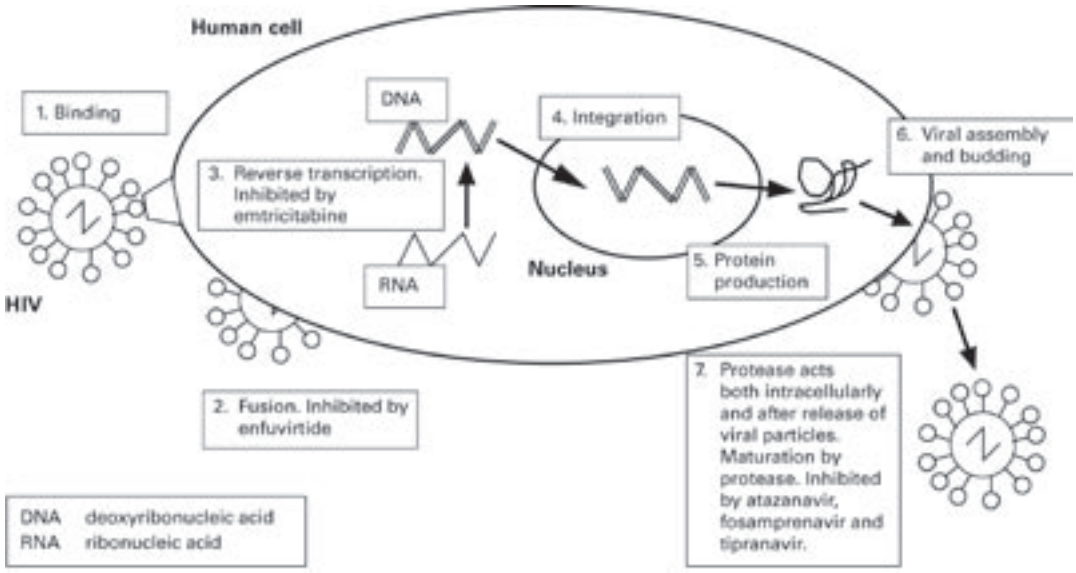

Table 1

Antiretroviral drugs available in Australia

Generic name	Trade name	Abbreviation
Nucleoside reverse transcriptase inhibitors		
abacavir	Ziagen	ABC
didanosine	Videx	DDI
emtricitabine	Emtriva	FTC
lamivudine	3TC	3TC
stavudine	Zerit	D4T
zalcitabine	Hivid	DDC
zidovudine	Retrovir	AZT, ZDV
Nucleotide reverse transcriptase inhibitors		
tenofovir	Viread	TFV
Nucleoside analogue combination preparations		
abacavir/lamivudine	Kivexa	ABC/3TC
zidovudine/lamivudine	Combivir	AZT/3TC
zidovudine/lamivudine/ abacavir	Trizivir	AZT/3TC/ABC
Non-nucleoside reverse transcriptase inhibitors		
delavirdine	Rescriptor	DLV
efavirenz	Stocrin	EFV, EFZ
nevirapine	Viramune	NVP
Protease inhibitors		
amprenavir	Agenerase	APV
fosamprenavir	Telzir	FPV
indinavir	Crixivan	IDV
lopinavir/ritonavir	Kaletra	LPV/r
nelfinavir	Viracept	NLV
ritonavir	Norvir	RTV
saquinavir	Invirase/Fortovase	SQV
tipranavir (currently available on Special Access Scheme)		
Fusion inhibitors		
enfuvirtide	Fuzeon	T20

Table 2

Summary of important features of new antiretroviral drugs

New drug	Usual dose	Common adverse events
atazanavir	400 mg daily OR 300 mg + 100 mg ritonavir daily	Jaundice Gastrointestinal disturbance
fosamprenavir	700 mg twice a day + 100 mg ritonavir twice a day OR 1400 mg daily + 200 mg ritonavir daily in antiretroviral therapy naive patients	Abdominal pain, diarrhoea, flatulence and vomiting
tipranavir	500 mg twice a day + 200 mg ritonavir twice a day	Gastrointestinal disturbance
emtricitabine	200 mg daily	Headache, dizziness, insomnia and rash
enfuvirtide	90 mg subcutaneously twice a day	Injection site reaction, hypersensitivity reactions

Drug interactions

Drug interactions involving antiretroviral drugs are significant. All Australian prescribers should be aware that these interactions can potentially result in increased toxicity or decreased efficacy. These interactions may be unexpected, but the effects can be severe. For example, there have been many reports of Cushing's syndrome in patients who have taken inhaled fluticasone while being treated with antiretroviral

combinations including ritonavir.[2] Consider potential interactions before prescribing any new medication for patients taking antiretroviral drugs. Consultation with a practitioner who is experienced in managing HIV is recommended, but there are also numerous information sources to assist clinicians. The University of Liverpool hosts a useful website.[†]

Comorbidities

People infected by HIV experience significant comorbidities that may lead them to seek care from health professionals with little experience of treating HIV. These comorbidities include smoking-related disorders, hypertension, drug-related dyslipidaemia, osteoporosis and liver disease associated with chronic viral hepatitis.

The care of HIV-infected patients is increasingly shared between multiple clinicians. This shared care should include a clinician who is experienced in treating HIV, as most practitioners will not be familiar with antiretroviral therapy. All treatment decisions should be made with consideration of potential antiretroviral drug interactions and toxicities. Minor clinical problems can be drug related and may be difficult to manage if the association is not recognised and the offending drug withdrawn. For example, ingrowing toenails have been associated with indinavir.

Cardiovascular disease

Antiretroviral therapy appears to be an independent risk factor for ischaemic coronary events. In a prospective observational multicentre study with more than 30 000 patient years of follow-up, each year of therapy was associated with a 26% increased risk of myocardial infarction.[3] This has resulted in a greater focus on strategies to reduce risk factors for ischaemic heart disease. Approximately 50% of people living with HIV/AIDS are smokers and 40% of those treated with antiretroviral therapy have hyperlipidaemia. Strategies to manage antiretroviral-induced hyperlipidaemia include ceasing the offending drug, dietary modification and the addition of lipid-lowering drugs. However, drug treatment has only a modest effect on lipids.[4] There are also significant interactions between antiretroviral and lipid-lowering drugs, and the risks of adverse events may well be higher than when lipid-lowering drugs are used alone. In the absence of clinical endpoint trials to date, the relative risk of treating versus not treating antiretroviral-associated hyperlipidaemia remains undetermined.

New protease inhibitors

These drugs prevent viral replication by inhibiting the proteases in HIV.

Atazanavir

Atazanavir has efficacy in previously untreated patients and in those who have previously taken protease inhibitors.[5] The recommended dose is either 400 mg daily, or 300 mg daily when boosted with ritonavir 100 mg daily. Atazanavir must be boosted with ritonavir when used in protease inhibitor-experienced patients or when used in combination with tenofovir, as tenofovir decreases atazanavir concentrations. Atazanavir is approved for once-daily dosing.

The main advantage of atazanavir over other protease inhibitors is that it is not associated with significant insulin resistance or elevation in serum lipid levels. However, it can cause unconjugated hyperbilirubinaemia. Some patients develop scleral icterus that may be cosmetically unpleasant, but less than 1% of patients in clinical trials ceased atazanavir because of this adverse effect.

Atazanavir should be taken with food. Its absorption is significantly decreased by reductions in gastric acidity. Drugs that reduce gastric acidity may decrease the concentrations of atazanavir. Proton pump inhibitors should therefore not be given to patients taking atazanavir.

Fosamprenavir

Fosamprenavir is the most recently approved protease inhibitor in Australia. When boosted with ritonavir it has efficacy in treated and previously untreated patients.[6] The recommended dose is 700 mg twice a day administered with 100 mg ritonavir twice a day. A once-daily dose of 1400 mg fosamprenavir with 200 mg ritonavir can be used in patients who have not previously received antiretroviral drugs. Fosamprenavir can be taken either with or without food although taking the medication with food is likely to reduce the nausea which is the most common adverse effect of fosamprenavir.

Other adverse effects of fosamprenavir include abdominal pain, diarrhoea, flatulence and vomiting. Rare adverse effects include depression, mood changes, perioral paraesthesia and rash. Drug interactions are significant with fosamprenavir, so it should not be combined with other protease inhibitors (apart from ritonavir).

Tipranavir

Tipranavir is a 'second-generation' protease inhibitor. It is active against a wide variety of isolates which are resistant to the other currently available protease inhibitors. Tipranavir is only available on the Special Access Scheme in Australia.

Emtricitabine

Emtricitabine (FTC) is a potent cytidine nucleoside analogue with a long plasma half-life. It has efficacy as part of a once-daily regimen for previously untreated patients.[7] The recommended dose is 200 mg once daily, but dose adjustments are required for patients with renal impairment. Common adverse effects include headache, dizziness, insomnia and rash. Lactic acidosis, hepatomegaly and liver failure have also been reported.

Like tenofovir and lamivudine, emtricitabine has activity against both HIV and hepatitis B virus. Patients should therefore be tested for hepatitis B infection before treatment to enable the

[†] http://www.hiv-druginteractions.org

strategic use of this drug in patients infected with both viruses. In general, drugs with activity against both hepatitis B virus and HIV are recommended for patients who need treatment for both viral diseases to reduce the risk of emergence of viral resistance. However, clinical endpoint data are not available to support this approach.

Enfuvirtide

Enfuvirtide (T20) is the first HIV fusion inhibitor to be licensed for use in clinical practice. It inhibits the fusion of the viral and human cell membranes following viral attachment (see Fig. 1). Given its novel site of action enfuvirtide has significant antiviral activity against isolates which have resistance to other drug classes. Its benefit is maximised if used with other active drugs, however its role in contemporary practice is limited by the fact that it needs to be injected subcutaneously twice daily.

Injection site reactions are common, but not usually dose limiting. Hypersensitivity reactions can occur.

Conclusion

The therapy of HIV infection continues to change. Clinicians need to be aware of developments in this field, as they are increasingly likely to need to provide care to people living with HIV/AIDS.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 159)

3. Inhaled corticosteroids may interact with ritonavir to cause Cushing's syndrome.
4. Patients treated for HIV have an increased risk of cardiovascular disease.

Dental notes

Prepared by Dr M. McCullough of the Australian Dental Association

Antiretroviral therapy for HIV infection

The prevalence of people living with HIV infection is expected to rise and these people are increasingly likely to seek care from practitioners who are not specialists in managing HIV. Dental clinicians need to be aware of changes occurring in the management of HIV infection, the increase in number and complexity of antiretroviral regimens and the potential for drug interactions with commonly prescribed drugs. For example, erythromycin, metronidazole and miconazole have potential interactions with some antiretroviral drugs that may require close monitoring, alteration of drug dosage or timing of administration. Consultation with an HIV expert is strongly recommended before starting any new medication in patients taking antiretroviral drugs. Furthermore, unusual and rare adverse effects such as peri-oral paraesthesia can occur with antiretroviral drugs.

Dental clinicians should be aware that approximately 50% of patients living with HIV/AIDS are smokers. These patients therefore have an increased likelihood of oral diseases such as periodontal disease, leucoplakia and oral squamous cell carcinoma so thorough dental examination, treatment and monitoring is required.

Amiodarone

Terence J. Campbell, Professor of Medicine, St Vincent's Hospital Clinical School, University of New South Wales, Sydney

Summary

Amiodarone is the most effective antiarrhythmic drug available. In most countries (including Australia), amiodarone is the most commonly prescribed antiarrhythmic apart from drugs such as digoxin and beta blockers. Amiodarone can be used to treat tachyarrhythmias, including atrial fibrillation, ventricular tachycardia and patients at high risk of sudden cardiac death. Although amiodarone is effective, it is not generally recommended for minor rhythm disturbances because of its toxicity. It is a difficult and challenging drug to use in clinical practice. This is because of its very prolonged half-life and because of its multiple adverse effects.

Key words: adverse effects, arrhythmia.

(Aust Prescr 2005;28:150–4)

Introduction

Amiodarone is an antiarrhythmic drug with structural similarities to thyroxine. It exhibits all four of the classic Vaughan Williams mechanisms of action, namely sodium and potassium channel blockade, a mild antisympathetic action and some calcium channel blockade, but it is usually classified as a Class III antiarrhythmic drug (see Table 1). It prolongs the refractory period in all cardiac tissues.

After oral administration, amiodarone only has a bioavailability of 30%. It also has a half-life of approximately 50 days, so it can take weeks for therapeutic effects to appear.

Table 1

Simplified Vaughan Williams classification of antiarrhythmic drugs

Class	Action	Examples
I	Interfere with depolarisation	disopyramide quinidine mexiletine flecainide
II	Beta blockade	beta blockers other than sotalol
III	Prolong repolarisation	amiodarone sotalol
IV	Calcium channel blockade	verapamil

While amiodarone has many pharmacological effects, it also has many adverse effects. As some of these adverse reactions are life-threatening, it is important only to prescribe amiodarone for indications where it has a significant benefit over other treatments.

Indications

Although amiodarone has many possible uses, its main indications are severe cases of tachyarrhythmia (see Box 1).

Atrial fibrillation

For acute reversion of recurrent episodes of atrial fibrillation, whether paroxysmal (reverting spontaneously within hours to days if left untreated) or persistent (generally requiring intervention to return the patient to sinus rhythm), amiodarone is approximately as effective as flecainide. Both drugs are significantly more effective than placebo. One advantage of amiodarone, despite its significantly slower onset of action, is that it slows the heart rate even if the heart does not revert to sinus rhythm, whereas flecainide does not normally slow the ventricular response to atrial fibrillation and has been known to accelerate it.

Sotalol is also commonly used for acute reversion of atrial fibrillation, but has not been convincingly shown to be any more effective than standard intravenous beta blockers or even placebo. Again, sotalol and other beta blockers do have the advantage of slowing the ventricular response even if reversion does not occur.

Three large randomised trials of chronic therapy for paroxysmal/persistent atrial fibrillation have convincingly shown amiodarone to be significantly superior to sotalol and

Box 1

Indications

- Recurrent (paroxysmal or persistent) atrial fibrillation or flutter.
- Patients at intermediate risk of arrhythmic death, especially post-myocardial infarction patients with moderate left ventricular dysfunction and patients with heart failure. Amiodarone is usually only given if significant or symptomatic ventricular arrhythmias are present.
- Patients with an implantable cardioverter-defibrillator whose quality of life is impaired by regular discharges of the defibrillator.

propafenone (a close relative of flecainide). Since sotalol has roughly equivalent efficacy to quinidine, and propafenone has very similar efficacy to flecainide, one can conclude that patients with recurrent atrial fibrillation given amiodarone are approximately twice as likely as those given one of the other drugs to be maintained in sinus rhythm 12 months after starting treatment.[1,2,3]

There is no point in using amiodarone in patients with established, permanent atrial fibrillation. There are safer drugs for achieving ventricular rate control, including beta blockers, diltiazem, verapamil and digoxin.

Ventricular tachyarrhythmias

Amiodarone is effective for minor ventricular arrhythmias such as ventricular ectopy and non-sustained ventricular tachycardia, both in patients with normal hearts and those with heart failure, coronary disease or hypertrophic cardiomyopathy. However, antiarrhythmic drugs are generally not recommended for these patients because of concern about possible aggravation of arrhythmia (so-called 'proarrhythmia'). Amiodarone should therefore be reserved for those at significant risk of life-threatening ventricular arrhythmias. These patients are subdivided into those at 'high' risk of fatal arrhythmia (survivors of life-threatening ventricular arrhythmia including ventricular fibrillation) and those at 'intermediate' risk (severe left ventricular dysfunction or non-sustained ventricular tachycardia).

High-risk patients

An early study of survivors of cardiac arrest in the era before implantable cardioverter-defibrillators became available, showed amiodarone to be superior to traditional antiarrhythmic drugs, such as quinidine and procainamide, in prolonging survival. More recent studies have compared implantable cardioverter-defibrillators with amiodarone in survivors of life-threatening ventricular arrhythmias.

Meta-analysis of three large studies showed clear superiority of implantable cardioverter-defibrillators over amiodarone overall.[4] However, when the patients in these studies were divided according to whether or not their left ventricular ejection fraction (EF) was moderately to severely impaired (defined as EF < 35%), it became apparent that the advantage of the defibrillators was largely confined to those patients with an EF < 35%.[4] Patients with a history of symptomatic ventricular tachyarrhythmias and normal left ventricular function had similar outcomes whether they were randomised to an implantable cardioverter-defibrillator or amiodarone.

Intermediate-risk patients

Patients at intermediate risk of arrhythmic death are those with left ventricular dysfunction and clinical heart failure, and those with additional risks such as low ejection fraction or non-sustained ventricular arrhythmias following a myocardial infarction. Meta-analysis of several large placebo-controlled trials in these patients suggests a 20–30% reduction in the risk of cardiac arrest or arrhythmic sudden death with amiodarone. This is statistically significant[5], however the reduction in overall mortality is of the order of 13% and is of borderline statistical significance. In view of the marginal efficacy in terms of total mortality, the serious adverse effects and the advent of implantable cardioverter-defibrillators, these studies (which did not include implantable cardioverter-defibrillators) have not led to the widespread use of amiodarone for patients of intermediate risk. In practice the decision is whether or not to implant a cardioverter-defibrillator.

More recently, a large randomised trial involving patients with severe left ventricular dysfunction (EF < 30%) has compared an implantable cardioverter-defibrillator with amiodarone and placebo. There was no difference in deaths from any cause between amiodarone and placebo at either three years or five years. Implantation of a cardioverter-defibrillator was associated with a clinically and statistically significant decrease in mortality at both time points.[6] Sub-group analysis also showed significant benefit for the implantable cardioverter-defibrillator in patients with underlying coronary artery disease, confirming the findings of the MADIT II study in post-myocardial infarction patients with ejection fractions less than 30%. The sub-group with normal coronary arteries (that is with dilated cardiomyopathy) showed a non-significant, but strong, trend in favour of treatment with an implantable cardioverter-defibrillator.[7]

Adjuvant therapy in patients with implantable cardioverter-defibrillators

A number of antiarrhythmic drugs, including amiodarone, have found a role in patients with implantable cardioverter-defibrillators which are functioning effectively but firing frequently and hence causing major reductions in quality of life. Antiarrhythmic drugs can reduce the frequency of shocks. The fear of lethal proarrhythmia associated with many of the drugs is lessened by the presence of the implantable cardioverter-defibrillator. A very recent comparative study reported combination therapy with amiodarone and a beta blocker to be markedly and significantly more effective at reducing implantable cardioverter-defibrillator shocks than either beta blocker alone or sotalol.

Administration and dosage (see Table 2)

Amiodarone can be given orally or intravenously. Intravenous administration is only appropriate in hospital with continuous ECG monitoring.

Intravenous dosing

Amiodarone can be given intravenously for supraventricular or ventricular arrhythmias, but should be reserved for urgent cases. Acute atrial fibrillation with a rapid ventricular response is

Table 2

Dosing	
Intravenous (use central vein where possible)	300 mg over 20 min–2 hours 900 mg infused over subsequent 24 hours (maximum 1200 mg in 24 hours) Then usually switch to oral maintenance dose if indicated
Oral	Loading dose of 200–400 mg three times a day for 10–14 days Maintenance of 200–400 mg/day thereafter (typically 200 mg/day and consider 100 mg/day for long-term treatment of atrial fibrillation)

not usually symptomatic enough to require intravenous therapy and often responds quite well to oral therapy with a range of drugs including amiodarone.

Life-threatening ventricular tachyarrhythmias are generally best treated with direct current cardioversion (definitely so if the patient is unconscious or markedly hypotensive). In some settings, however, particularly if the arrhythmia is recurrent despite direct current shocks, intravenous amiodarone can be very useful.

Intravenous amiodarone can cause acute hypotensive reactions and is often damaging to veins so it should normally be given through a central line. Dosage regimens vary, but a regimen commonly used in adults in Australia is 300 mg infused over a period of 20 minutes to two hours, followed by a further 900 mg over the next 24 hours (with continuous ECG and blood pressure monitoring). Unless the patient is unable to take amiodarone orally, it is unusual to continue intravenous therapy beyond 24 hours and a switch to oral therapy would normally be made at this time.

Oral dosing

Dosage regimens for oral amiodarone vary even more widely than the intravenous ones. While the drug will often be commenced in hospital, it is not unusual for oral amiodarone to be started in the community. Typical maintenance doses are approximately 200 mg daily and in non-urgent situations it may well be appropriate to start the patient on this dose. As amiodarone has an extremely long plasma half-life, it can take a long time to reach a therapeutic concentration and loading doses are therefore frequently used to accelerate this process.

When loading is desired, doses of 200–400 mg three times daily for 10–14 days may be used, followed by a reduction in one or two steps to a maintenance dose of 200–400 mg/day (usually 200 mg). It is very important to remember to reduce the dose. In some patients (for example the elderly), it is worth trying to reduce further to 100 mg/day after 2–3 months at 200 mg/day.

As a general rule, the doses used for life-threatening arrhythmias are higher than those for atrial fibrillation. Loading doses are sometimes associated with nausea, and this may limit their use.

There is some correlation between efficacy and the plasma concentration of amiodarone. There may be a little more correlation between adverse effects and plasma concentration, but adverse effects can occur within the therapeutic range. Routine measurement of plasma concentrations is not commonly performed.

Adverse effects

Nausea and vomiting are common and tend to occur early, particularly with loading doses. Many other adverse effects are chronic rather than acute and may appear months or even years after starting amiodarone. Constipation, anorexia, taste disturbance, benign corneal microdeposits, and blue-grey pigmentation of the skin which is slow to appear but generally irreversible, are all relatively common in chronic usage. Increased sensitivity to sunlight is often seen. Patients should be cautioned against exposure to the sun and warned that traditional 'UV blockout' lotions may not protect them, as some of the increased sensitivity is to visible light rather than ultra-violet light. If specifically asked, 10–20% of patients will report sleep disturbance with vivid dreams, although this often improves with time and/or a dose reduction. Some patients develop extrapyramidal symptoms or peripheral neuropathy.

Neurological complications occur, particularly in patients taking long-term amiodarone at relatively high doses (generally 300–400 mg/day). The commonest manifestation of this is a peripheral neuropathy which can be sensory and/or motor, with a glove and stocking distribution. This is not always reversed by stopping amiodarone, so treating physicians must be alert for the first signs of neuropathy.

A number of syndromes cause considerable concern in the medium to long term. These include chronic hepatitis, thyroid dysfunction and pulmonary toxicity (which can be acute and responsive to steroids, but more commonly is a chronic fibrotic form). There is no real evidence for the widely-held belief that patients with pre-existing chronic lung disease are more susceptible to pulmonary complications, although once again it is probably wise to be cautious and perhaps to monitor these patients more closely. If the indication for amiodarone is compelling, lung disease should not necessarily be an absolute contraindication.

Hypothyroidism is more common in iodine-replete regions of the world while thyrotoxicosis is seen more frequently in areas where iodine is relatively deficient in the diet. It is sometimes possible to continue amiodarone therapy and treat thyroid toxicity, but whenever possible the drug should be ceased if thyroid toxicity is detected. Amiodarone should also be stopped if hepatitis or lung disease are suspected or proven.

A major electrophysiological effect of amiodarone is prolonging the repolarisation of the cardiac action potential.

This automatically prolongs the QT interval on the ECG so QT prolongation, sometimes quite marked, is a feature of the therapeutic effect of amiodarone. For reasons which are not entirely clear, the much feared complication of torsades de pointes is much less commonly seen with amiodarone than with other drugs that prolong the QT interval. This is probably because amiodarone also blocks calcium channels. Anything that reduces intracellular calcium concentrations tends to make torsades de pointes less common in experimental models. However, patients are not protected if they have already experienced torsades de pointes with other QT-prolonging drugs. These patients should not be treated with amiodarone unless there is absolutely no alternative.

Amiodarone can cause atrio-ventricular block. The drug should be ceased, but if continued therapy is considered essential permanent pacing will probably be required.

As amiodarone is a 'Category C' drug it should not be used during pregnancy or lactation.

Drug interactions

There are a number of important drug interactions with amiodarone (see Box 2). Some of these interactions are related to the inhibition of cytochrome P450 3A4. The long half-life gives amiodarone the potential to cause interactions weeks after it has been ceased.

Amiodarone increases concentrations of digoxin (sometimes to a clinically significant degree) and impairs the metabolism of warfarin, tending to potentiate its anticoagulant effect. Similarly the concentrations and effects of flecainide, quinidine, phenytoin and cyclosporin tend to rise with amiodarone. These interactions and others need to be taken into account when patients taking these drugs start amiodarone. Similar considerations apply to drugs such as atorvastatin and simvastatin which are metabolised in the liver by cytochrome P450 3A4. Amiodarone may impair their metabolism and hence potentially increase the risk of myopathy or rhabdomyolysis. The use of pravastatin as an alternative is probably to be preferred as it is not metabolised by cytochrome P450 3A4.

In the liver, amiodarone is metabolised to desethylamiodarone, which has similar activity and kinetics to the parent compound. This metabolism is almost completely inhibited by grapefruit juice, although it is not clear that this alters the clinical efficacy or toxicity in any significant way.

Amiodarone can cause bradyarrhythmias and this effect will be enhanced by co-administration with beta blockers, verapamil or diltiazem. There is some evidence of synergy between beta blockers and amiodarone in terms of efficacy against tachyarrhythmias and the combination is not necessarily contraindicated. It should simply be used with caution.

Box 2

Drug interactions of amiodarone

Anaesthetics

Antiarrhythmic drugs
disopyramide, flecainide, procainamide, quinidine

Cyclosporin

Digoxin

HMG CoA reductase inhibitors
atorvastatin, simvastatin

Phenytoin

Protease inhibitors
indinavir, ritonavir

Warfarin

Potential interactions with other drugs

- metabolised by cytochrome P450 3A4
- prolonging the QT interval

Baseline assessment and long-term monitoring

There are several guidelines for prescribing amiodarone. The most widely cited guideline is that of the North American Society of Pacing and Electrophysiology (recently renamed Heart Rhythm Society).[8] This recommends a number of baseline and follow-up tests (Table 3). It is clear, however, that these guidelines are variably applied by clinicians. A recent review suggested about 50% of the patients starting amiodarone received minimum baseline evaluation and less than 25% received the recommended ongoing surveillance.[9]

Baseline and intermittent (every 3–6 months) measurement of thyroid and liver function is certainly a sensible precaution. A high level of awareness is at least as important in detecting the often subtle changes of thyroid dysfunction in an ageing patient. Both interpretation of thyroid function tests and treatment of abnormalities, particularly hyperthyroidism, can be difficult in a patient taking amiodarone.[10]

Table 3

Recommendations for monitoring of chronic dosing [8]

Test	Timing
Liver function tests	Baseline and every 6 months
Thyroid function tests	Baseline and every 6 months
Serum creatinine and electrolytes	Baseline and as indicated
Chest X-ray	Baseline and yearly
Ophthalmic evaluation	Baseline if visual impairment or for symptoms
Pulmonary function tests (including testing the diffusion capacity for carbon monoxide (DLCO))	Baseline and for unexplained symptoms or X-ray changes

Amiodarone-induced hepatic toxicity can manifest subtly as general malaise, anorexia, nausea or as classic hepatitis with right upper quadrant pain. Most frequently it is mild and essentially asymptomatic.

There is disagreement and a lack of evidence to guide monitoring for pulmonary toxicity. The Adverse Drug Reactions Advisory Committee has recently recommended that 'Lung function should be monitored including 6-monthly chest x-ray, and the development of dyspnoea or cough should be investigated immediately'.[11] This differs from the recommendations in Table 3, which include pulmonary function tests, including diffusion capacity, at baseline. The safest advice would be to follow the recommendations given in Table 3, but these are not currently widely practised in Australia. As there is no good evidence that any of these recommendations reduce the risk of life-threatening pulmonary complications, it is really left to the individual practitioner to decide what to do.

The development of a new cough or unexplained febrile syndrome during amiodarone therapy should certainly alert one to the possibility of pulmonary toxicity. Amiodarone should be ceased at once and formal pulmonary function testing undertaken.

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In 1997 Professor Campbell chaired the group which produced the 'Amiodarone Consensus Guidelines: use in Australasian clinincal practice' for Sanofi Winthrop.

Self-test questions

The following statements are either true or false (answers on page 159)

5. Amiodarone can cause hypothyroidism or hyperthyroidism.
6. Amiodarone can slow the heart rate of patients with atrial fibrillation even if they do not revert to sinus rhythm.

Wallchart

Copies of the wallchart 'Medical management of severe anaphylactoid and anaphylactic reactions' are still available from *Australian Prescriber*. This A3-sized chart was published as an insert to *Australian Prescriber* Vol 24 No. 5, 2001. It was endorsed by the Australasian College for Emergency Medicine, the Australasian Society of Clinical Immunology and Allergy, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Radiologists, and the Royal Australian College of General Practitioners.

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Case study

Community-acquired methicillin-resistant *Staphylococcus aureus* infection

Prepared by Ronan J. Murray, Consultant infectious diseases physician and Clinical microbiologist, Royal Perth Hospital, Perth

Case

A 25-year-old previously healthy male presented to his general practitioner with a painful lesion on his right leg. On examination, he appeared generally fit and well, but had a temperature of 37.8°C. There was a large carbuncle on the upper anterior aspect of his right thigh, with surrounding cellulitis and associated tender inguinal lymphadenopathy. The general practitioner prescribed oral dicloxacillin 250 mg four times daily and advised local application of heat to the area to encourage spontaneous drainage of the carbuncle.

The patient presented to the local emergency department 72 hours later with fevers, rigors and severe pain. He was commenced on intravenous flucloxacillin, and underwent incision and drainage of the carbuncle in theatre later that day. Methicillin-resistant *Staphylococcus aureus* (MRSA) was cultured from the copious pus. The organism was susceptible to erythromycin, clindamycin, doxycycline and trimethoprim with sulfamethoxazole. After discussion with a clinical microbiologist, treatment was changed to oral clindamycin 450 mg three times daily and the patient was discharged to complete a seven-day course of treatment.

Comment

Until recently, MRSA was considered to be an organism exclusively found in hospitals, long-term healthcare facilities or in patients with recent contact with such institutions. However, MRSA infection acquired in the community is becoming increasingly common.[1] Disease caused by community-acquired MRSA ranges in severity from mild skin and soft tissue infection to life-threatening systemic infection.[1,2] Some strains of community-acquired MRSA produce exotoxins (for example Panton-Valentine leukocidin) and are therefore not only resistant to usual first-line antistaphylococcal beta-lactam antimicrobials (for example flucloxacillin, dicloxacillin and cephalexin), but are also potentially more virulent than other *Staphylococcus aureus* strains which do not usually produce these toxins.[3]

In all cases of suspected *Staphylococcus aureus* infection, drainage of pus and debridement of infected tissue is critical to ensure an optimal clinical response to antimicrobial therapy. Given the increasing prevalence of community-acquired MRSA, any specimens (for example swabs, pus or tissue) obtained at the time of presentation with suspected *Staphylococcus aureus* infection should routinely be sent to the laboratory for microscopy, culture and susceptibility testing.

Quality clinical data regarding the optimal antimicrobial treatment of community-acquired MRSA infection are currently lacking. At present, therapy should be based on susceptibility testing results and current knowledge of the efficacy of non-beta-lactam antimicrobial drugs in treating suspected or proven staphylococcal infection. Options for mild to moderate infection include clindamycin, trimethoprim with sulfamethoxazole, and doxycycline. Vancomycin is usually recommended for severe or invasive infection.

Conclusion

Antistaphylococcal/streptococcal beta-lactam antimicrobials are currently still recommended for empiric treatment of most uncomplicated skin or soft tissue infections. However, MRSA is an increasingly important cause of these and other infections acquired in the general community. If practical, clinical specimens should be submitted to the microbiology laboratory in order to detect infection with community-acquired MRSA. Antimicrobial therapy should be reviewed once results are available, or if the clinical response to empiric therapy is not as expected.

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Dr Murray has received funding from Pfizer to attend an international conference.

Message to all 2005 graduates in medicine, pharmacy and dentistry

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New drugs

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

Palifermin

Kepivance (Amgen)

vials containing 6.25 mg as lyophilised powder for reconstitution

Approved indication: oral mucositis

Australian Medicines Handbook section 14.5.2

Many patients who are treated with high doses of chemotherapy or radiation, particularly for head and neck cancers, develop oral mucositis. This can be very painful and in severe cases the patient may be unable to swallow. Mucositis increases the risk of the patient developing serious infections.

If mucositis is the result of damage to the oral tissues, then it could be ameliorated by giving growth factors. Palifermin is a genetically engineered form of keratinocyte growth factor which stimulates the development of epithelial cells.

The efficacy of palifermin has been assessed in 212 patients having chemotherapy and radiation before stem cell transplantation for haematological malignancies. These patients were given a daily intravenous injection of palifermin or placebo for three days before their treatment. They received three more doses following transplantation. Significant mucositis developed in 98% of the placebo group, but only in 63% of the patients given palifermin. It lasted six days with palifermin, but nine days with placebo. This probably contributed to the reduced use of opioid analgesics with palifermin. Although 75% of the patients given palifermin developed febrile neutropenia, this was significantly less than the 92% in the placebo group.[1]

Adverse effects which occur more frequently in patients given palifermin include rash, itching, erythema and altered taste and other sensations in the mouth. Patients may also complain of arthralgia, paraesthesia, oedema and cough. There is a theoretical risk that palifermin could promote cataract formation.

Animal studies suggest that palifermin can enhance the growth of epithelial tumours. As safety and efficacy have not been shown in other tumours, palifermin is currently only approved for patients with haematological malignancies receiving myelotoxic therapy requiring stem cell support.

☒ manufacturer declined to supply data

Reference †

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Quinagolide

Norprolac (Ferring)

25 microgram and 50 microgram tablets

Approved indication: hyperprolactinaemia

Australian Medicines Handbook section 16.2.1

The secretion of prolactin from the anterior pituitary is inhibited by dopamine. Dopamine agonists have therefore been used to treat hyperprolactinaemia, a condition which has several possible causes including prolactinomas in the pituitary.

Quinagolide is a selective agonist at the dopamine D_2 receptor. It has been approved for the treatment of idiopathic hyperprolactinaemia and prolactin secreting pituitary tumours.

Patients take quinagolide once a day. The drug is well absorbed but there is extensive first-pass metabolism. Prolactin concentrations start to fall within two hours of a dose and are suppressed for 24 hours. Most of the drug is metabolised with the metabolites being excreted in the faeces and urine. Therefore, impaired hepatic or renal function are contraindications to quinagolide.

As quinagolide has been available overseas for several years, long-term data are available. One study reported on a group of 40 patients treated for a mean of 32 months. The serum prolactin fell in all patients and the tumour size was reduced in 55% of the patients with microadenomas and 75% of the patients with macroadenomas. Hyperprolactinaemia can be a cause of infertility, but 10 of the 38 women in the study became pregnant while taking quinagolide.[1]

Most of the early comparative studies of quinagolide used bromocriptine. A study of 41 women found both drugs significantly reduced serum prolactin within eight weeks. Prolactin concentrations normalised in 81% of those given quinagolide and 70% of those given bromocriptine. Tolerability was higher in the women given quinagolide.[2] Another study showed that 39% of patients with prolactinomas that were resistant to treatment with bromocriptine responded to quinagolide.[3]

Bromocriptine is no longer first-line therapy because treatment with cabergoline is more effective. Quinagolide has therefore been compared with cabergoline. In one small study patients took one of the drugs for 12 weeks then stopped. When their hyperprolactinaemia returned they took the other drug for 12 weeks. Although only nine patients completed the study,

there were significant differences in the duration of efficacy and tolerability favouring cabergoline.[4] A similar study stopped treating 39 patients with quinagolide after a year then, when their hyperprolactinaemia returned, treated them with cabergoline for a year. Cabergoline had a greater effect on tumour size and was better tolerated.[5]

The adverse effects of quinagolide include nausea, vomiting, headache and dizziness. Some of these symptoms improve after a few days of treatment. It is therefore recommended that quinagolide is taken with food at night and that treatment is introduced gradually. In some cases the dopaminergic action of quinagolide may cause an acute psychosis.

The once-daily dose and better tolerability give quinagolide an advantage over bromocriptine. Any differences between quinagolide and cabergoline are less clear. Cabergoline needs to be given less frequently and if the patient only needs one dose a week, a month's treatment will be cheaper than daily treatment with quinagolide.

T T T manufacturer provided all requested information

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Sevelamer hydrochloride

Renagel (Genzyme)

800 mg tablets

Approved indication: hyperphosphataemia in chronic renal disease

Australian Medicines Handbook section 7.8

Patients with end-stage renal disease are at risk of hyperphosphataemia. This is associated with hyperparathyroidism, bone resorption and increased mortality. One strategy to control hyperphosphataemia is to reduce the absorption of phosphate from the gut. This can be achieved with a binding agent such as calcium acetate.

Sevelamer is a polymer which binds phosphates in the gut. The complex is not absorbed, so serum concentrations of phosphate should fall. Patients take tablets with every meal, at a dose determined by the serum phosphorus. The target concentration is 1.78 mmol/L or less.

Several studies have compared sevelamer with calcium acetate. In one study 83 patients having haemodialysis took calcium acetate or sevelamer for eight weeks, then after a two-week washout, swapped to the other drug for eight weeks. The effects on serum phosphate were similar, but patients taking calcium acetate were more prone to develop hypercalcaemia.[1]

Another comparative study found that although patients given calcium acetate were more likely to develop hypercalcaemia, they were also more likely to reach the target phosphate concentration. This study concluded that calcium acetate should remain the treatment of choice, because of its significantly lower cost.[2]

The cost-benefit assessment may be changed if the results of an unpublished long-term study are confirmed. This study of more than 2000 patients found reduced mortality in elderly people and patients treated with sevelamer for more than two years. Although the benefit was significant in these sub-groups, there was no significant overall advantage over calcium-based phosphate binders.[3]

Although sevelamer causes less hypercalcaemia, it may cause more dyspepsia than calcium acetate. In a pooled analysis of 384 patients, 58 discontinued sevelamer because of adverse events. These included dyspepsia, abdominal pain, diarrhoea, nausea and vomiting. As sevelamer binds bile acids there is a theoretical possibility it could reduce the absorption of fat soluble vitamins.

Sevelamer reduces concentrations of low density lipoprotein cholesterol. This could help to prevent cardiovascular calcification in patients having haemodialysis, however this strategy is likely to be more expensive than giving calcium acetate and a lipid-lowering drug.[2] Until the long-term effects of sevelamer are clearer it seems likely that its use will be determined by its cost.

X manufacturer declined to supply data

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Strontium ranelate

Protos (Servier)

sachets containing 2 g granules for oral suspension

Approved indication: postmenopausal osteoporosis

Australian Medicines Handbook section 10.3

Strontium is an element which was used in the past to treat osteoporosis. It fell out of use because it was associated with defects in bone mineralisation. Strontium ranelate aims to overcome the problems associated with strontium.

Patients take 2 g of granules in water. As the slow absorption is reduced by food, the dose should be taken at bedtime at least two hours after eating. Binding in the gut can reduce the absorption of some antibiotics. Tetracyclines and quinolones should therefore not be taken with strontium ranelate.

When the molecule dissociates, the strontium is taken into bone. It is thought to stimulate osteoblasts to make bone and to decrease the resorption of bone by osteoclasts. Strontium is slowly released from bone and excreted by the gut and kidney. Clearance is reduced by renal disease. The half-life of strontium is approximately 60 hours.

Strontium ranelate was studied in 353 women with postmenopausal vertebral osteoporosis and a history of at least one vertebral fracture. These women were randomised to take different doses of strontium ranelate or a placebo for two years. They also took calcium and vitamin D. There was a rise in alkaline phosphatase activity and a dose-dependent increase in lumbar bone density in the women who took strontium ranelate.[1]

A subsequent trial enrolled 1649 postmenopausal women with a history of osteoporosis and at least one vertebral fracture. These women took calcium and vitamin D with either 2 g of strontium ranelate or a daily placebo. After three years the bone mineral density of the lumbar spine had increased by 6.8% in the women taking strontium ranelate, but decreased by 1.3% in the placebo group. New vertebral fractures appeared on the X-rays of 20.9% of those taking strontium ranelate and 32.8% of those taking placebo. Symptomatic vertebral fractures occurred in 11.3% of the strontium group and 17.4% of the placebo group – a small, but statistically significant difference.[2]

Another study looked at the effect of strontium ranelate on non-vertebral fractures in 4932 elderly women with reduced bone density. Strontium increased bone density and over three years there was a 16% reduction in the relative risk of fractures. The absolute difference in fractures was small, with a cumulative incidence of 12.9% in the placebo group and 11.2% in the women taking strontium. There was only a 0.5% overall reduction in hip fractures over three years.[3]

Common adverse effects of strontium ranelate include headache, nausea and diarrhoea. Although the incidence is less than 1%, there is a higher risk of venous thromboembolism in patients taking strontium ranelate. Neurological problems such as altered consciousness or seizures occurred more frequently with strontium in placebo-controlled trials.

While serum calcium may fall during treatment, strontium can interfere with some of the laboratory assays used to measure calcium concentrations. At present there are limited histomorphometric data to assess the mineralisation of bone during treatment.

Based on the trial of the 2 g dose, nine patients, with osteoporosis and a history of fracture, would need to take strontium ranelate, calcium and vitamin D for three years to prevent one radiological fracture of a vertebra.[2] The reduction in the risk of vertebral fracture is similar to that seen with bisphosphonates, but the drugs do not seem to have been directly compared in published trials.

[T][T] manufacturer provided some data

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NEW FORMULATION

Tramadol hydrochloride

Tramal oral drops (CSL)

10mL and 30 mL bottles containing 100 mg/mL

(Tramal oral drops are not approved for use in children)

See also NPS RADAR review at www.npsradar.org.au

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

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

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

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3. True
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