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EDITORIAL

Efficacy, effectiveness, efficiency

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Index words: drug utilisation, cost-effectiveness, drug evaluation.

(Aust Prescr 2000;23:114–5)

How is it, that guidelines for treatment often seem unrelated to the patient sitting in front of the doctor? Guidelines are mostly based on evidence gathered from randomised controlled trials. These trials are very good at assessing efficacy – that is, can a treatment work? Despite this, trials are not without substantial biases. Many people may be screened before a few are chosen to be included in a study, yet the results of the study will be applied to the very people who were excluded. The population studied in trials tends to be young, male, white, suffering from a single condition and using a single treatment. Most patients, at least in general practice, do not fit this description. They often have multiple illnesses, take multiple medications and are either too young or too old to have been included in clinical trials. Perhaps we should accept a proposal to define efficacy in relation to medications as 'the extent to which a drug has the ability to bring about its intended effect under ideal circumstances, such as in a randomised clinical trial'.*

In this issue...

The new drugs reviewed in this issue have all been assessed for safety and efficacy. Although a treatment may be efficacious, John Marley points out that it may not be effective or efficient.

Heart failure needs effective treatment, but there are often difficulties in managing the condition. Henry Krum suggests some solutions to these therapeutic dilemmas. Peter Fletcher believes that beta blockers are the solution for some patients, even though these drugs were once contraindicated in heart failure.

While the cost-effectiveness of bisphosphonates may be questioned, they do have a role in some patients with low bone density, particularly postmenopausal women. John Martin and Vivian Grill inform us how the drugs work, while Peter Ebeling discusses their clinical use in osteoporosis.

The most effective treatment may not be a drug. In his article on panic disorder John Tiller tells us that cognitive behaviour therapy helps many patients. One of these patients is actor Garry McDonald who reveals how he overcame his anxiety.

Efficacy is not the same as effectiveness.[1] A treatment is effective if it works in real life in non-ideal circumstances. In real life, medications will be used in doses and frequencies never studied and in patient groups never assessed in the trials. Drugs will be used in combination with other medications that have not been tested for interactions, and by people other than the patient – the 'over the garden fence' syndrome. Effectiveness cannot be measured in controlled trials, because the act of inclusion into a study is a distortion of usual practice.

Effectiveness can be defined as 'the extent to which a drug achieves its intended effect in the usual clinical setting'.* It can be evaluated through observational studies of real practice. This allows practice to be assessed in qualitative as well as quantitative terms.[2]

Australia is well suited to conduct observational studies because we have a high standard of relatively unrestricted practice and good national databases, such as those held by the Health Insurance Commission. These databases can be used for validating researchers' separate database effectiveness studies. In America there are very large patient databases held by the Health Maintenance Organisations. Their size is impressive, but size is not everything. The data may have been collected primarily for billing and they may be incomplete. Clinical practice is often governed by protocols, and medications are limited to those supplied by the current preferred providers. The reimbursement mechanism for doctors may mean that they code conditions at the highest severity level. Patients belonging to one of these organisations may not represent the American population as a whole. In Britain, the General Practice Research Database, compiled from practice electronic records, is very useful, especially for studies in pharmacoepidemiology. The British enjoy relatively unrestricted clinical practice, but they do not have readily usable national datasets against which to check the validity of their database studies.

It is an irony that drugs are licensed for use almost exclusively on the results of controlled trials, yet they are withdrawn from use because of observational data that would not be acceptable to licensing authorities. Biases are present in observational studies, just as they are in trials, but they can be defined and often controlled for, giving these studies a much greater value than that currently awarded to them.

* From a suggested dictionary of pharmacoepidemiology by C. Ineke Neutel, University of Ottawa Institute on Health of the Elderly, Research Department, SCO Health Services. 43 Bruyere Street, Ottawa CANADA K1N 5C8.

Efficiency depends on whether a drug is worth its cost to individuals or society. The most efficacious treatment, based on the best evidence, may not be the most cost-effective option. It may not be acceptable to patients. In every country, rationing of health care is a reality. There is no country, however wealthy, that can afford to deliver all the health care possible to the whole of its population at all times. Rationing may be implicit or explicit, but it will happen. Good effectiveness and efficiency studies will make this rationing more informed.

Good practical guidelines, such as the Therapeutic Guidelines series, are clearly very important and extremely useful. They could be made even more relevant to the patient in front of the doctor, by being less dependent on efficacy studies. We should make more use of effectiveness and efficiency studies and abandon the censorship of the evidence drawn from them.

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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.

Prescribing by numbers

Editor, – It was interesting to see an article on the number needed to treat (NNT) (Aust Prescr 2000;23:38). NNT is better than looking at relative risk reductions but NNT still does not always give you a feel for the relevance of an intervention.

I believe clinical decision-making needs to consider two numbers. These are the paired absolute incidences.

X = Event rate control (the outcome with placebo, or the outcome if you do nothing)

Y = Event rate active (the outcome with treatment)

Consider a room full of 100 people with a clinical problem. Put it to them, 'Do nothing and the event will happen to X of you, and if all of you take the pill it will happen to Y of you.' Using the Helsinki Heart study as quoted in the article, how would 100 men respond if told 'Take gemfibrozil for five years and 4.1 of you will have an event, do nothing and 2.7 of you will have an event'? I suspect many would say why bother with treatment, but some would say OK.

Clinical decision-making needs to be made in the context of real people. Other comorbidity, patient attitude, patient expectations, the psychological burden of disease label, adverse effects, secondary costs (for example, more visits to the doctor) all need consideration. I believe that by looking at the two numbers (X and Y) I can get a better feel for the relevance of an intervention, and also inform my patients about 'doing something' versus 'doing nothing'.

I believe the treatment of risk and risk factors is greatly overrated, and that many are treated for risk without a genuine consideration of how much of a difference it could make for the individual. As the surgeons learn to withhold the knife, I believe we should learn to hold back the drug treatment of risk factors, not because there is no evidence, but because in the bigger picture it is irrelevant to the patient – this will be facilitated by looking at the X and Y numbers.

Paul Neeskens
General Practitioner
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Medicines and the media

Editor, – The *Australian Prescriber* editorial (Aust Prescr 2000;23:70–1) regarding reporting of medicines in the media is timely. On 13 April 2000, an article in the Adelaide 'Advertiser' included the headline 'Accepted safe levels of cholesterol "still too high"' and pictured a young woman having a cholesterol test. The commentary continued, 'Worldwide evidence proved "normal" cholesterol levels in healthy men and women were too high, an international authority on heart disease said in Adelaide yesterday'. The article went on to talk about '...a new ultra-low dose cholesterol-reducing drug called cerivastatin, ...recently approved for use in Australia...'

Assuming a new study had been released assessing health outcomes associated with cerivastatin, we contacted the reporter. He could not provide any information to support the story, but suggested we contact the Adelaide marketing company publicising the visit of the overseas specialist. The marketing company supplied their media release, but could not provide a reference. They reported the media release was redrafted from one produced by a Sydney company. The Sydney marketing company also could not provide a reference. They said their media release was based on information supplied by Bayer, but they had returned all material to Bayer.

We rang Bayer on five occasions. The product manager was never available to speak to us, nor has he returned our call.

The Adelaide marketing company, however, was more sympathetic. They rang us back to say the West of Scotland Coronary Prevention Study, a 1995 study involving pravastatin, was the basis for the story. Was the story 'news' or advertising? How can consumers tell the difference?

Libby Roughead and
Andrew Gilbert
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Paracetamol in childhood fever

Editor, – I am writing about the use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) ('Paracetamol: overused in childhood fever' Aust Prescr 2000;23:60–1). For a while we have been bogged down with the controversy about the concurrent prescribing of paracetamol and ibuprofen to children who have fever which is not controlled by paracetamol alone.

The current practice here is not to give paracetamol four-hourly for more than one day, after which the patient is advised to switch to six-hourly. As such, if breakthrough fever occurs after one day on paracetamol, some doctors advise patients to stagger the paracetamol dose with ibuprofen three hours inbetween.

What would be the concern about nephrotoxicity/ hepatotoxicity when giving the two preparations concurrently to children?

Hing Wee Chuan
Drug Information Pharmacist
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Professor Ric Day and Dr Robert Graham, St Vincent's Hospital, Sydney, and Dr Noel Cranswick, Royal Children's Hospital, Melbourne, comment:

Mr Hing Wee Chuan enquires about the use of paracetamol in combination with ibuprofen in children whose pyrexia does not respond to paracetamol alone. Firstly, the question should be asked whether the temperature needs to be lowered at all. There is increasing evidence[1] that routine fever reduction is unnecessary, with no evidence that the risk of febrile seizures is reduced[2] and some viral illnesses may even be prolonged.[3]

Prolonged dosing of paracetamol needs to be kept below 60 mg/kg/day in children to minimise the risk of liver toxicity. The practice of dosing four-hourly on day 1 and six-hourly thereafter as is practised in Mr Hing's hospital is acceptable as long as the daily dose limits are not exceeded. However, there is no evidence that the practice has any safety advantage. A clear upper limit for ibuprofen dosage in children for antipyresis has not been established. However, some adverse effects may be dose related. Uncommon but potentially serious adverse effects include aspirin-like sensitivity, renal toxicity and gastrointestinal bleeding.

If it is decided to treat fever, there is no evidence that the combination of paracetamol and ibuprofen is more effective than either drug alone. However, there is evidence from adult studies that the dose of NSAIDs can be reduced without loss of analgesic efficacy when paracetamol is used concomitantly.[4] In this study there were fewer minor adverse effects such as dyspepsia when naproxen was combined with paracetamol in the treatment of rheumatoid arthritis, probably related to the lower dose of NSAID employed in the combination regimen. There is a safety benefit in combining NSAIDs with paracetamol if the dose of NSAID used is less than would normally be the case. We know that the risk of serious upper gastrointestinal adverse reactions to NSAIDs increases with the dose rate of NSAID.[5] This would be most pertinent in those at increased risk, particularly the elderly.

Ibuprofen, like all NSAIDs, can be hazardous in patients with hepatic or renal impairment or in hypovolaemic situations.[6] Paracetamol in this context could theoretically increase the risk of further hepatic damage.

Whether there is any merit in using the combination to treat fever would need to be subject to controlled studies. In the interim, there seems little evidence either to support or to raise concerns about the practice.

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Treating acute sinusitis

Editor, – In the article 'Treating acute sinusitis' (Aust Prescr 2000;23:39–41), the author stated that 'patients allergic to penicillin should be treated with either trimethoprim-sulfamethoxazole or cefaclor'. Because cefaclor is a cephalosporin, the statement raises questions about cross-sensitivity with penicillins.

In my experience, substantial numbers of clinicians are still confused about the possibility of cross-sensitivity between various beta-lactam antibiotics. I think this topic deserves clarification.

It is well known that cephalosporins might show cross-sensitivity with penicillins. The frequency of cross-reactions is uncertain, but is probably relatively low, around 5–10% (in immunological studies up to 20%). It seems that the patients with a history of mild reactions to penicillins are at low risk of developing an allergic reaction following administration of a cephalosporin. On the other hand, many authorities recommend that if a patient has ever experienced a severe allergic reaction (anaphylaxis) to penicillin, it is strongly advisable not to give a cephalosporin.

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Management of hypertension

Editor, – The National Heart Foundation of Australia released its 1999 Guide to Management of Hypertension for Doctors in October last year.[1] Since then a large outcome study (ALLHAT) in the USA has demonstrated that antihypertensive therapy with the alpha blocker doxazosin is associated with more cardiovascular events and a greater chance of patients being hospitalised for congestive heart failure than therapy with a regimen based on a thiazide diuretic.[2] As a result of this study, the National Heart Foundation does not recommend that alpha blockers be considered as an option in the first-line management of hypertension.

This recommendation does not preclude considering alpha blockers as additional drugs, after initiation with a first-line drug, if combination therapy is required to achieve good blood pressure control.

Although alpha blockers may still be used for symptom relief in patients with prostatism without manifest or suspected heart failure, the ALLHAT results suggest that, if the person is also hypertensive, their outcome will not be as good as if they were treated with a regimen based on a thiazide diuretic. It is also likely that they will have a higher chance of being admitted to hospital with heart failure.

Professor Lindon Wing
Chair and members
National Blood Pressure Advisory Committee
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Volume 1 Number 1

It was twenty-five years ago that the first issue of *Australian Prescriber* was published.

Volume 1 Number 1 of October/December 1975 carried an editorial on the journal's launch and its purpose. The Editorial Board had six members, the Advisory Editorial Panel thirty member societies. Contents of this first issue were:

Lofty, but attainable, aims? The prescriber's pen (and pad) is mightier than the sword (scalpel).

The use of diuretics in the treatment of hypertension – Certain diuretics remain the initial treatment of choice in most patients with hypertension. The article includes some analysis of cost and prescription volume.

Phenytoin plasma levels: the measurement of plasma levels of antiepileptic drugs – Modern techniques may improve management of a common condition.

Mazindol (anorectic) – The first of a series of monographs on new drugs, including comparative costs of five anorectics.

Adverse drug reactions – The Adverse Drug Reactions Bulletin was incorporated in *Australian Prescriber*. Six topics are reported on, including deafness and chlorhexidine drops, and oral contraceptives and the eye.

Nocturnal cramps – A common complaint with no single treatment.

The treatment of enuresis in childhood – The article was reproduced from the UK Prescriber's Journal, with comment by two Australian consultants.

Quiz – your diagnosis, doctor?

Should diazepam be used in epilepsy? – A paper suggesting that only intravenous diazepam has a place.

Metric only in 'Prescriber' – The medical profession is familiar with most metric units. It will be the policy of *Australian Prescriber* to use SI units.

Book review: 'Medical Nemesis' – The reviewer discovers some 'rays of truth' in Ivan Illich's critique of the 'medicalisation' of industrial society, and clinical iatrogenesis.

Theriac – an old-time panacea.

An accompanying letter from the then Minister for Health stated that *Australian Prescriber* aimed to meet the need for 'balanced, impartial, reliable, up-to-date information on therapy and preventive patient care'.

He said, 'The Department of Health has a clear responsibility to provide information and to ventilate informed opinions on which practitioners may confidently base the critical decisions they are called on to make daily. The journal will aim to indicate to the practitioner the part, large or small, played by drugs in the treatment of any given condition.'

Twenty-five years later the journal is still expanding its audience thanks to the internet. It has grown to six issues per year, and continues to publish critical reviews of the drugs Australian doctors prescribe for their patients.

Look at the Gallery of past *Australian Prescriber* covers on the internet home page (www.australianprescriber.com) for a colourful display of covers since the seventies.

Dilemmas in the drug treatment of heart failure

Henry Krum, Clinical Pharmacology Unit, Department of Epidemiology and Preventive Medicine, and Department of Medicine, Monash University, Alfred Hospital, Melbourne

SYNOPSIS

The clinical outcomes for patients in chronic heart failure can be improved by optimising drug and non-drug treatments. The cornerstones of drug therapies for heart failure are diuretics to achieve and maintain euvolemia, and ACE inhibitors to provide symptomatic benefits and prolong survival. There are many additional options for treatment and these often pose a therapeutic dilemma for the treating physician.

Index words: ACE inhibitors, beta blockers, spironolactone, digoxin.

(Aust Prescr 2000;23:118–20)

Introduction

Chronic heart failure is a syndrome associated with high mortality, frequent hospitalisation and poor quality of life. The increasing prevalence and incidence are creating a major public health problem.

Therapeutic strategies which favourably impact upon clinical outcomes in chronic heart failure include optimisation of non-pharmacological therapy (salt restriction, alcohol restriction, exercise and weight loss). Devices and surgery (primarily revascularisation) have a limited role. Optimising drug therapy for each patient also improves outcomes.

Nearly all patients should be treated with ACE inhibitors to provide symptomatic benefits and prolong survival. Diuretics are often added to achieve and maintain euvolaemia. Adding other treatments can create a therapeutic dilemma for the treating physician.

Dilemma 1: Should the dose be increased in a symptomatic patient tolerating low to moderate doses of an ACE inhibitor?

Many physicians view maximising the dose of ACE inhibitors as an important strategy in optimising the management of patients with heart failure. Data in support of this approach come from the ATLAS trial[1], a comparison of high-dose versus low-dose lisinopril (32.5–35 mg versus 2.5–5 mg/day). High doses resulted in a small but beneficial impact on mortality. There was also a significant reduction in the combined end-point of mortality and hospitalisation for heart failure.

A practical approach may be to slowly increase the ACE inhibitor to the maximal dose tolerated by the patient. One of the major limitations to increasing the dose of ACE inhibitor may be worsening of renal function. Often this is related to hypovolaemia which should be identified and managed appropriately, for example by reduction of diuretic dose. A small increase in serum creatinine is normal and to be expected as part of the mechanism of action of the drug on the kidney. Substantial rises in serum creatinine may necessitate reduction in dose or even cessation of the ACE inhibitor. Monitoring renal function is particularly important in patients who have underlying renovascular disease, or are taking non-steroidal anti-inflammatory drugs.

Dilemma 2: When should beta blockers be introduced?

Beta blocker therapy prolongs survival in patients with mild, moderate and severe symptoms.[2] It also improves the well-being of patients who are moderately to severely symptomatic. The patients in the studies that showed these benefits were also taking ACE inhibitors, usually in moderate doses. Beta blockers should therefore be added to the standard therapy of ACE inhibitor and diuretics in all symptomatic but stable patients, unless they have an absolute contraindication such as reversible airflow obstruction or atrioventricular block.

Dilemma 3: When should spironolactone be added?

In the RALES study[3] spironolactone improved well-being and prolonged survival in patients with severe (Class III-IV) heart failure. This suggests that a patient who remains severely symptomatic after optimising ACE inhibitor and loop diuretic therapy is a candidate for treatment with spironolactone. Interestingly, this drug appears to provide benefit whether or not patients are taking beta blockers.

Physicians should be aware of the potential for clinically significant hyperkalaemia in combining spironolactone with an ACE inhibitor. Major problems with hyperkalaemia were not observed in the RALES study, possibly because of the relatively low doses of spironolactone (25 mg per day) and the frequent monitoring of potassium.

Dilemma 4: Is there still a role for digoxin?

With the recent demonstration of survival benefits for beta blockade and spironolactone, there is less place for digoxin in the treatment of heart failure. This is because the only major trial of digoxin in patients with systolic heart failure and sinus rhythm did not find a survival benefit.[4] Nevertheless, this

study and others (primarily studies of withdrawal of digoxin) did show a beneficial effect of digoxin on patients' symptoms, with an overall reduction in hospitalisation due to heart failure. Digoxin may therefore still have a limited role, purely for symptom relief, in patients with severe heart failure.

Digoxin remains valuable therapy for patients in systolic heart failure with atrial fibrillation. It has an established role in controlling the ventricular response.

Dilemma 5: What is the best alternative for patients who cannot tolerate ACE inhibitors?

The commonest reason for intolerance of ACE inhibitors in patients with heart failure is cough. However, this problem seems less frequent than it is in patients with hypertension.

Angiotensin (AT_1) receptor antagonists have been suggested as potential alternatives in patients who cannot take ACE inhibitors. Indeed, the ELITE I study suggested that angiotensin receptor antagonists were better at prolonging survival than ACE inhibitors. This finding was, however, unable to be replicated in a much larger study adequately powered for mortality (ELITE II).[5] Indeed, in the ACE inhibitor group slightly fewer patients died than in the angiotensin receptor antagonist group. This was also observed in the RESOLVD pilot study.[6]

The only other drugs compared in a head-to-head manner with ACE inhibitors have been hydralazine and nitrates, in the Ve-HeFT II study. This study found a short-term symptomatic benefit with the vasodilators, however they were clearly inferior to ACE inhibitors in prolonging survival.

Angiotensin receptor antagonists are probably the drugs of choice for patients who are truly intolerant of ACE inhibitors, providing that the intolerance is not due to factors such as angioedema or bilateral renal artery stenosis that would contraindicate the use of either class of drug. The benefits of blocking the renin angiotensin system are undisputed and drugs that act on this system (albeit via a different approach to ACE inhibitors) would be expected to offer at least some potential benefit. However, angiotensin receptor antagonists are not currently approved by the Therapeutic Goods Administration for the treatment of heart failure, even in patients who cannot tolerate ACE inhibitors.

Dilemma 6: Should patients with systolic heart failure be routinely anticoagulated?

There is no doubt that patients with heart failure have an increased risk for thromboembolism with sequelae such as cerebrovascular accident. However, it is not clear from retrospective studies whether routine anticoagulation in all patients reduces this risk sufficiently to offset the risk of serious bleeding.

The WASH study was a small open-label study of patients with heart failure and sinus rhythm, which compared aspirin or warfarin with no anti-thrombotic therapy. Preliminary data suggest that there were no major differences between the three approaches.

A pragmatic approach may be to continue anticoagulation in those patients who are already on it, but not to start anticoagulants in other patients unless there is another overwhelming indication, for example atrial fibrillation, substantial anterior wall akinesis or ventricular thrombus on echocardiography.

Dilemma 7: When should a patient with heart failure be referred to a specialist?

Referral for specialist assessment is warranted for many patients, given the complexities of the disease process, the possible aetiologies that may be contributing and the dilemmas in the management of heart failure. Many heart failure specialists have organised multidisciplinary approaches to the management of these patients. This involves close interaction between the heart failure specialist, the referring general practitioner, and a co-ordinating nurse practitioner, as well as ancillary paramedical staff including dietitians, physiotherapists and psychologists. These multidisciplinary approaches can improve outcomes by reducing the readmission of high-risk patients to hospital.

Dilemma 8: When should heart failure therapy be aimed at palliation rather than survival?

Patients with severe symptoms of heart failure have a quality of life worse than most chronic diseases, and a prognosis worse than most cancers. Many of these patients may benefit from shifting the focus of treatment from improving survival to improving quality of life.

Components of this care include strategies to relieve dyspnoea (diuretics, oxygen, opioids, benzodiazepines), improve uraemia and reduce lower limb oedema. Other components of palliation include the maximisation of comfort and dignity during the terminal stages of the illness, and the potential for receiving this support at home.

Summary

Heart failure is a complex disease requiring a multifaceted approach to management. Fortunately, a number of drugs can be used to optimise treatment of this condition. However, these therapeutic options raise a number of dilemmas and choices. Appropriate use of diuretics and ACE inhibitors is the cornerstone of medical therapy, and now beta blockers appear to offer substantial additional benefit. Patients with severe heart failure may also benefit from spironolactone.

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Self-test questions

The following statements are either true or false (answers on page 139)

1. Digoxin remains the first-line treatment for patients with heart failure who are in sinus rhythm.
2. Beta blockers are contraindicated in heart failure.

Beta blockers in heart failure

Peter Fletcher, Professor and Head, Cardiovascular Medicine, John Hunter Hospital, Newcastle

SYNOPSIS

Recent trials have shown the unequivocal benefits of beta blockers in patients with chronic systolic heart failure. These benefits include improved survival (30-35%) and a reduced need for hospitalisation. However, beta blockers may also make a patient with heart failure worse, especially when treatment begins. Complications can generally be avoided by starting with extremely low doses and increasing the dose very slowly. Beta blockers should be added to optimal conventional therapy for heart failure, and started only when the patient is stable.

Index words: carvedilol, digoxin, metoprolol.

(Aust Prescr 2000;23:120–3)

Introduction

Traditional teaching was that beta blockers should be avoided in patients with heart failure. The rationale was that the sympathetic nervous system was overactive and provided a crucial level of compensation for the failing heart. To remove this by using a beta blocker would risk precipitating or exacerbating heart failure.

Recent trials have seriously challenged this conventional wisdom. The risks remain, but now need to be balanced against the major long-term benefits of beta blockade in chronic systolic heart failure (see box).

History

The Scandinavians have been promoting the use of beta blockers in systolic heart failure since the mid-1970s. A number of relatively small trials showed benefits, primarily in patients with non-ischaemic dilated cardiomyopathy. The MDC trial of Metoprolol in Dilated Cardiomyopathy in 1985 failed to show either harm or benefit.

In 1998 there was a meta-analysis of 18 double-blind placebo-controlled trials of beta blockers in chronic systolic heart failure (see Table 1).[1] The overall reduction of total mortality from chronic beta blockade was 32%, with a 41% reduction in sudden deaths and a 37% reduction in hospitalisation.

Mechanism of action

The benefit of beta blockers almost certainly depends on blockade of beta-1 receptors. This action is consistent with the large body of data documenting high plasma catecholamines in severe heart failure, and more sophisticated studies demonstrating increased cardiac sympathetic activity and catecholamine release. Possible mechanisms for beta receptor blockade improving survival include:

- antiarrhythmic action
- anti-ischaemic action
- attenuation of catecholamine toxicity
- reduced cardiac remodelling.

Metoprolol and bisoprolol are both cardioselective beta blockers acting primarily on beta-1 receptors. By comparison,

Beta blockers in systolic heart failure

In patients with primarily severe systolic heart failure (low ejection fraction) beta blockade has the following long-term benefits which must be balanced against the short-term risks.

Long-term benefits	*Short-term risks*
• improved survival	• worsening heart failure
• improved control of heart failure	• bradyarrhythmias
• reduced need for hospitalisation	• prolonged intraventricular conduction
• improved quality of life	• hypotension
• improved left ventricular ejection fraction	• worsening renal function

carvedilol is a non-selective beta blocker with additional alpha-receptor blocking and antioxidant properties. Based on the unequivocal treatment benefits seen in the CIBIS[2] and MERIT[3] studies, the principal mechanism by which these drugs improve outcome in heart failure is likely to be via their beta-1 receptor blocking action. We will not know if the additional properties of carvedilol are important, and whether carvedilol actually produces a larger benefit than standard beta blockers, until the results of current head-to-head comparisons are reported.

Indications other than systolic heart failure

There are two other types of heart failure where use of beta blockers provides clear benefits and little risk.

Atrial fibrillation

In some patients, atrial fibrillation with rapid ventricular response is a major factor which worsens the severity of their heart failure. In this situation, controlling the ventricular response alone can produce a major improvement in heart failure. Digoxin is usually effective in this situation. Beta blockers are also effective in slowing the ventricular rate, and rarely worsen the situation providing ventricular systolic function is reasonably well preserved.

Diastolic heart failure

Possibly as many as one third of patients with heart failure have normal ventricular systolic function. In these patients, the primary cardiac abnormality leading to heart failure is an abnormality of ventricular filling. They have so-called 'diastolic heart failure'. In this situation, beta blockers can also produce improvement with little risk of the patient deteriorating. The drugs slow the heart rate and allow a longer period for diastolic filling, particularly if atrial fibrillation is also present. Patients with mitral stenosis are the best example. Beta blockers can also facilitate diastolic filling by improving abnormal myocardial relaxation, for example in patients with diastolic failure due to severe left ventricular hypertrophy. This is generally in patients with severe, long-standing, poorly-controlled hypertension.

Clinical trials in systolic heart failure (Table 1)

Patients with primarily **systolic heart failure** with low ejection fraction may deteriorate when given a beta blocker. Paradoxically, it is this very group of patients that had unequivocal long-term benefits in recent trials (see box).

Carvedilol trials

In the meta-analysis of beta blockade[1], there were eight trials of carvedilol, with a total of 1657 patients. Carvedilol appeared to reduce total mortality by 49%. However, only one of the eight individual carvedilol trials produced a statistically significant reduction in total mortality. This trial markedly influences the overall estimate of the treatment benefit of carvedilol. The ANZ trial was the largest of the carvedilol trials (415 patients). Although it found a 27% reduction in total mortality and a 30% reduction in hospitalisation, neither result was statistically significant. None of the carvedilol trials were sufficiently powered to be able to detect a significant difference in these end-points.

It was pooled data from a number of relatively small trials of carvedilol which convinced the Therapeutic Goods Administration to approve carvedilol for systolic heart failure in 1998. Carvedilol requires an authority prescription under the Pharmaceutical Benefits Scheme.

Table 1

Summary of beta blocker trials in chronic systolic heart failure

Trial	*Meta-analysis of 18 pre-1998 trials*[1]	*Carvedilol meta-analysis*	*CIBIS-II 1999*[2]	*MERIT-HF 1999*[3]	*COPERNICUS 2000**
Number of patients	3023	1657	2647	3991	2289
Severity†			III/IV	II/III	III/IV
Placebo mortality	156/1305 (11.9%)	62/665 (9.3%)	228/1320 (17.3%)	217/2001 (11.0%)	NA/1133 (18.6%)
Beta blocker mortality	130/1718 (7.5%)	47/992 (4.7%)	156/1327 (11.8%)	145/1990 (7.2%)	NA/1156 (11.4%)
Reduction in relative risk: total mortality	32%	49%	34%	34%	35%
Number needed to treat††			23	26	14
Reduction in relative risk: sudden death	41%		44%	41%	NA
Reduction in relative risk: hospitalisation	37%	40%	20%		

* Not yet published, data preliminary and incomplete
† New York Heart Association functional class
†† Number of patients who must be treated with beta blocker for one year to prevent one death
NA = not available

CIBIS-II

CIBIS stands for **C**ardiac **I**nsufficiency **Bi**soprolol **S**tudy.[2] Bisoprolol is a beta-1 selective blocker not available in Australia. A total of 2647 patients, mostly in Class III heart failure, had either bisoprolol or a placebo added to optimal therapy. (Most patients were taking a loop diuretic and ACE inhibitor in reasonable doses, and 50% were taking digoxin.) The trial was stopped early because of an unequivocally statistically significant reduction in total mortality of 34%. There were also significant reductions in sudden death (44%) and in hospitalisation for congestive cardiac failure (20%).

MERIT-HF

MERIT-HF stands for **Me**toprolol **R**andomised **I**ntervention **T**rial in **H**eart **F**ailure.[3] Metoprolol is a beta-1 selective blocker which has been available in Australia for many years. However, this trial used a slow-release formulation not currently available in Australia. A total of 3991 patients, with predominantly Class III heart failure, were randomised to have either a placebo or metoprolol, added to the optimal conventional therapy of a loop diuretic and ACE inhibitor. The trial was stopped early because of an unequivocally statistically significant reduction in total mortality of 34%. There was also a significant reduction in sudden death (41%).

COPERNICUS

This stands for **C**arvedil**o**l **P**rosp**e**ctive **R**a**n**dom**i**zed **Cu**mulative **S**urvival Trial. This trial compared carvedilol with placebo in 2289 patients with severe Class III/IV heart failure and ejection fraction of less than 25%. Carvedilol or placebo was added to optimal conventional therapy for heart failure. The trial has been stopped prematurely because of a beneficial effect of carvedilol on the primary end-point of all cause mortality. The results have been presented at an international meeting, but have not yet been published. Carvedilol was associated with a 35% reduction in total mortality.

In COPERNICUS, the annual mortality in the placebo group (18.6%) was higher than in either the MERIT (11.0%) or CIBIS (13.2%) studies. This reflects a generally sicker group of patients in COPERNICUS with more severe heart failure. As a result, the same **relative** risk reduction has resulted in a larger **absolute** mortality benefit and a smaller number needed to treat. However, the relative risk reduction was similar between the three studies.

Unresolved issues

Severity of heart failure

Both the CIBIS and MERIT trials enrolled predominantly patients with Class III heart failure. The number of patients with more severe Class IV heart failure was small (17% and 3% respectively) and the treatment benefit was not statistically significant in this sub-group. Nevertheless, on average, the **magnitude** of benefit was not different in the patients with more severe failure. The COPERNICUS study enrolled more patients with Class IV heart failure, yet produced virtually the same relative reduction in total mortality. It must be emphasised that patients with very severe heart failure are a much more difficult group in which to start beta blockers because of the risk of exacerbating their already severe heart failure.

Co-medication

Digoxin

Approximately 50% of patients in both the CIBIS and MERIT studies were taking digoxin. Randomisation was not performed in relation to digoxin, but there was no difference between the treatment benefit from beta blockade in those taking and those not taking digoxin. Given that there is no mortality benefit from digoxin[4], it seems logical to recommend that patients in sinus rhythm should have a beta blocker added to optimal therapy before digoxin is introduced. However, this recommendation is **not** based on any definitive data.

Spironolactone

In the recently published RALES trial[5] there was a highly significant 30% reduction in total mortality when a low dose of spironolactone (25 mg daily) was added to conventional therapy in patients with very severe heart failure. Only 10% of the patients were taking beta blockers. The patients in this study had much more severe heart failure than in most of the beta blocker studies. As a result of this trial, many physicians are now including low dose spironolactone as part of 'optimal conventional therapy' in patients with very severe heart failure before introducing a beta blocker.

Antiarrhythmics

There is no consensus on the role of conventional antiarrhythmics in severe heart failure. What is clear is that the beta blocker trials have shown a clear reduction in the very substantial risk of sudden death. This is assumed to be because they prevent ventricular tachyarrhythmias. It seems logical to recommend that, in the absence of documented sustained ventricular tachycardia, beta blockers should be used **before** any consideration of antiarrhythmic drug therapy.

Recommendations

A beta blocker should be considered for all patients with systolic heart failure who are stable on optimal doses of a diuretic and ACE inhibitor. If patients are not stable on optimal treatment, then digoxin and perhaps spironolactone should be added before a beta blocker.

Which beta blocker to use?

Both carvedilol and standard beta-1 blockers appear to be effective. There are currently multiple trials in progress of carvedilol in various different groups of heart failure patients. The results should tell us if carvedilol is more effective than standard beta-1 blockers. Carvedilol has the advantage of a lower dose formulation for starting treatment. However, carvedilol is also much more expensive than standard beta blockers (up to 10 times the cost of the standard form of metoprolol).

What dose for starting therapy?

Starting a beta blocker can make heart failure worse, so low doses are used. For most patients you can cautiously start with carvedilol 3.125 mg twice a day or metoprolol 12.5 mg twice a day. Patients with very severe heart failure should probably start on only a morning dose.

How rapidly can the dose be increased?

The dose can be doubled every 2–4 weeks providing the patient is stable. If the heart failure has deteriorated, the doses of diuretic, ACE inhibitor or digoxin should be adjusted first before any further increase in beta blocker. The dose of beta blocker may need to be reduced, particularly if there is undue bradycardia or worsening cardiac conduction.

What is the target dose?

For carvedilol, the target dose is 25 mg twice a day. For metoprolol it is 100 mg twice a day. Many patients will not reach these doses. Substantial benefits are almost certainly achieved with doses which are lower than these targets.

What about patients who are already taking a beta blocker?

Some patients who have been taking beta blockers long term for other indications such as angina or hypertension will develop heart failure. The clinician must first determine why the patient has developed heart failure (for example, new atrial fibrillation, silent myocardial infarction). Both the underlying cause and the heart failure must be treated appropriately. In many patients the degree of heart failure may not be too severe, and the beta blocker will be able to be continued. In other patients it may be necessary to either reduce the dose or even withdraw the beta blocker completely until the heart failure is under control. Once this has been achieved, the beta blocker should be cautiously reintroduced.

Who should manage the patient?

These patients are extremely fragile and difficult to treat. Occasional patients will deteriorate markedly after starting a beta blocker and may even require intensive or coronary care with intravenous beta agonist support. In Australia carvedilol can only be started in hospital patients. General practitioners should always consider involving a physician or cardiologist before starting or changing beta blocker therapy.

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Self-test questions

The following statements are either true or false (answers on page 139)

3. Patients with heart failure should be treated with an ACE inhibitor and a diuretic before starting a beta blocker.
4. Beta blockers reduce total mortality in heart failure, but do not reduce sudden deaths.

Medicinal mishaps

Allergy to an antihistamine

Prepared by Christian Hamilton-Craig and J. McNeece, Royal Adelaide Hospital, Adelaide

An 18-year-old woman took a dose of a friend's nizatidine for an upset stomach. About one hour after taking 150 mg of nizatidine she experienced shortness of breath, tachypnoea, wheezing and a mild visible swelling of the neck. On presentation to the Emergency Department she was visibly distressed. Her lung expansion was poor with diffuse coarse polyphonic inspiratory and expiratory wheezes. There was no rash. After treatment with adrenaline, promethazine and prednisolone, she improved rapidly.

We can only find two other reports of allergic reactions to nizatidine[1,2], (although cases of allergy to other H_2 histamine receptor antagonists have been published). The first report described a leukocytoclastic vasculitis associated with nizatidine. The second described a situation which was very similar to our case. In the report the patient was rechallenged with nizatidine and other H_2 antagonists. Results of the oral challenge were negative for cimetidine, ranitidine and famotidine. However, within 15 minutes of nizatadine administration the patient again experienced laryngeal oppression, dysphonia, dysphagia, dry mouth, moderate flushing and generalised pruritis.

The ability of H_2 histamine antagonists to increase serum histamine by displacing it from its receptors is well known, particularly after a rapid intravenous infusion. A similar effect would account for the appearance of anaphylactoid symptoms on some occasions. However, the second study[2] suggested an anaphylactic, rather than anaphylactoid, mechanism caused the symptoms as there was no reaction to the other H_2 antagonists.

Our case also shows the dangers of using other people's medicines.

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Treatment of panic disorder

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SYNOPSIS

Panic disorder consists of recurrent, disabling attacks of panic. It is frequently complicated by agoraphobia and other anxiety disorders or depression. Panic disorder differs from an isolated panic attack, both clinically and in treatment. Many patients respond to a combination of lifestyle change, especially control of caffeine and alcohol use, and cognitive behaviour therapy. For panic disorder, high potency benzodiazepines are effective for acute and long-term treatment, but have the disadvantages of sedation, drug interactions and discontinuation problems. For long-term treatment, imipramine is effective, but a lack of tolerability substantially limits its use. Most new antidepressants are probably effective for panic disorder, but few have been approved for this indication.

Index words: cognitive behaviour therapy, benzodiazepines, antidepressants.

(Aust Prescr 2000;23:124–6)

Introduction

The separation of anxiety disorders into a number of discrete conditions has improved our understanding of these problems, and enabled better-focused treatment. Approximately one third of people will experience at least one panic attack in their life. This may typically occur after excessive caffeine or alcohol use, or when fatigued, or otherwise stressed. This is quite different from panic disorder in which there are recurrent and unexpected panic attacks and at least one of the attacks has been followed by a month or more of persistent concern about having additional attacks. There is also a significant change in behaviour related to the attacks. Panic disorder may occur with or without agoraphobia. Panic attack and panic disorder should be differentiated as they need different interventions.

Panic attack

A panic attack is a discrete period of intense fear or discomfort, in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes[1]:

- palpitations, pounding heart, or accelerated heart rate
- sweating
- trembling or shaking
- sensations of shortness of breath or smothering
- feeling of choking
- chest pain or discomfort
- nausea or abdominal distress
- feeling dizzy, unsteady, light-headed, or faint
- derealisation (feelings of unreality) or depersonalisation (being detached from oneself)
- fear of losing control or going crazy
- fear of dying
- paraesthesias (numbness or tingling sensations)
- chills or hot flushes.

Panic disorder

The criteria for panic disorder[1] are the occurrence of recurrent and unexpected panic attacks with at least one of the attacks having been followed by a month or more of:

- persistent concern about having additional attacks
- worry about the implications of the attack or its consequences, for example, losing control, having a heart attack, or going crazy
- a significant change in behaviour related to the attacks.

Panic disorder may be spontaneous, or a reaction to certain situations. Spontaneous panic occurs in any circumstances, often seemingly 'out of the blue'. While it may be possible to identify pre-existing vulnerability such as fatigue, work or family stress, for many patients this is not the case. There may be a genetic factor which increases people's vulnerability to panic disorder.

Situational panic occurs when a patient is exposed to trigger events or circumstances. These may be when in a lift, car, bus, tunnel or on a bridge or in situations where the patient fears they will not be able to escape. The added fear of their situation, coupled with some pre-existing vulnerability, results in the panic occurring in that particular setting or settings.

Patients with panic disorder may present to doctors' surgeries or emergency departments. They may feel that they are having a 'heart-attack' or are about to die, or cannot get their breath or have 'air hunger', usually in the absence of any signs of respiratory disorder.

Agoraphobia

Panic disorder may occur with agoraphobia. The essential agoraphobic features are:

- anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having a panic attack
- avoidance behaviour.

Agoraphobic fears involve situations that include the following: being alone outside the home, or being home alone, being in a crowd, standing in a queue, being on a bridge, and travelling

in a bus, train or car. The patient avoids these (for example, travel is restricted) or else they are endured with marked distress or anxiety, or require the presence of a companion.[1]

Differential diagnosis

All the above disorders require that the anxiety or phobic avoidance is not caused by other conditions, for example substance abuse, general medical conditions such as thyrotoxicosis, or another mental disorder such as the avoidance associated with social phobia (social anxiety disorder). Anxiety disorders may occur alone, together, or with other psychiatric illnesses, most commonly depression. The panic disorder commonly precedes the depression, but may follow it. If there are psychiatric comorbidities, treat each disorder.

Investigation

If there are concerns about the patient's physical health these should be investigated. Some patients present with respiratory symptoms such as a feeling of choking or having difficulty getting their breath. While they may clearly have a mental health problem a respiratory disorder should be excluded. Palpitations, tachycardia and chest pain may warrant an ECG. Difficulties in swallowing, a 'lump in the throat', gastrointestinal discomfort, constipation or diarrhoea may also require further investigation. Feelings of numbness with tingling and pins and needles may suggest a transient ischaemic attack, but bilateral symptoms, and the absence of focal signs normally point to a psychological cause.

The presence of symptoms which occur in multiple systems for brief periods of time without a change in consciousness, can usually suggest a panic attack or panic disorder rather than other disease. **These patients should not be over-investigated, or referred from specialist to specialist.** Recognise and diagnose panic disorder on its clinical criteria, not just as a diagnosis of exclusion.

Treatment of panic attacks

Any underlying problems should be treated. For example, if the patient has been drinking to excess and their panic attacks are triggered by either intoxication or withdrawal, reducing their intake of alcohol is central to treatment. Restricting caffeine intake or eliminating it from the diet may also help.

Spontaneous isolated panic attacks can be managed with simple lifestyle changes and stress management techniques. Education about the attack and the fact that it does not indicate a dire physical disease is important, as most isolated panic attacks will not recur. There is almost no role for pharmacotherapy in this case.

Treatment of panic disorder

Although there may be a slightly increased cardiovascular risk associated with panic disorder, for the vast majority of cases, the major disadvantages are the patient's emotional and behavioural responses to the symptoms. Cognitive behaviour therapy[2] is the treatment of choice, and helps many patients. It involves firstly educating the patient about panic disorder, its causes, outcome and management.

Teaching the patient relaxation techniques and how to deal with hyperventilation can help them to stop or control a panic attack. Rebreathing in a paper bag for someone who is hyperventilating, is rarely indicated in a general practice, or in emergency departments. The hyperventilation has usually settled by the time the patient presents. Encouragement to take slow deep measured breaths, using a watch or clock as a guide to respiratory rate, is a technique that patients can use anywhere. This is more socially acceptable than starting to breathe noisily into a paper bag when they fear an attack.

Cognitive behaviour therapy for panic disorder involves both cognitive and behavioural elements, but the cognitive elements may be more prominent. Behavioural elements may be more helpful with exposure and response prevention for situational panic. These behavioural treatments are useful in helping people gradually gain mastery of a feared situation and avoidance to dramatically free up their lives.

Drug treatment can be added to cognitive behaviour therapy. There is the suggestion that the response to this combined approach is better than either treatment alone and there may be a lower risk of relapse when medication is discontinued.

Pharmacotherapy[3]

Benzodiazepines

Alprazolam and clonazepam are effective for the acute therapy and the maintenance treatment of panic disorder. Effectiveness is probably not confined to these potent benzodiazepines and all benzodiazepines may be effective in high enough doses. They need to be taken continuously as the onset of panic is usually so fast that the worst of the panic attack is over before an acute dose of a benzodiazepine can be effective. As a result, there is the potential for problems with sedation, co-ordination, interaction with other sedatives and cognitive effects, which often impair the ability to benefit from psychological therapy. In part, the reduction in the effectiveness of psychological therapy caused by benzodiazepines, may be from a reduction in motivation. At the end of a course of therapy when the benzodiazepine is reduced, typically after some months of panic control, about a third of patients have difficulties in discontinuing the drugs. The dose should therefore be gradually tapered over a period as long as six months to a year. Despite the major limitations of benzodiazepines, they are uniquely effective for the acute control of panic disorder and agoraphobia.

The dose of a benzodiazepine to control agoraphobia is typically higher than that to control panic. Typical doses of alprazolam for controlling panic are 4 mg daily compared to 6 mg daily for agoraphobia.

Antidepressants

Several antidepressants have been used to treat panic disorder. As with depression, and unlike treatment with benzodiazepines, it is typically 2–4 weeks or even 6–8 weeks of treatment with an antidepressant before reduction in the frequency or severity of panic attacks is apparent. The response rate to antidepressants varies from 60–90%. Approximately 10–40% of patients (typically about 20–30%) will therefore need to be changed to another drug because of lack of benefit.[4] If there is no response

to the medication after 6–8 weeks the dose should be slowly reduced, and an alternative drug prescribed.

If antidepressants work they should be continued for a minimum of six months. An extended panic-free period gives the patient the confidence to start new activities in their lives and return to a normal balance.

Antidepressants should be gradually reduced before stopping them. This typically takes 2–4 weeks, or occasionally longer if a more rapid reduction results in discontinuation effects.

Tricyclic antidepressants

Imipramine and clomipramine have been widely studied in the treatment of panic disorder. Both are effective but poorly tolerated. This generally precludes their use in patients with panic disorder.

Monoamine oxidase inhibitors (MAOIs)

The irreversible non-selective inhibitors of monoamine oxidases A and B are effective, with phenelzine possibly being the most effective pharmacological treatment for panic disorder. Quite apart from the risk of dietary interactions, these medicines are not well tolerated when given in an effective dose. The recommended dose of phenelzine in the treatment of panic disorder is approximately 1 mg/kg/day, at which dose postural hypotension is a common disabling adverse event.

Newer antidepressants

All of the new antidepressants are probably effective in treating panic disorder. Their effectiveness seems to occur even in the absence of coexisting or comorbid depression. For some newer antidepressants there are extensive research data. Paroxetine has been approved for the treatment of panic disorder and the prevention of relapse. Sertraline is also approved in Australia for panic disorder. As with the tricyclics and MAOIs, the initial dose should be low and then gradually increased as these patients seem to experience more adverse effects when they start treatment. The final therapeutic dose which is required for the treatment of panic disorder is typically higher than the dose for the treatment of depression. For example, with paroxetine a common antidepressant dose is 20 mg/day while the dose is 40 mg/day or more for panic disorder. When treating agoraphobia with antidepressants, as with benzodiazepines, some patients need a higher dose than those with panic alone.

Summary

When a patient presents with panic disorder it is important to ascertain that this is not simply an isolated panic attack, or the consequences of maladaptive behaviours, or circumscribed stress. Brief counselling and some lifestyle changes could deal with such disorders. Panic disorder itself, with or without agoraphobia, can be usefully helped with cognitive behaviour therapy.

If symptoms are more marked, if the patient cannot relate to cognitive behaviour therapy, or if improvement is inadequate with the psychological approach alone, medications can be very helpful. Drugs can also be useful when there is not ready access to cognitive behaviour therapy. If immediate relief is essential, benzodiazepines may be uniquely effective, although they have the potential for long-term adverse consequences. In general, one of the newer antidepressants is more appropriate. There is little merit in combining a benzodiazepine with an antidepressant for these patients. This is because the panic disorder has usually been long-standing, the time taken to respond to the antidepressant is relatively short, and the potential adverse consequences of benzodiazepines are substantial. After a response most patients on pharmacotherapy would be expected to continue treatment for 6–12 months usually in conjunction with cognitive behaviour therapy.

If a patient does not respond, their diagnosis should be reviewed, and consideration given to specialist referral. A specialist referral may also be indicated for those who are severely incapacitated by their panic disorder.

NOTE

The diagnostic features which are highlighted in this paper have been adapted from DSM-IV, the American Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.[1] These are similar though not identical to diagnostic criteria for panic disorder in ICD-10 of the World Health Organization.[5] DSM-IV Criteria have been referred to in this paper as they are the most commonly used by psychiatrists in Australia.

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Associate Professor Tiller has been a consultant to, or conducted medical research sponsored in whole or in part by, producers of all the new antidepressants, as well as producers of tricyclic antidepressants, monoamine oxidase inhibitors and benzodiazepines.

Self-test questions

The following statements are either true or false (answers on page 139)

5. Cognitive behaviour therapy is the treatment of choice for panic disorder.
6. New antidepressants usually need to be given in doses which are higher for panic disorder than the doses needed to treat depression.

Treatment of panic disorder: a personal experience

Editor's note:

Garry McDonald is one of Australia's best known comedians. He has successfully overcome problems with panic disorder which at one stage threatened his career.

AP: *How did you realise you had a problem?*

GM: I have been an anxious person for many years, but did not know what the problem was. In 1992 I became severely stressed when the director of a play I was appearing in announced that it would be presented to an audience after only 10 days of rehearsals. This was too soon for me to cope with and I just wanted to run away. As it turned out I had no need to panic. Rehearsals got so far behind that only Act 1 was presented to the invited audience, and my character only appeared in Act 2.

AP: *How was your life affected?*

GM: I had a low opinion of myself. I became fearful of not reaching the standard that people expected of me in a performance, or the standards I had set for myself. My mind was racing with negative thoughts and I was afraid of making a fool of myself.

When I was having an attack, I would become tongue-tied and stammer. My sleep was reduced. I could feel like this for days.

Worrying about having another attack made me change some of my activities. Anxiety made me want to avoid going to parties. I was worried that I would be boring. If I went to a party, I almost immediately had to go into the toilet because of my anxiety.

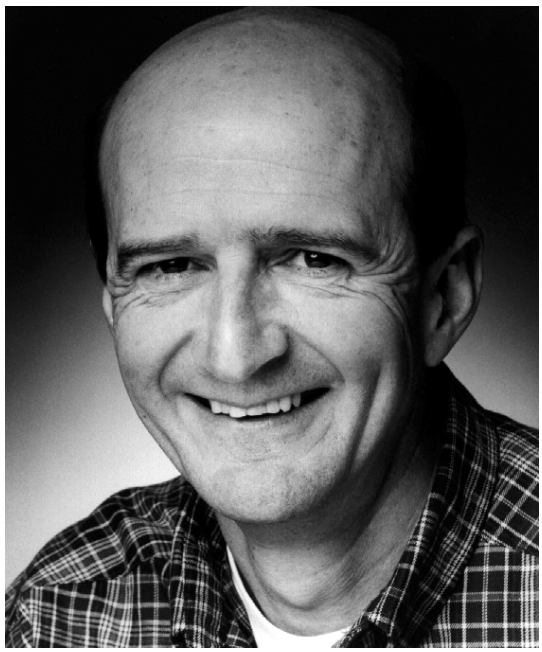
AP: *Did the people around you realise there was a problem or did they just expect you to 'pull yourself together'?*

GM: People expect you to perform. They do not expect you to throw in the towel. I was having trouble standing up for what I knew was right for me. At one stage someone threatened to sue me if I did not perform as they wanted.

AP: *When did you seek help?*

GM: Although I had some psychological therapy, my breakdown was a real wake-up call. In 1993 I descended into depression. I felt ashamed and unable to concentrate. Suicidal thoughts really frightened me. Although I felt dreadful, by evening I was able to manage to pull together some kind of a performance in my show, then I would spiral down again.

Somebody made me go and talk to my general practitioner. I remember sitting in the gutter waiting to see the doctor. I was then referred for a psychiatric opinion.



AP: *What treatment did you have?*

GM: My depression was treated with drugs such as dothiepin and moclobemide.

For my anxiety I have had alprazolam and buspirone. The problem with these drugs is that they suppress the problem. They hold down your anxiety, they do not make the problem go away.

Buspirone caused me a few problems. It made me disinhibited and I would say strange things at the most inappropriate times.

AP: *Which was the most effective treatment?*

GM: Bronwyn Fox sent me a copy of her book 'Anxiety attack: don't panic'.* Reading that book was a revelation. For the first time I realised that I had a recognised disorder. This was a huge turning point and I arranged to see a specialist in the disorder.

I had eight sessions of cognitive behaviour therapy. This was very effective and taught me how to recognise and challenge my negative thoughts.

The skills you learn in cognitive behaviour therapy can be used to reduce relapses. About 18 months after my therapy I began to feel frantic and nervous again. I was reassured that this was just a temporary setback. After just one visit to the specialist I was again able to control my thoughts. I now try to practise these skills all the time.

* Melbourne: Longman Cheshire; 1993. Currently out of print.

AP: *How could health professionals be more helpful?*

GM: Telling the patient that they have panic disorder is not enough. You need to describe the symptoms to the person. They will be greatly relieved that their symptoms are being recognised. Providing an information leaflet, which includes a list of typical symptoms, can also be helpful.

The person should be reassured that there is a very successful treatment, but it requires their co-operation. There is no magic pill. If the patient is referred, it is important that they are seen by someone skilled in cognitive behaviour therapy.

AP: *What would you advise people with similar symptoms to do?*

GM: Australians have a tendency to put themselves down. This can result in people with anxiety blaming themselves and not doing anything about it. If people cannot function because of panic they need to go and see a specialist in anxiety disorders.

People have to be willing to work for themselves as part of cognitive behaviour therapy. Once they have learned the technique, people will realise that it works quickly and with practice they will be able to master their fears.

They should not expect to jump straight to their goal. With cognitive behaviour therapy, the journey to that goal is just as important as the outcome. Making your own discoveries on the way is empowering.

People should be aware that if they have had panic disorder for 20 years it is likely to recur. If they keep practising how to challenge worrying thoughts they will retain control.

Cognitive behaviour therapy has given me a sense of being stronger because I am looking after myself without the need for drugs.

Patient support organisations

Panic and anxiety disorders associations/ foundations

Community organisations in several states provide counselling, education and support to people living with panic and anxiety disorders. Services include telephone counselling, support groups, workshops, books and tapes, and a wide range of programs.

Contacts

A.C.T.

Anxiety Support Group
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New South Wales

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The effect of antifungal creams and pessaries on latex

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Index words: adverse effects, contraception.

(Aust Prescr 2000;23:129)

Introduction

One of the cornerstones of safer sex programs is correct condom use to prevent both unplanned pregnancies and the spread of sexually transmissible infections, including HIV/AIDS. However, many people are unaware that commonly used products may have an adverse effect on the protective properties of barrier contraceptives made of latex.

The products most likely to come into contact with condoms or diaphragms are personal lubricants, spermicidal preparations, personal hygiene products, hormonal preparations, acidifying agents, and preparations used for the treatment of the common vaginal infections, especially candida. It is possible of course, that any dermatological product used on the genital area in both sexes, may have an effect on latex rubber.

Research

The London International Group, a major manufacturer of condoms, reported the deleterious effects of mineral and vegetable oils on condoms in 1988.[1] The company tested all the leading brands of condoms and found that baby oil, petroleum jelly and corn oil all caused major reductions in tensile strength, elongation at break, burst pressure and burst volume. Water based lubricants did not adversely affect the physical properties of condoms.

Mineral oil products can damage latex rubber condoms within 60 seconds, causing defects which may allow the passage of sperm or micro-organisms.[2] There is no deterioration with glycerol, a frequent component of hand lotions and personal lubricants or with aqueous nonoxynol–9, the most commonly used spermicide.

Although more than 10 years has passed since this information was published, harmful products are still available without sufficient warnings for the health professionals who may prescribe them or for the consumers who may use them. Current formulations of antifungal drugs can damage latex. The imidazole antifungals themselves are not thought to be incompatible with latex, but the various mineral and vegetable oils which are used as excipients in the pessary or cream may damage latex. These warnings do not apply to polyurethane condoms.

There has been very little independent research on the topic[3,4,5], but the New Zealand Ministry of Health has published a report on the interaction with latex.[6]

Conclusion

Under international standards for condoms, the packaging or leaflet must advise consumers to avoid the use of oil-based lubricants and to consult a doctor or pharmacist about the compatibility of topical medicines applied in the genital area. However, this advice is meaningless unless such information is available. Unless the manufacturers have tested the compatibility of their products, it should be assumed that topical antifungal medications can damage the latex in barrier contraceptives.

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EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Bisphosphonates – mechanisms of action

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SYNOPSIS

The bisphosphonates inhibit the resorption of bone by osteoclasts and may have an effect on osteoblasts. They are structurally similar to pyrophosphate, a normal product of human metabolism. This structure gives the drugs a high affinity for bone and they probably remain in bone for many years. A high affinity for hydroxyapatite enables radiolabelled bisphosphonates to be used in bone scanning. The bisphosphonates are effective in the treatment of diseases of increased resorption.

Index words: bone metabolism, pharmacokinetics.

(Aust Prescr 2000;23:130–2)

Introduction

Pyrophosphate is a normal by-product of metabolism. Bisphosphonates are analogues of pyrophosphate which have potent inhibitory effects on bone resorption. They are effective drugs in bone disorders characterised by increased bone resorption, such as Paget's disease, osteoporosis, hypercalcaemia of cancer, multiple myeloma and bony metastases. The bisphosphonates adsorb very effectively to hydroxyapatite, the crystalline form of calcium and phosphate in bone. This makes them a useful component in bone scanning agents.

The pharmacological actions of all bisphosphonates are similar, but the marketing strategies of the pharmaceutical industry have directed different compounds to the treatment of particular disorders of bone resorption.

Chemistry of bisphosphonates

Pyrophosphate is produced by many anabolic processes. It is rapidly hydrolysed to its two constituent phosphate groups. If the linking oxygen atom in the pyrophosphate molecule is replaced by a carbon atom, a bisphosphonate is formed (Fig. 1). These analogues are completely resistant to hydrolysis and are chemically extremely stable. Like pyrophosphate, the bisphosphonates bind to the hydroxyapatite crystals of bone and prevent both their growth and their dissolution.

Structure-activity relationships

The biological activity of the bisphosphonates can be modified by altering the structure of the two side chains on the carbon atom. The binding to bone mineral depends upon the P–C–P structure and is enhanced by including a hydroxyl group at R_1.

The structure and three-dimensional configuration of the R_2 side chain determines the cellular effects of bisphosphonates, and their relative efficacies as inhibitors of bone resorption. Each bisphosphonate has its own profile of activity, determined by its unique side chain (Fig. 2).

After the promise shown in the early clinical use of etidronate and clodronate, newer bisphosphonates were synthesised, containing a primary nitrogen atom in an alkyl chain (pamidronate, alendronate). This increased the antiresorptive potency by up to one hundred times. Later modifications of the R_2 side chain to produce compounds containing tertiary nitrogen groups, such as ibandronate and olpadronate, further increased potency. The most potent bisphosphonates to date, risedronate and zoledronate, contain a nitrogen atom within a heterocyclic ring. They are up to 10 000 times more potent than etidronate in some experimental systems. Although the structure of the R_2 side chain is the major determinant of antiresorptive potency, both phosphonate groups are required for the drugs to be pharmacologically active.

Clinical pharmacology

Bisphosphonates are characterised by poor intestinal absorption but highly selective localisation and prolonged storage in bone. Due to their stability the bisphosphonates are absorbed, stored and excreted unchanged.

Absorption

Intestinal absorption is very low and variable (1–10%). It takes place by passive diffusion in the stomach and upper small intestine, and is reduced if the drug is given with calcium or iron. Bisphosphonates are therefore never given at meal times or with dairy products.

Fig. 1

Chemical structure of pyrophosphate and bisphosphonates

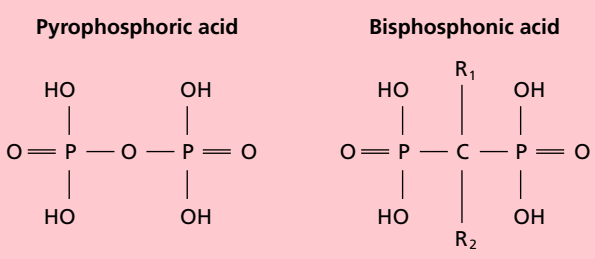
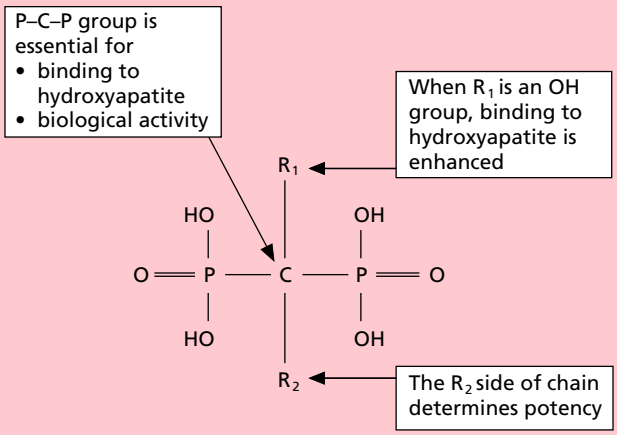


Fig. 2

Structure-activity relationships of bisphosphonates

The binding to hydroxyapatite and the biological activity of bisphosphonates depends on the P–C–P group and the structure of the R_1 and R_2 side chains. (Modified with permission from Russell et al, 1999).



Bisphosphonate	R_1 side chain	R_2 side chain
Etidronate*	OH	CH_3
Clodronate*	Cl	Cl
Pamidronate*	OH	$CH_2CH_2NH_2$
Alendronate*	OH	$(CH_2)_3NH_2$
Risedronate*	OH	CH_2–3–pyridine
Tiludronate*	H	CH_2–S–phenyl-Cl
Ibandronate*	OH	$CH_2CH_2N(CH_3)$(pentyl)
Zoledronate	OH	CH_2–imidazole
YH529	OH	CH_2–2–imidazo-pyridinyl
Incadronate (YM175)	H	N–(cyclo-heptyl)
Olpadronate	OH	$CH_2CH_2N(CH_3)_2$
Neridronate	OH	$(CH_2)_5NH_2$
EB-1053	OH	CH_2–1–pyrrolidinyl

* Indicates bisphosphonates already approved for one or more indications in one or more countries

Clearance

With 20–80% of absorbed bisphosphonate rapidly taken up by bone and the remainder rapidly excreted in the urine, the half-life of bisphosphonates in the circulation is short (0.5–2 hours). Deposition in bone takes place at sites of bone formation and resorption. This property is made use of in nuclear medicine when bisphosphonate labelled with technetium 99 is used in bone scanning.

After being taken up by bone and producing an effect, bisphosphonates are stored in bone. The half-life appears to be very long (probably up to several years) because of this skeletal storage. It is this prolonged skeletal retention that explains why single or short courses of intravenous injections can be effective for a long time in patients with diseases which have a high turnover of bone, such as Paget's disease. Bisphosphonates stored deep in bone are probably inactive, but clearly significant amounts can be released in the resorptive process.

Intravenous administration

The poor and variable absorption, prolonged effects with storage in bone, together with the development of new, highly potent bisphosphonates, can explain why intermittent intravenous administration is efficacious in disorders of increased bone resorption. Although successful trials of bisphosphonates in osteoporosis have used oral formulations, a current trial is studying three-monthly intravenous injections of a potent member of this class.

Intermittent intravenous infusion is a successful and convenient means of treating hypercalcaemia of cancer, multiple myeloma, or bone metastases from solid tumours. With the ever increasing potency of bisphosphonates, single rapid intravenous injection is now being studied as an alternative to the less convenient and prolonged infusions.

Mechanisms of action of bisphosphonates

Ectopic calcification

Pyrophosphate inhibits ectopic calcification *in vivo*, and this was one of the earliest observed actions of bisphosphonates.[1] Etidronate remains the bisphosphonate most likely to inhibit calcification when given experimentally or clinically. The concentrations of etidronate required to inhibit bone resorption are similar to those which prevent calcification. This has the disadvantage that significant undermineralisation of bone can occur if etidronate is not administered with care in limited dosage. As new bisphosphonate analogues came along, the alterations to the carbon side chains had the effect of progressively increasing their potency as inhibitors of bone resorption, so that they have essentially no effect on calcification.

Remodelling

When bisphosphonates are given to growing rats, remodelling at the ends of long bones is reduced and an abnormal shape results. This effect is currently used as a model to estimate the potency of new compounds.

Resorption

Bisphosphonates are very effective inhibitors of bone resorption *in vivo* and *in vitro*.[2] They act rapidly, and the maximum effect and its duration are related to the dose. In organ cultures of bone, whatever treatment is used to enhance bone resorption can be inhibited by bisphosphonates. In many of these organ culture systems the structure-activity relationships seen among the bisphosphonates *in vitro* are preserved in *in vivo* studies in the rat. When the resorption of isolated osteoclasts is studied on bone or dentine slices, this too is inhibited by bisphosphonates. The bisphosphonates appear to be taken up by osteoclasts active upon bone, and to inhibit crucial intracellular processes.

Osteoclastic and osteoblastic activity

Bisphosphonates may not act solely through direct actions on osteoclasts. They can inhibit the activity and proliferation of osteoblasts *in vitro*. Osteoblasts are important stimulators of osteoclast formation and activity, and many factors that stimulate bone resorption do so through an effect on the osteoblast. One of the possible mechanisms of bisphosphonate action is to stimulate the osteoblast to produce inhibitor(s) of osteoclast formation and therefore of bone resorption.[3]

New insights into molecular mechanisms of bisphosphonate action

The molecular mechanisms by which these effects on osteoclasts are produced are currently being unravelled.[4] The first pyrophosphate-like bisphosphonates (such as etidronate and clodronate) are incorporated into adenosine triphosphate (ATP), a source of energy in the cell. The resulting compounds are resistant to hydrolysis and their accumulation leads to the death of the osteoclast.[5]

It is not known whether the nitrogen-containing bisphosphonates are also incorporated into ATP. They probably are not, since their cellular effects are produced at concentrations much lower than those of the first generation bisphosphonates. The more potent nitrogen-containing bisphosphonates have been recently shown to inhibit enzymes in the mevalonate pathway.[6] This biosynthetic pathway is responsible for the production of cholesterol and also of isoprenoid compounds (farnesyldiphosphate and geranylgeranyldiphosphate) which are required for the post-translational modification (prenylation) of small GTPases. These small GTPases are signalling proteins that regulate a number of cell processes such as membrane ruffling, cytoskeletal organisation and trafficking of vesicles, which are required for osteoclast function.

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Self-test questions

The following statements are either true or false (answers on page 139)

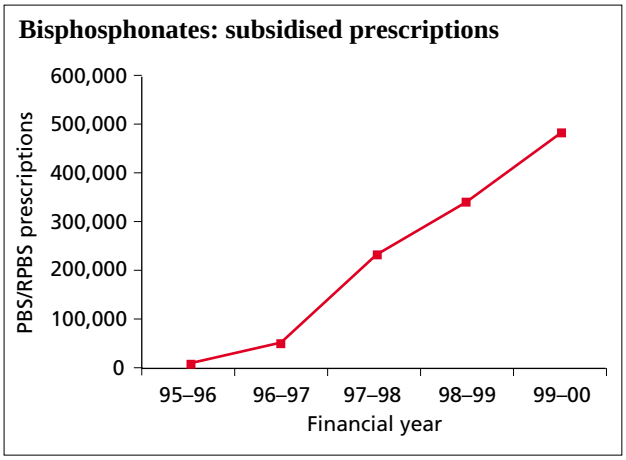
7. Etidronate can interfere with bone mineralisation as well as inhibit resorption.
8. The similarity of the bisphosphonate molecules means there is little variation in their potency.

Subsidised prescriptions for bisphosphonates

The bisphosphonates are available through the Pharmaceutical Benefits Scheme and the Repatriation Pharmaceutical Benefits Scheme. Their use is increasing, with alendronate accounting for most of the prescriptions.

Bisphosphonates: subsidised prescriptions 1999–2000

Alendronate	428,912
Clodronate	5,230
Etidronate	1,932
Pamidronate	1,008
Calcium and etidronate	43,441
Tiludronate	3,022
Total	**483,545**



Data supplied by the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Bisphosphonates – clinical applications in osteoporosis

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SYNOPSIS

Bisphosphonates are effective treatments for the prevention and treatment of osteoporosis. In particular, alendronate and risedronate increase bone mineral density and reduce the spinal fracture rate to approximately 50% of that in controls, within one year. A less potent, 'first generation' bisphosphonate, etidronate, has also shown anti-fracture efficacy. Alendronate also reduces fracture rates at the hip and other non-vertebral sites in osteoporotic postmenopausal women. Pamidronate is available for intravenous therapy and ibandronate and zoledronate may also become available for injection. Current research studies are examining new compounds, treatment regimens and the combination of bisphosphonates with other drugs such as oestrogen, which currently remains the first-line therapy for the prevention and treatment of osteoporosis in women.

Index words: bone mineral density, fractures, etidronate, alendronate, risedronate.

(Aust Prescr 2000;23:133–6)

Introduction

Bisphosphonates inhibit bone resorption. The structure of the R_2 side chain determines the potency of bisphosphonates (see 'Bisphosphonates – mechanisms of action' Aust Prescr 2000;23:130–2). Differences in the potency of the different bisphosphonates can be accommodated by the use of appropriate doses. Their effect on osteoclasts makes the bisphosphonates useful in several conditions including osteoporosis where bone metabolism is abnormal.

In selecting women for treatment, the presence of a fragility fracture and/or low bone mineral density (BMD) are the best independent predictors of future fracture risk. In elderly women, the presence of a fragility fracture is the best predictor of future fracture risk. In perimenopausal women the harm: benefit ratio is less clear. Hormone replacement therapy may be the preferred treatment for perimenopausal women with a fragility fracture or low BMD. It remains the first-line therapy for the prevention and treatment of osteoporosis.

Hip fracture is the major clinical problem in osteoporosis and low BMD at the femoral neck is a good predictor of future hip fracture.[1] Only vitamin D and calcium supplementation in the institutionalised elderly, or alendronate therapy in postmenopausal women with osteoporosis have been demonstrated to reduce hip fractures.

Evidence of efficacy in postmenopausal osteoporosis

Etidronate

The first randomised controlled trials of bisphosphonates in postmenopausal osteoporosis used cyclical etidronate (400 mg/day for two weeks, then repeated every three months). This treatment resulted in increases in spinal BMD of 4–5% and a 50% reduction of vertebral fractures in the first and second year of these three-year studies. However, after three years, no reduction in vertebral fractures was seen.[2] These trials did not study hip or non-vertebral fractures, however, a subsequent large retrospective cohort study found that these fractures were significantly reduced by etidronate.[3]

Alendronate

Alendronate is a more potent bisphosphonate than etidronate. A number of large studies have found that alendronate can prevent further fractures in women with postmenopausal osteoporosis and at least one vertebral fracture.[4,5]

Significant increases in spinal BMD occur as early as the duration of one remodelling cycle (about three months) in women with low BMD. Biochemical markers of bone resorption are reduced to levels seen in premenopausal women after only four weeks of treatment. Spinal and femoral neck BMD increase by about 8% and 5% after three years of therapy.

The absolute and relative reductions in fracture risk (see box) vary with the fracture site in women with postmenopausal

Definitions of relative risk reduction and number needed to treat to prevent one incident

$$\text{Relative risk reduction} = \frac{\text{placebo incidence} - \text{treatment incidence}}{\text{placebo incidence}}$$

$$\text{Number needed to treat} = \frac{100}{\text{placebo incidence} - \text{treatment incidence}}$$

osteoporosis and at least one vertebral fracture. In addition to reducing the relative risk of vertebral fractures by 47%, alendronate reduces hip fractures by 28% and non-vertebral fractures by 51%. Forearm fractures are also reduced by 48%. For women with a history of vertebral fracture, 16 need to be treated for five years to prevent one further vertebral fracture. To prevent one hip fracture the number needed to treat (NNT) is 91 (Table 1).

The lower (or more negative) the T-score[6], the greater is the deficit in bone density. For postmenopausal women who do not have a vertebral fracture, the T-score at which treatment can be recommended is not clear. Alendronate was most efficacious in women who had a baseline T-score at the femoral neck which was more negative than –2.5. In these women there was a 36% reduction in clinical fractures (NNT = 15) and a 56% reduction in hip fracture (NNT = 81) (Table 2). This compares with an NNT of 10 for women with one pre-existing vertebral fracture and low femoral neck BMD. The duration of treatment probably needs to be greater than four years in postmenopausal women with low bone density alone. Women who have increases in BMD of greater than 3% after one or two years have the greatest reduction in fractures. Alendronate showed no efficacy in women with a BMD T-score[6] that was more positive than –2.5. In this group, there was an increase in forearm fractures.

Quantitative bone histomorphometry does not show that women treated with alendronate have abnormal mineralisation. Their BMD decreases, but not to pretreatment levels, in the first two years after stopping alendronate.

Oestrogen and alendronate

Some women taking hormone replacement therapy may continue to be at risk of fractures because of a low BMD or other factors. There are now data from at least two studies showing that the addition of alendronate to oestrogen can result in further increases in the BMD of these women. After 12 months, alendronate increased the BMD by up to an additional 2.6% in the spine and 2.2% in the femoral trochanter. However, the additional increase of approximately 1% in the BMD of the femoral neck was not significant[7] and there are no data to show that adding alendronate to oestrogen further reduces fracture rates.

Risedronate

In postmenopausal women with at least one vertebral fracture risedronate increases BMD. Increases were 4.3% greater than placebo in the lumbar spine, 2.8% in the femoral neck and 1.6% in the shaft of the radius.[8] Vertebral fractures were decreased by 41% after three years. The absolute reduction in fracture risk was 5%. Non-vertebral fractures were decreased by 39% (3.2% absolute risk decrease). The NNT to prevent a fracture was similar to that of alendronate (Table 1).

Pamidronate

For patients who are intolerant of oral bisphosphonates, pamidronate is the only intravenous bisphosphonate currently available. A dose of 30 mg intravenously every three months increases spinal BMD by 6.4% and BMD in the hip by 4.1%, over approximately eight months. The optimal duration of treatment is unknown and no fracture data are available. BMD falls but does not return to baseline levels after stopping pamidronate.

Selection of patients for bisphosphonate therapy

When deciding to use a bisphosphonate, the age and menopausal status of the woman should be considered in

Table 1

Number of women with a baseline spinal fracture who need to be treated to prevent one fracture

Category	*NNT to prevent one radiological vertebral fracture*	*NNT to prevent one clinical fracture*	*NNT to prevent one hip fracture*
Alendronate (5 years)			
Baseline bone density at femoral neck			
T-score ≤ –3.0 approximately (<0.59 g/cm^2)	7	10	
T-score ≥ –3.0 approximately (>0.59 g/cm^2)	13	30	
Number of baseline vertebral fractures			
1	16	26	91
2	4	6	
Age			
<75 yrs	9	13	
>75 yrs	8	15	
Risedronate (3 years)			
Number of baseline vertebral fractures			
At least 1	20	31	

NNT = Number needed to treat

addition to the severity of her osteoporosis. There are no data showing anti-fracture efficacy of bisphosphonates in premenopausal women with osteoporosis. Peri- or early postmenopausal women may prefer treatment with oestrogen to reduce symptoms of oestrogen deficiency. Postmenopausal women who are more than 75 years old are less likely to accept hormone replacement therapy. It should be noted that bisphosphonates are equally efficacious in younger and older postmenopausal women and that it is 'never too late' to prevent a fracture.

Dosing

Adequate calcium and vitamin D nutrition in the diet are prerequisites for treatment with bisphophonates. All the studies of bisphosphonates have included at least 600 mg of calcium so all patients should take supplemental calcium with their bisphosphonate. Measures to minimise falls, including regular exercise to maintain balance, are also important to prevent fractures.

The bisphosphonates have very low solubility and low oral bioavailability (approximately 0.5%). Patients should only take them with plain tap water at least half an hour before any food or fluid. Absorption is particularly reduced by antacids and calcium supplements.

Appropriate dosing is critical to ensure anti-fracture efficacy. Too low a dose may reduce anti-fracture efficacy as seen in clinical trials of tiludronate. High doses, in animal studies, impaired repair of bone microfracture damage and caused increased bone fragility.

Adverse effects

Bisphosphonates can cause gastrointestinal upsets. The incidence of moderate to severe upper gastrointestinal events with risedronate[8] is similar to placebo as it was in the clinical studies involving alendronate. However, 35% of subjects in the risedronate trial had ongoing, or a history of, gastrointestinal disorders on entry to the study. In the alendronate studies, subjects with specific gastrointestinal disorders were excluded from the study. This supports the gastrointestinal safety of risedronate, but it will require validation by post-marketing studies.

Although there was no increase in upper gastrointestinal adverse events in randomised clinical studies[4,5], alendronate may cause upper gastrointestinal irritation. Oesophagitis and oesophageal ulceration are particularly concerning. They probably result from gastro-oesophageal reflux and acidification of the oesophagus, causing the release of alendronic acid. To avoid this, patients should take alendronate with a glass of water at least half an hour before a meal and remain upright for one hour. Alendronate may also cause oral ulcerations if it is inadvertently sucked or chewed.

Bisphosphonates can also alter electrolyte balance. The drugs should therefore be used with caution if renal function is impaired.

Monitoring of treatment and treatment failure

Treatment with bisphosphonates is currently best monitored by bone densitometry. There is growing evidence that a measurement at two years after starting therapy is a better indicator of response than a measurement at one year. Currently tests for bone turnover lack sensitivity in the individual patient.

Patients may fail treatment with bisphosphonates and continue to sustain fragility fractures. The decision to stop the bisphosphonate will depend on the BMD and the timing of the fracture in relation to the start of therapy.

Most of the anti-fracture efficacy of bisphosphonates occurs within one to two years of starting therapy. To maintain this benefit, treatment may need to continue for at least five years. If the patient's bone density does not respond during the first two years of therapy, or if she continues to sustain fractures, another treatment should be considered.

Treatment with a bisphosphonate need not stop following a fracture. There is no evidence in humans to suggest that fracture healing is impaired by bisphosphonates.

Other possible indications for bisphosphonates

Osteoporosis in men

Retrospective cohort studies have suggested that etidronate may be an effective treatment for osteoporosis in men. Alendronate has been studied in a recently published

Table 2

Number of women with low bone density who need to be treated for four years to prevent one fracture

Category	*NNT to prevent one clinical fracture*	*NNT to prevent one hip fracture*
Alendronate		
Baseline bone density at femoral neck		
T-score ≤ -2.5	15	81
T-score ≥ -2.0	30	No effect

NNT = Number needed to treat

randomised, controlled trial of men with primary osteoporosis or osteoporosis related to hypogonadism. There were increases in the BMD of the spine (7.1%), femoral neck (2.5%) and femoral trochanter (4.4%). Height loss was prevented by alendronate and there was also a reduction in the incidence of radiographic vertebral fractures.[9]

Glucocorticoid-induced osteoporosis

Bisphosphonates may prevent glucocorticoid-induced osteoblast and osteocyte apoptosis. Two large multicentre trials of etidronate and alendronate in glucocorticoid-induced osteoporosis show that both are effective at increasing spinal BMD at 12 months.[10,11] Only alendronate increased BMD in the femoral neck, but both drugs significantly increased the BMD in the femoral trochanter. There was a non-significant trend for a reduction in vertebral fractures in postmenopausal women in both studies.

Risedronate increases BMD.[12] A daily dose of 5 mg has also recently been reported to significantly decrease vertebral fractures by 70% in patients with glucocorticoid-induced osteoporosis.[13]

In a preliminary uncontrolled study in glucocorticoid-induced osteoporosis, pamidronate significantly increased spinal BMD by 4.7% at one year. There was no change in hip BMD.

By comparison, calcitriol therapy prevents spinal bone loss in glucocorticoid-induced osteoporosis. However, it does not prevent bone loss from the femoral neck, nor are there anti-fracture efficacy data.

Prevention of postmenopausal bone loss

Women with low BMD who are either intolerant of or unwilling to accept therapy with either oestrogen or raloxifene (see 'New drugs' Aust Prescr 1999;22:96–7) would be suitable for treatment with a bisphosphonate. Bisphosphonates have been shown to prevent postmenopausal bone loss. In early postmenopausal women without osteoporosis, alendronate prevents bone loss at all sites except the forearm. In similar women risedronate increases the BMD of the spine and hip, and decreases bone turnover.[14] In studies of these drugs fracture reduction was not an end-point.

Future directions

Current clinical studies are examining the comparison of intravenous and oral dosing, and the optimal frequency and duration of oral dosing. In the future there may be additional indications for this class of drugs as they affect metabolic pathways throughout the body, not just in bone cells.

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Self-test questions

The following statements are either true or false (answers on page 139)

9. Bisphosphonates should be taken after food to reduce the risk of oesophagitis.
10. Alendronate may increase forearm fractures in some women with low bone density.

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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Ancestim

Stemgen (Amgen Australia)

vials containing 1.875 mg as powder for reconstitution

Approved indication: stem cell transplant

Australian Medicines Handbook Section 14.2

Some cancer treatments require the patient to have an autologous stem cell transplant after chemotherapy. The cells for transplant are collected before treatment. Granulocyte colony stimulating factor (G-CSF) is often used to increase the number of circulating haemopoietic precursor cells available for collection. Ancestim has been developed for use with G-CSF to further increase the number of cells which can be harvested for transplant. It is a recombinant form of human stem cell factor, the protein which normally stimulates stem cell production.

Ancestim and G-CSF have been compared with G-CSF alone in 205 women with breast cancer. The objective was to collect a target number (5×10^6/kg) of $CD34^+$ cells. Treatment continued until the target was reached or aphoresis had been carried out five times. The proportion of the patients given the combination who reached the target was 63% compared with only 47% of the patients given G-CSF alone. Fewer collections were needed in the combination group; a median of four aphoresis procedures was required.

Everyone prescribed ancestim must be given a bronchodilator and H_1 and H_2 antagonists before each subcutaneous injection. There is a risk that ancestim will stimulate mast cells and cause allergic reactions. Nearly all patients will experience an injection site reaction. Other common adverse effects include respiratory symptoms, paraesthesia and rashes.

The stimulant effect of ancestim may promote the growth of tumour cells. Particular caution is needed if the drug is considered for use in patients with myeloid malignancies, melanomas, or small cell lung cancers.

While ancestim has achieved its targets for efficacy, there is little information on its benefits for the patients. Although the patients may be spared additional aphoresis, it is unknown if adding ancestim to G-CSF will ultimately improve end-points such as survival.

Desirudin

Revasc (Aventis Pharma)

vials containing 15 mg as lyophilised powder

Approved indication: prevention of thromboembolism

Australian Medicines Handbook Section 7.1

The influence of the leech on medical practice seems set to continue into the next century following the approval of desirudin. This is a recombinant product with a structure that is almost identical to hirudin, an anticoagulant found in the saliva of *Hirudo medicinalis*. It has been approved for the prevention of thromboembolism after hip replacement surgery.

Desirudin is reconstituted with mannitol and injected subcutaneously no more than 30 minutes before elective hip replacement. Twice daily injections continue for 9–12 days until the patient is walking. The injections should be rotated through at least four different sites.

The maximum plasma concentrations occur within three hours of injection. Desirudin is partly metabolised before excretion. Approximately half the dose is excreted unchanged in the urine. The APTT should be monitored in patients with impaired hepatic or renal function.

Desirudin acts by specifically inhibiting thrombin. As desirudin can inactivate thrombin bound to fibrin, it has a potential advantage over heparin which also has a less specific action.

A double-blind trial has compared subcutaneous heparin and desirudin in 1119 patients having hip surgery.[1] Patients given the dose of desirudin recommended for use in Australia (15 mg twice daily) were significantly less likely to develop deep vein thrombosis than those given unfractionated heparin (18.4% versus 34.2%). The respective frequencies of proximal thrombosis were 3.1% versus 19.6%. The frequency of bleeding complications was similar in both groups.

Episodes of bleeding occurred in 13% of patients given desirudin in clinical trials. There is no antidote. Other adverse effects include haematoma, injection site masses and secretion from the wound.

While hirudin is more effective than subcutaneous unfractionated heparin, its role in clinical practice is not yet clear. There needs to be a comparison between hirudin and other approaches to preventing thrombosis such as adjusted dose intravenous heparin or subcutaneous low molecular weight heparin.

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Rofecoxib

Vioxx (Merck Sharp & Dohme)

12.5 mg and 25 mg tablets

Approved indication: osteoarthritis

Australian Medicines Handbook Section 15.1

Rofecoxib is the second inhibitor of cyclo-oxygenase 2 (COX-2) to be marketed in Australia. Unlike celecoxib

(see 'New drugs' Aust Prescr 1999;22:147-8), in Australia its approval is limited to osteoarthritis.

Compared to celecoxib, rofecoxib is more selective for COX-2. It therefore has little effect on the synthesis of prostaglandins in the gut. Rofecoxib has a half-life of 17 hours and can be taken once a day. Each dose is well absorbed resulting in a bioavailability of 93%. The drug is metabolised in the liver and most of the metabolites are excreted in the urine.

In clinical trials rofecoxib has reduced joint pain in osteoarthritis more than placebo. It also improves stiffness and joint function. During a six-week study the efficacy of 12.5 mg or 25 mg rofecoxib daily was similar to that of 800 mg ibuprofen three times a day. In a year-long comparison, rofecoxib was comparable to 50 mg diclofenac three times a day.

Studies which used endoscopy to look for gastroduodenal ulcers, found that rofecoxib 25 mg or 50 mg/day caused significantly fewer ulcers than ibuprofen 2400 mg/day during 24 weeks of treatment. However, gastrointestinal bleeding can still occur. Among the 3357 patients treated with rofecoxib in clinical trials, three experienced a haemorrhage. This incidence is lower than that seen with non-steroidal anti-inflammatory drugs, but a long-term study of comparative safety has not been performed.

In the clinical trials of rofecoxib the most commonly reported adverse effects were headache, diarrhoea and abdominal pain. Some patients will have increased blood pressure or fluid retention so extra caution is required if a patient has heart failure or reduced renal function. Approximately 1% of patients will develop abnormal liver function tests. Rofecoxib interacts with several drugs including warfarin and ACE inhibitors.

For patients with osteoarthritis, who cannot be managed with other analgesics, prescribers now have a choice between celecoxib and rofecoxib. Although rofecoxib is more selective it may not be safer. Until evidence of long-term safety and efficacy is available the choice of treatment will be influenced by the cost of the drugs.

Verteporfin

Visudyne (CIBA Vision)

vials containing 15 mg as powder for reconstitution

Approved indication: macular degeneration

Australian Medicines Handbook Section 11.4

As people grow older they can develop macular degeneration. This is caused by a failure to clear the products of retinal metabolism. In some patients this prompts vessels to grow from the choroid into the retina. If these abnormal vessels leak or bleed, the resulting scar reduces the patient's central vision. The only treatment is laser photocoagulation, but this has several limitations.[1]

Verteporfin is a drug treatment which aims to destroy new blood vessels affecting the retina. As verteporfin is not very soluble it has to be formulated in a liposomal delivery system. This is diluted and given as an infusion over 10 minutes. Verteporfin is transported around the body by lipoproteins.

To activate the drug a non-thermal laser light is shone into the affected eye 15 minutes after the infusion begins. An exposure of 83 seconds generates reactive oxygen radicals which may cause damage to vascular endothelium. This can lead to the occlusion of the abnormal vessels.

In double-blind trials involving 609 patients, 402 eyes were given photodynamic therapy with verteporfin and 207 eyes were treated with a placebo. The treatments were repeated every three months if fluoroscein angiography revealed leaking vessels. After one year the visual acuity and angiographic assessments were significantly better in the eyes exposed to verteporfin. The loss of visual acuity was particularly reduced in a sub-group of patients with classic choroidal revascularisation. Only 33% of this group had a substantial loss of vision compared with 61% of the placebo group.[2] Verteporfin has only been approved for use in patients with predominantly classic subfoveal choroidal neovascularisation.

There were few serious adverse reactions to verteporfin. Compared to placebo, there were more complaints about visual disturbance, injection site reactions and nausea.[2] Although verteporfin has a half-life of 5-6 hours, patients are advised to remain indoors for five days after treatment. This is because they become photosensitive after treatment. Although verteporfin may tend to accumulate in abnormal vessels it can also enter the retina. This could result in retinal damage when the drug is activated.

The long-term effects of verteporfin are currently unknown. Although it can help some patients with macular degeneration, future research is needed to prevent this common cause of blindness.[1]

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NEW FORMULATION

Ibuprofen

Nurofen Meltlets (Boots Healthcare)

200 mg tablets

NEW STRENGTHS

Desferrioxamine mesylate

Desferrioxamine for injection BP (Faulding)

2 g vials

Sodium tetradecyl sulfate

Fibro-vein (Australasian Medical and Scientific)

0.2%, 0.5% and 1% injections

Sotalol hydrochloride

Sotacor (Bristol-Myers Squibb)

80 mg tablets

NEW COMBINATIONS

Fosinopril sodium/hydrochlorothiazide

Monoplus (Bristol-Myers Squibb)

10 mg fosinopril sodium/12.5 mg hydrochlorothiazide and 20 mg fosinopril sodium/12.5 mg hydrochlorothiazide tablets

Irbesartan/hydrochlorothiazide

Avapro HCT (Bristol-Myers Squibb)

150 mg irbesartan/12.5 mg hydrochlorothiazide and 300 mg irbesartan/12.5 mg hydrochlorothiazide tablets

Karvezide (Sanofi-Synthelabo)

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