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The prescribing cascade

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Summary

A prescribing cascade occurs when a new medicine is prescribed to 'treat' an adverse reaction to another drug in the mistaken belief that a new medical condition requiring treatment has developed. Adverse outcomes associated with prescribing cascades can result when the second drug increases the severity of the adverse reaction to the first drug or when the second drug places the patient at risk of additional adverse drug reactions. The factors that are associated with an increased likelihood of an adverse drug reaction may also lead to prescribing cascades. The elderly, those using multiple medicines, women, and people using high risk medicines are more likely to get adverse drug reactions. The key to preventing prescribing cascades lies in the avoidance and early detection of adverse drug reactions and an increased awareness and recognition of the potential for adverse reactions.

In this issue…

This year's top ten drug lists show that thousands of Australians are taking drugs to lower cholesterol. Jane Smith thinks there may be some inappropriate prescribing which may lead to unnecessary adverse effects.

All medicines can cause adverse effects. Sometimes another drug is prescribed to treat these adverse effects and this could result in a prescribing cascade, according to Lisa Kalisch and colleagues. One way to manage a prescribing cascade is to 'deprescribe', and David Le Couteur and his co-authors advise us how to do this.

The new drugs for osteoporosis reviewed by Peter Ebeling have a range of adverse effects. Whether these drugs have long-term advantages over oral bisphosphonates is not yet known.

Key words: adverse effects, polypharmacy.

(Aust Prescr 2011;34:162–6)

Introduction

Adverse events associated with medicines are common and place a significant burden on the healthcare system in terms of both health outcomes and cost. It is estimated that 10% of patients visiting general practices will have had an adverse drug event in the previous six months.[1] This affects more than 1.5 million people per year[2] and results in at least 190 000 hospital admissions annually.[3] Adverse drug events include errors in the way the medicine is used, and adverse drug reactions that result from the pharmacological properties of the drug itself, either alone or in combination with other medicines. Recognising and preventing all types of adverse drug events is therefore a high priority. Failure to recognise an adverse drug reaction has the potential to further compound poor health, particularly when the reaction is mistaken for a symptom of a new health problem. If this is subsequently treated with another drug a prescribing cascade results. This can make the original adverse drug reaction even more difficult to recognise and puts the patient at further risk of adverse reactions.

What is a prescribing cascade?

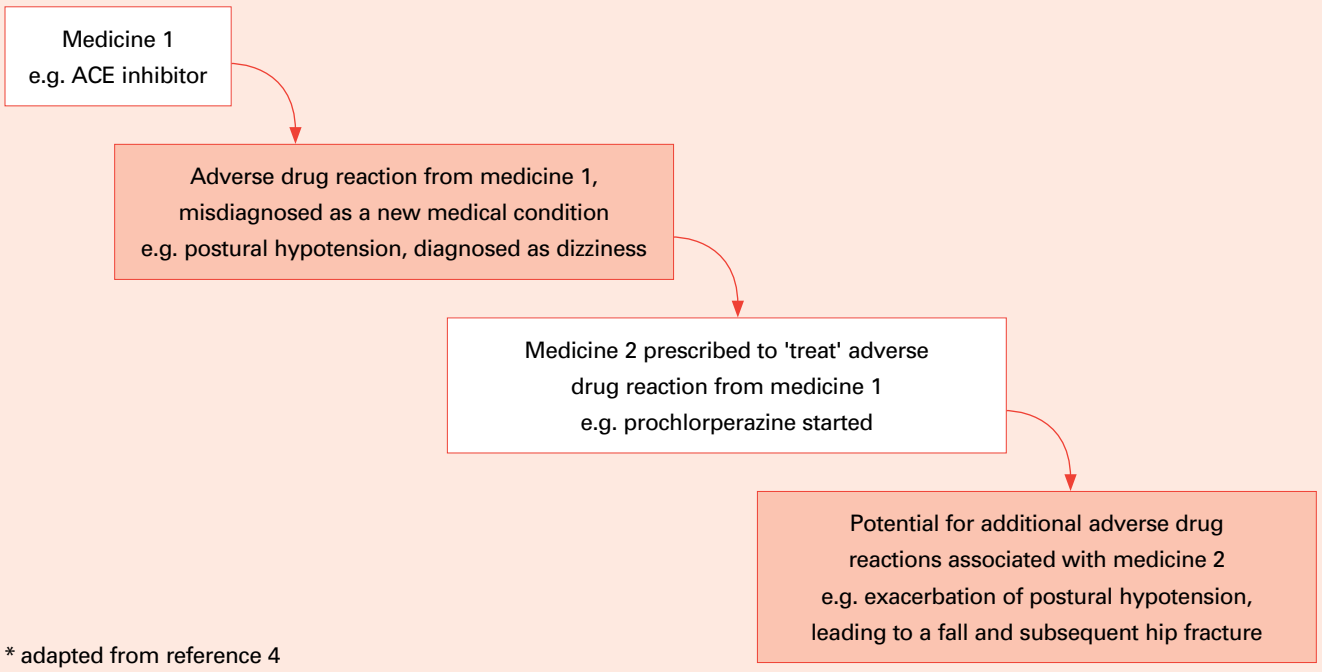
A prescribing cascade occurs when a new medicine is prescribed to 'treat' an adverse drug reaction associated with another medicine, in the mistaken belief that a new medical condition requiring treatment is present (Fig. 1).[4] Prescribing cascades may also occur when an adverse drug reaction is anticipated. An example is the prescription of a proton pump inhibitor to reduce gastrointestinal adverse effects associated with non-steroidal anti-inflammatory drugs (NSAIDs). Prescribing cascades resulting from both unrecognised and recognised adverse reactions put the patient at further risk of harm.

Drugs commonly involved in prescribing cascades

Many frequently prescribed drugs have been implicated in prescribing cascades. They include drugs for dementia, antihypertensives, sedatives, opioids, NSAIDs, antiepileptics,

Fig. 1

The prescribing cascade *



* adapted from reference 4

antibiotics, and medicines for nausea. Table 1 shows some of the prescribing cascades reported with these medicines. The cascades include the prescription of prochlorperazine to counteract drug-induced dizziness, antihypertensives to treat NSAID-induced hypertension and levodopa to manage metoclopramide-induced movement disorder. Many other medicines may be involved in prescribing cascades, but many adverse drug reactions go unrecognised and unreported.

Potential for harm

Prescribing cascades can exacerbate the harmful effects of an unrecognised adverse drug reaction. A study conducted in Australian veterans found an increased rate of prochlorperazine prescription following the prescription of drugs which cause dizziness, such as antihypertensives.[5] Prochlorperazine itself is associated with postural hypotension which may exacerbate any hypotensive effect. This may account for the increased rate of hospitalisation for hip fracture which was observed after patients started prochlorperazine.[5] Although the absolute risk of hip fracture was small, the relative risk of having a hip fracture after starting prochlorperazine increased by nearly 50%.[5] Hip fracture is associated with increased morbidity and mortality,[6] highlighting the potential for serious harm associated with this prescribing cascade.

A published report illustrates the potential for harm arising from a prescribing cascade, involving an antihypertensive drug.[7] An elderly woman developed a cough, which was not recognised as being caused by the ACE inhibitor she was taking, so she was given a codeine-based cough suppressant. When the cough persisted an antibiotic was started. The prescribing cascade went further, when the antibiotic caused *Clostridium difficile* diarrhoea. This prescribing cascade culminated in the patient being hospitalised for delirium and severe diarrhoea.[7]

What are the contributing factors?

Although factors specifically contributing to prescribing cascades have not been studied, the factors which are associated with adverse drug reactions, that may lead to prescribing cascades, are well known.

The elderly, those using multiple medicines, women, and people using 'high risk medicines', including cardiovascular drugs, NSAIDs, anticoagulants and antibiotics, are at higher risk of adverse drug reactions.[1,8,9]

In the elderly, specific drug classes – anticholinergics, antipsychotics, benzodiazepines, hypnotics and sedatives – increase the risk of adverse drug reactions.[9] Elderly people may be at higher risk of prescribing cascades than younger people because the adverse drug reaction is more likely to be misinterpreted as the onset of a new medical condition.[4] For example, a movement disorder induced by metoclopramide may be misinterpreted as Parkinson's disease, but this misinterpretation would be less likely in a young person as Parkinson's disease is less prevalent in younger people.[4]

Patients are at the highest risk of having an adverse drug reaction soon after starting a medicine. Approximately 90%

Table 1

Medicines implicated in the prescribing cascade

Medicine		Adverse drug reaction		Second medicine prescribed to treat adverse drug reaction of first medicine
Cholinesterase inhibitor[17]	→	Incontinence	→	Anticholinergics (e.g. oxybutynin)
Vasodilators, diuretics, beta blockers, calcium channel blockers, ACE inhibitors, NSAIDs, opioid analgesics, sedatives, statins[5]	→	Dizziness	→	Prochlorperazine
NSAIDs[4]	→	Hypertension	→	Antihypertensives
Thiazide diuretics[4]	→	Hyperuricaemia, gout	→	Allopurinol or colchicine
Metoclopramide[4]	→	Movement disorder	→	Levodopa
ACE inhibitor[7,18]	→	Cough	→	Cough suppressant and/or antibiotic
Paroxetine, haloperidol[19]	→	Tremor	→	Levodopa-carbidopa
Erythromycin[20]	→	Arrhythmia	→	Antiarrhythmics
Antiepileptic medicines[21]	→	Rash	→	Topical corticosteroids
Antiepileptic medicines[21]	→	Nausea	→	Metoclopramide, domperidone
Digoxin, nitrates, loop diuretics, ACE inhibitors, oral corticosteroids, antibiotics, NSAIDs, opioid analgesics, methylxanthines (e.g. theophylline)[22]	→	Nausea	→	Metoclopramide
Antipsychotics[23]	→	Extrapyramidal adverse effects	→	Levodopa, anticholinergics

NSAIDs non-steroidal anti-inflammatory drugs ACE angiotensin converting enzyme

of patients who experience an adverse drug reaction report it within four months of starting a new drug, with 75% of these patients experiencing the adverse drug reaction within one month.[10] Many adverse drug reactions are dose related, and starting therapy at high doses is associated with an increased risk of adverse drug reactions in the elderly.[11] Adverse drug reactions may also occur following dose increases.

Patients may not tell their doctor or pharmacist when they experience an adverse drug reaction. Approximately 15% of patients will stop treatment because of an adverse drug reaction without advising their doctor.[12] A quarter of patients report that they are not provided with information about the potential adverse effects of their medicine,[13] meaning that they do not have the knowledge or awareness to identify adverse drug reactions. Poor communication between health professionals and patients increases the risk of adverse drug reactions,[9] so multiple care providers may contribute to the prescribing cascade. With the increase in non-medical prescribing, effective communication and reconciliation of all of the medicines prescribed by the different health professionals caring for a patient is important to avoid the prescribing cascade. The interface between hospital and community care is also a high risk area if timely handover does not occur.

Preventing the prescribing cascade

Quality use of medicines is the judicious selection of management options, appropriate choice of medicines when a medicine is considered necessary, and safe and effective use

of medicines. These principles can be applied in preventing the prescribing cascade (see Box).

Adverse drug reactions precipitate the prescribing cascade, so the key to preventing prescribing cascades is the avoidance and early detection of adverse drug reactions. Since many adverse drug reactions in the elderly are dose related, starting treatment at low doses and titrating to effect will reduce the risk of adverse drug reactions. Most adverse drug reactions occur within a few months of starting a medicine, so health professionals should consider the potential for an adverse drug reaction to be the cause of any new symptoms, particularly if a drug has been recently started or changed. Health professionals should remember to ask patients about new symptoms, because many patients do not report adverse drug reactions.

When drug reactions occur, non-drug treatment strategies are likely to be the most appropriate first-line management, rather than starting a second medicine to counteract adverse effects. Reducing the dose of the medicine causing the adverse drug reaction is appropriate if the reaction is dose related. Trying a different drug with a similar effect, but less risk of causing the adverse drug reaction, may be another way to avoid the prescribing cascade. For example, a patient using metoclopramide for the relief of nausea and vomiting who develops extrapyramidal adverse effects, could be changed to domperidone therapy, with reduced risk of movement disorder. Reconsidering the need for the medicine causing the adverse drug reaction is also an appropriate management strategy. If the risks associated with continuing to use the medicine outweigh the benefits, then stopping it may be appropriate. The decision to prescribe a second medicine to counteract an adverse drug reaction from a first medicine should only occur after careful consideration. The benefits of continuing therapy with the first medicine must outweigh the risks of additional adverse drug reactions from the second medicine.

Patients should be provided with the skills and information they need to help them identify adverse drug reactions to avoid prescribing cascades. This includes information that outlines the drug's possible adverse effects and what to do when adverse drug reactions occur. This information is available in Consumer Medicines Information and should be provided to patients whenever a medicine is started or the dose changed. Home medicines reviews should also be considered for patients who are at risk of adverse drug reactions, and therefore at risk of prescribing cascades. These reviews increase the identification and resolution of medicine-related problems,[14] and reduce medicine-related hospitalisations.[15,16]

Conclusion

Prescribing cascades have the potential to result in serious harm to patients. Prescribers need to be mindful of the potential for drugs to cause adverse events, particularly in the elderly or patients using medicines commonly associated with adverse drug reactions. An increased awareness and recognition of the potential for adverse drug reactions to lead to prescribing cascades is required. Home medicines reviews should also be considered for those patients at risk of prescribing cascades.

Box

Preventing a prescribing cascade

Begin new medicines at low doses and tailor the dose to reduce the risk of adverse reactions

Consider the potential for any new symptoms to be caused by an adverse reaction, particularly if a medicine has been recently started or the dose changed

Ask patients if they have experienced any new symptoms, particularly if a medicine has been recently started or the dose changed

Provide patients with information about possible adverse effects of medicines and what to do when adverse drug reactions occur, e.g. in the form of Consumer Medicines Information

The decision to prescribe a second medicine to counteract an adverse drug reaction from a first medicine should only occur after careful consideration, and where the benefits of continuing therapy with the first medicine outweigh the risks of additional adverse reactions from the second medicine

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Conflict of interest: none declared

Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

Hyperferritinaemia without positive HFE gene mutation

Editor, – I read the article about testing for HFE-related haemochromatosis with interest (Aust Prescr 2011;34:73-6). Over the last 10 years I have ordered ferritin tests in over 1211 individual patients – 229 of them were found to have abnormally elevated ferritin levels. Haemochromatosis gene testing was ordered for 120 of them and there were 47 positive results. This means a significant cohort of patients with elevated ferritin do not have a positively identified mutation. My casual observation seems to give the impression that a significant number of these patients are Asian people.

Anecdotally, diabetes and lipid control in many of these patients improved when they started donating blood regularly.

My hypothesis is that:

- there are more genotypes yet to be discovered which are responsible for elevated ferritin levels in Asian people
- this (undetected and untreated) elevated ferritin may deposit in the pancreas and liver, and to some extent contributes to the high rate of diabetes and fatty livers that are so prevalent in Asian people.

Unfortunately, this is just a hunch and I do not have the detailed breakdown of these tests.

Chenault Doug Lee
General practitioner
Erindale Medical Practice, ACT

Professor Crawford, Dr Stuart and Dr St John, authors of the article, comment:

We thank Dr Lee for his interesting comments and important observations. He has raised a number of issues that are worthy of further consideration. Whilst non-HFE related iron overload is uncommon, some cases have been described in Asian patients.

Our research team has methodology to sequence many genes involved in iron metabolism, and we would be happy to assist Dr Lee (and other clinicians) to define the exact nature of the genetic defect in his Asian patients who do not carry conventional mutations in the HFE gene.

However, as Dr Lee infers, the cause of the elevated serum ferritin concentration in the majority of his Asian patients is hepatic necroinflammation, often due to non-alcoholic fatty liver disease. The growing frequency of this problem probably reflects increased exposure of his patients to a Western diet rich in carbohydrates and saturated fats. Dr Lee infers that his patients benefit from venesection, and there is some evidence to support an improvement in insulin resistance associated with such therapy. There is also recent evidence of a strong association between altered iron metabolism and lipid metabolism. However, the benefit of venesection in patients with non-alcoholic fatty liver disease, elevated serum ferritin concentration and heterozygosity for HFE mutations in relation to lipid profiles, cardiovascular mortality and liver histology is controversial and awaits definitive study.

Managing aggressive and violent patients

Editor, – We have some concerns about the approach to sedation of patients with aggression and violence suggested by Professor Fulde and Associate Professor Preisz (Aust Prescr 2011;34:115-8). Large numbers of patients require parenteral sedation with physical containment which can be hazardous to staff and requires a standardised approach.

Recent research supports the use of different drugs and initial intramuscular sedation for most patients. One study demonstrated that the duration of acute behavioural disturbance was reduced when intramuscular sedation was employed.[1] Intravenous sedation requires sufficient staff to restrain the patient, otherwise it is dangerous with the risk of needle stick or physical injury. However although intramuscular midazolam is used most commonly, recent evidence demonstrates that it is unpredictable due to over- or under-sedation.[2] A controlled trial found that 10 mg intramuscular midazolam caused adverse events in 28% of patients compared to 6% with droperidol.[2]

Only the antipsychotics olanzapine and haloperidol were suggested for sedation in the article. Haloperidol is not very sedative and has a black box warning by the US Food and Drug Administration (FDA) for confirmed reports of QT prolongation and torsades des pointes. Parenteral olanzapine has never been shown to be effective in the emergency department setting.[3] Droperidol is safer and more effective for sedation of acute behavioural disturbance in the emergency department.[2] It has been used extensively and rarely causes over-sedation. There have been concerns about QT prolongation and torsades des pointes. Despite an FDA black box warning this has not been confirmed in a systematic review.[4]

We now routinely use 10 mg intramuscular droperidol for initial sedation and repeat the dose after 15 minutes if required. In 412 patients sedated this way, 66% became sedated with one dose. Minor adverse events occurred in 5.5% of patients but no patient had QT prolongation.

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Emergency Department

Leonie A Calver
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Improving Aboriginal and Torres Strait Islander people's access to the Pharmaceutical Benefits Scheme

Editor, – While the article by Noel Hayman (Aust Prescr 2011;34:38-40) is factual and highlights the benefit of the Closing the Gap (CTG) Pharmaceutical Benefits Scheme (PBS) incentive payment scheme, it does not highlight the gaps that were not addressed in the implementation of the scheme.

In many locations there is very limited access to mainstream general practitioner services or to an Aboriginal health service and many of the 'general practitioner' services are provided by state hospitals that have the right to prescribe PBS-subsidised medications.

These state hospitals provide general practitioner services and provide PBS prescriptions to Aboriginal and Torres Strait

Islander patients but community pharmacy cannot provide a subsidised service as the CTG initiative does not include state hospital services. In August 2010, the CTG PBS initiative was expanded to include prescriptions written by specialists but state hospital doctors were still excluded.

Many Aboriginal and Torres Strait Islander patients become very confused because when they access a mainstream general practitioner they can receive a CTG prescription which is subsidised for them in community pharmacy, but if they access the hospital service after hours the PBS prescription they receive is not subsidised and they have to pay the full PBS price. Many general practitioner practices no longer provide after hours or weekend services so these patients are forced to use the state hospital services outside of normal practice hours.

This disparity of access has been discussed many times and is still a major issue in providing optimal care for Aboriginal and Torres Strait Islander people.

Karalyn J Huxhagen
Pharmacist
Mackay, Qld

Associate Professor Hayman, author of the article, comments:

It is not uncommon after the implementation of government policy that unexpected gaps in delivery become apparent. I have been aware of the problem that Karalyn Huxhagen highlights for some time.

Another gap I have identified is in medical services that are not accredited in quality of practice and therefore their patients cannot access the CTG PBS initiative. While this may be satisfactory in urban settings it is very problematic in rural and remote areas where unaccredited medical services are common. Aboriginal and Torres Strait Islander patients from these clinics are disadvantaged causing the disparity of access pointed out by Karalyn Huxhagen. The CTG PBS policy causes conflict where there is a combination of accredited and non-accredited services in a rural or remote area. Aboriginal patients are forced to go to the accredited service to access the CTG PBS program, leaving their preferred doctor of choice. This leads to disjointed care.

The Department of Health and Ageing is committed to an evaluation process of all CTG programs. Sentinel sites have been established across Australia to evaluate CTG initiatives. I have personally given feedback on the problems outlined in this response. The evaluation process will continue over the next year and hopefully all gaps identified will influence a change in policy, particularly those that will correct the gaps in service delivery and access for all Aboriginal and Torres Strait Islander peoples.

Anaphylaxis wallchart

Editor, – I write in response to the anaphylaxis wallchart[1] and would like to comment on the impracticality of advising Epipen as an alternative to adrenaline ampoules and syringe.

I am sure the Editorial Committee of *Australian Prescriber* are aware that Epipen is only subsidised when it is prescribed by clinical immunologists, paediatricians and respiratory physicians but not by other health professionals. Other doctors must purchase it privately at a cost of $104. Because it does not last long, replacing stock is costly. Even when I was a member of the Australasian Society of Clinical Immunology and Allergy, I could not prescribe Epipen on authority as I am a dermatologist. It did not matter that some of my patients with eczema had a severe peanut or latex allergy, I still was not allowed to write an authority prescription.

Perhaps if Epipen was available as a doctor's bag item under the Pharmaceutical Benefits Scheme (PBS),[2] health professionals may have better access. It would make sense to have Epipen as an alternative on the wallchart, but until such time, it is too expensive to place it as a viable alternative to adrenaline ampoules for health professionals.

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Margaret Oziemski
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The Australasian Society of Clinical Immunology and Allergy comments:

Both Epipen and Anapen are classified as Schedule 3 medicines and are available without prescription at full retail price or through PBS authority prescriptions. As determined by Medicare, PBS regulations stipulate that initial authority prescriptions are given when risk and clinical need has been assessed by, or in consultation with, a clinical immunologist, allergist, paediatrician or respiratory physician **or** after hospital or emergency department discharge for acute allergic anaphylaxis treated with adrenaline.

Any medical practitioner can prescribe an adrenaline autoinjector in consultation with one of the specialists listed above, initially by telephone. The patient should then be referred to an allergy specialist for assessment. Renewal prescriptions for adrenaline autoinjectors can be provided by any medical practitioner, and both adults and children at risk of anaphylaxis are eligible for up to two adrenaline autoinjectors per authority prescription.

Appropriate primary prevention of cardiovascular disease: does this mean more or less statin use?

***Jane Smith**, Associate professor, General Practice, Faculty of Health Science and Medicine, Centre for Research in Evidence-based Practice, Bond University, Gold Coast, Queensland*

Summary

Treatment with HMG-CoA reductase inhibitors, commonly known as statins, is beneficial for people at high risk of a cardiovascular event. However, guidelines recommend against routine statin treatment for those with a lower risk. They also recommend waiting until after 45 years of age to assess cardiovascular risk in healthy individuals. Aboriginal and Torres Strait Islander people should be assessed from age 35 years. These recommendations are based on current evidence of who is more likely to benefit from statin treatment.

Key words: antilipidaemic drugs, cholesterol, HMG-CoA reductase inhibitors.

(Aust Prescr 2011;34:169–72)

Introduction

Cardiovascular disease is a common problem causing 16% of the total disease burden, second to cancer. The mortality from cardiovascular disease has decreased by at least 80% in the last 50 years, mostly before the introduction of statins (HMG-CoA reductase inhibitors). Although Australians are living longer, greater rates of physical inactivity, obesity and diabetes all threaten this trend.[1]

The absolute risk of developing cardiovascular disease is predictable using risk calculation tools.[2] Statins are known to reduce this risk in people with existing ischaemic cardiovascular disease, or those at high risk of developing it – defined as more than 15% risk of an event in five years. However it is less clear whether people with a lower cardiovascular risk, benefit from statins.

Statin use

The number of patients diagnosed with high cholesterol has doubled between 2004 and 2009.[3] The focus on single risk factors like cholesterol translates to 27% of adult general practice patients being managed for cholesterol[4] – three-quarters of them are treated with statins.

Patients and health providers alike tend to focus on cholesterol, perhaps because it is an easy target to test and treat. A possible consequence of this is that statins are the most prescribed of all drugs both in quantity and cost on the Pharmaceutical Benefits Scheme (PBS). There are three individual statins in the top 10 of all prescribed drugs – atorvastatin, simvastatin and rosuvastatin.[5] Suggestions have been made about both under- and over-prescribing of statins in Australia. Women are far more likely to be treated with statins relative to their risk for cardiovascular disease than men, with the exception of men in the highest socioeconomic group. Rural people are less likely to be treated with a statin.[6]

Cardiovascular risk

The term cardiovascular risk refers to the risk of ischaemic disease defined as acute coronary events, angina, stroke, transient ischaemic events, and peripheral vascular disease with or without fatal outcomes. There are multiple modifiable factors that influence the risk of developing cardiovascular disease (Box 1). Modifying these factors can improve morbidity and mortality and includes lifestyle factors such as increasing physical activity and cardiorespiratory fitness, and not smoking.[7,8] If these interventions do not sufficiently reduce the risk of cardiovascular disease, pharmacological interventions may need to be considered.

Generally people under 45 years are likely to have a low risk of cardiovascular disease, as age is one of the biggest determinants of risk, and multiple risk factors are not common in younger people.

A family history of high cholesterol affects 5–20% of the population, depending on how one defines high cholesterol.

Box 1

Modifiable risk factors for cardiovascular disease

Smoking
High blood pressure
Elevated cholesterol (total or low density lipoprotein)
Decreased high density lipoprotein cholesterol
Diabetes
Obesity (large waist measurement, high body mass index)
Lifestyle (minimal exercise, poor nutrition, high stress, excess alcohol)

This is sometimes confused with familial hypercholesterolaemia (LDL >4.9 mmol/L usually with tendon xanthoma) which affects 1 in 500 (0.2%) people.[9] This is a high risk condition and results in coronary heart disease or stroke at a young age (under 60 years).

Risk calculation

Calculating absolute risk using Framingham data adapted for Australia is well validated, based on multiple factors including cholesterol levels, but is underused.[2] These tools tend to overestimate the risk in those of European descent but underestimate the risk in high risk groups such as Aboriginal and Torres Strait Islander, Pacific Islander or Indian people. Easy-to-use online tools for calculating cardiovascular risk are shown in Box 2.

Table 1 shows who should have a cardiovascular risk calculation. Conversely, some patients' risk is high enough to not need any risk calculation. These are patients who have had a previous cardiovascular event. It also includes some patients with hypercholesterolaemia, diabetes, hypertension or moderate to severe chronic kidney disease (Box 3).

Recommendations for cholesterol testing

About 8% of adult patient encounters in general practice involve cholesterol testing but evidence suggests most of these tests do not result in any benefit to patients.[3,10] The Royal Australian College of General Practitioners guidelines for preventive activities in general practice recommend testing adults over 45 years of age for their cholesterol levels every five years (or from 35 years if Aboriginal and Torres Strait Islander).[11,12] Similar recommendations are given by the National Vascular Disease Prevention Alliance (Table 1).[2]

Evidence

Most of the evidence about the effect of statins in primary prevention is based on treatment of high-risk males aged 55–65 years.[13] There is little evidence about benefit in younger age groups. In those at high risk, statins lower ischaemic event rates and all-cause mortality, and are cost-effective. This has not been shown in lower-risk populations.[14]

Table 1

Who needs risk calculation for cardiovascular disease? [2]

Patient characteristics	Recommendation *
All adults 45–75 years of age	B (strong)
Aboriginal and Torres Strait Islander people from 35 years of age	C (medium)
Diabetes <60 years	C (medium)
Overweight or obese	D (weak)

* Based on the National Vascular Disease Prevention Alliance guidelines

National Health and Medical Research Council gradings:

A Body of evidence can be trusted to guide practice
B Body of evidence can be trusted to guide practice in most situations
C Body of evidence provides some support for recommendation but care should be taken in its application
D Body of evidence is weak and recommendation must be applied with caution

Box 2

Online tools for calculating cardiovascular risk

www.heartfoundation.org.au/information-for-professionals/Clinical-Information/Pages/absolute-risk.aspx [cited 2011 Nov 7]

www.racgp.org.au/redbook/app3 [cited 2011 Nov 7]

National Vascular Disease Prevention Alliance: Australian absolute cardiovascular disease risk calculator. 2010. www.cvdcheck.org.au [cited 2011 Nov 7]

www.knowyournumbers.co.nz/heart-age-forecast.aspx [cited 2011 Nov 7]

Other sources of the same risk calculators are in the Royal Australian College of General Practitioners primary care sidebar and some pathology laboratory reports

Box 3

People at high risk of a cardiovascular event (>15% in the next 5 years) who therefore do not require cardiovascular risk calculation [2]

Characteristics

Known cardiovascular disease

Diabetes with microalbuminuria

(>20 microgram/minute or urinary albumin:creatinine ratio >2.5 mg/mmol for males and >3.5 mg/mmol for females)

Diabetes >60 years

Moderate or severe chronic kidney disease

(eGFR <45 mL/minute/1.73 m^2)

Familial hypercholesterolaemia

Serum cholesterol >7.5 mmol/L

Systolic blood pressure >180 mmHg or diastolic >110 mmHg

eGFR estimated glomerular filtration rate

Systematic reviews of trials differ in their conclusions about the benefits of statins in patients who do not have a high risk. When patients with prior cardiovascular disease are excluded, there is no evidence of benefit from statin therapy on all-cause mortality.[13] This suggests that caution should be used when recommending statins for primary prevention of cardiovascular disease in those at low risk (that is with a risk of cardiovascular disease less than 2% in one year) because of limited benefit and a potential for harm (Table 2).[15,16]

In those with moderate to severe chronic kidney disease, statin treatment reduces cardiovascular events but not overall mortality.[17] However, statin treatment of those with less severe chronic kidney disease appears to reduce cardiovascular events and overall mortality.[18]

PBS listing

The PBS general statement for using lipid-lowering drugs defines patients at risk who would be expected to benefit from statin therapy. The wording is intended to mirror the absolute cardiovascular disease risk calculation, but is an imperfect match.

Conclusion

It is likely that we are over-prescribing statins to low-risk patients. A focus on single risk factors such as high cholesterol promotes statin treatment. This will not benefit patients unless they have a high risk of cardiovascular disease, and it could result in harm. It is appropriate to assess absolute cardiovascular risk in people aged over 45 years (or from 35 years if Aboriginal and Torres Strait Islander) using tools that integrate multiple risk factors.

Table 2

Benefits and harms associated with statin treatment over five years in patients at high risk[†] of cardiovascular disease [16]

Event	Men	Women
	Number needed to treat	
Cardiovascular disease	33	37
	Number needed to harm	
Myopathy	91	259
Liver dysfunction	142	136
Acute renal failure	346	434
Cataract	52	33

[†] Patients had a 20% or more risk of cardiovascular event over 10 years

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Associate professor Smith is a member of the Editorial Advisory Committee of the Australian Medicines Handbook, member of the Advisory Editorial Panel of Australian Prescriber, and an author of the guidelines for preventive activities in general practice.

Self-test questions

The following statements are either true or false (answers on page 195)

1. Statins do not reduce overall mortality in people with severe renal impairment.
2. The National Vascular Disease Prevention Alliance recommends assessing the absolute cardiovascular risk in people over the age of 75.

Top 10 drugs

These tables show the top 10 subsidised drugs for the year July 2010 – June 2011.

Table 1

Top 10 drugs by DDD/1000 pop/day *†

Constituent drug	PBS/RPBS ‡
1. atorvastatin	82.87
2. irbesartan	33.02
3. rosuvastatin	32.37
4. perindopril	29.94
5. paracetamol	26.88
6. ramipril	26.16
7. candesartan	25.25
8. simvastatin	23.90
9. esomeprazole	21.32
10. amlodipine	19.92

DDDs in this table include use in combination products

Table 2

Top 10 drugs by prescription counts †

Drug	PBS/RPBS ‡
1. atorvastatin	11 020 969
2. esomeprazole	6 099 877
3. rosuvastatin	5 975 902
4. paracetamol	4 840 331
5. simvastatin	4 245 616
6. perindopril	3 995 257
7. pantoprazole	3 549 374
8. metformin hydrochloride	3 383 078
9. irbesartan	3 098 162
10. atenolol	3 070 515

Table 3

Top 10 drugs by cost to government †

Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1. atorvastatin	637 426 978	82.87	11 020 969
2. rosuvastatin	334 168 383	32.37	5 975 902
3. ranibizumab	310 399 773	– ¶	146 272
4. esomeprazole	184 167 326	21.32	6 099 877
5. clopidogrel	173 946 446	10.94	2 774 567
6. salmeterol and fluticasone	173 934 061	– §	3 065 047
7. adalimumab	173 892 033	0.33	97 834
8. olanzapine	161 933 986	2.99	950 386
9. simvastatin	139 642 087	23.90	4 245 616
10. etanercept	122 729 015	0.24	69 742

* The defined daily dose (DDD)/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people, in every thousand Australians, are taking the standard dose of a drug every day.

† Based on date of supply. Does not include private prescriptions or prescriptions under PBS co-payment.

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

¶ The World Health Organization has not allocated a DDD for this drug

§ This combination does not have a DDD allocated

Source: Drug Utilisation Sub-Committee (DUSC) Database, as at September 2011.

Alkalinisation of local anaesthetic solutions

***Kerry Brandis**, Director of Anaesthetics, Gold Coast Health Service District, Queensland*

Summary

Commercial local anaesthetic solutions have an acidic pH to maximise their water solubility and chemical stability. This increases their shelf-life. Immediately before injection, alkali can be added to raise the pH towards the physiological pH. This is called 'alkalinisation' or 'buffering' of the solution. Anaesthetic activity is dependent on having both the ionised and non-ionised forms of the drug present after injection. Alkalinisation increases the proportion of non-ionised drug and this could be advantageous. Care must be taken, because if too much alkali is added, the local anaesthetic will precipitate. When used for infiltration anaesthesia or block of small nerves, alkalinised solutions of local anaesthetic are less painful when injected. The onset of local anaesthesia may also be slightly quicker. For epidural anaesthesia or block of large nerves the amount of time saved is minimal and so alkalinisation is not practically useful for these procedures.

Key words: buffering, lignocaine, pain.

(Aust Prescr 2011;34:173–5)

Introduction

After the injection of a local anaesthetic solution into the tissues there is a delay until the anaesthetic block is working satisfactorily. One technique that may decrease this delay is referred to as 'alkalinisation' of the local anaesthetic solution.[1] This means adding a planned amount of a basic solution (typically sodium bicarbonate) to the local anaesthetic solution before injecting it into the target tissues. This practice may also decrease the pain on injection of the solution.[2] Two key questions to be addressed are:

- What is the basis for this practice?
- Does it make a practically useful difference?

Local anaesthetic solutions and the pKa-pH relationship

Local anaesthetics are basic drugs which have a pKa (derived from the dissociation constant) close to the normal extracellular pH of 7.4, for example lignocaine has a pKa of 7.9. The drugs exist in two forms in the solution – the uncharged basic form (B) and the charged form (BH^+).

$$B + H^+ \leftrightarrow BH^+$$

The importance of the pKa-pH relationship is that this knowledge allows the calculation of the relative amounts of these two forms. When the pH is equal to the drug's pKa, 50% of the drug is in the uncharged form, and 50% is in the charged form. In acidic solutions most of the drug will be in the charged form. (The exception to this is the topical anaesthetic agent benzocaine which is noncharged and not used for infiltration anaesthesia.) To be useful when injected the local anaesthetic solution must be present in the tissues in both forms. The reason is that the drug has to diffuse to the site of action across several tissue barriers. The uncharged lipid-soluble form will diffuse across lipid barriers, for example, perineural sheath or cell membrane. The charged water soluble form will diffuse across tissue fluid barriers, for example interstitial fluid.

The site of action of the local anaesthetic molecule is the inner (or cytoplasmic) end of the sodium channel in the cell membrane. The final pathway for all injected local anaesthetics is to diffuse to the cell membrane (in the charged form) then re-equilibrate to form both charged and uncharged forms adjacent to the outside of the nerve cell membrane. The molecules diffuse across the nerve cell membrane in the uncharged form then re-equilibrate in the cytoplasm to have both forms present again. Next the charged form diffuses to and binds to its 'receptor' on the inside of the transmembrane sodium channel. This binding results in a conformational change in the channel protein to block the passage of sodium ions into the cell in response to a subsequent action potential.

When a sufficient length of an unmyelinated nerve is impaired in this way, a nerve action potential in that nerve axon is blocked. For a myelinated nerve, the sodium channels are located primarily at the nodes of Ranvier. The channels in several adjacent nodes in the axon have to be blocked to prevent transmission of an action potential.

Commercial local anaesthetic solutions

The pH of a commercially available local anaesthetic solution has to be acidic to maximise stability in solution and shelf-life. The reasons include:

- solubility – local anaesthetic solutions are aqueous solutions and if provided at a pH close to 7.4 the lipid soluble uncharged form could precipitate out due to its lower water solubility

- stability – the uncharged base form is more unstable at physiological pH so degradation is minimised at a low pH where the drug is predominantly in the charged form
- stability of adrenaline – the adrenaline added to some local anaesthetic solutions is unstable at the physiological pH and more stable at an acidic pH.

Commercially available acidic local anaesthetic solutions have a pH of typically 3.5 to 5.5 and have a shelf-life of three to four years. This pH is so far below the drug's pKa that essentially all the drug is present in the more stable, charged, water-soluble form. Hydrochloric acid is added to lignocaine solutions to achieve this low pH.

Local anaesthetic solutions containing adrenaline are generally at a lower pH than the same solution without adrenaline ('plain solution'). The low pH is often said to be the cause of the pain on injection, but the relationship between this pain and pH is not simple.

Alkalinisation of local anaesthetic solutions

A basic solution can be added to a local anaesthetic solution immediately before injection to raise the pH. Suitable sterile solutions of sodium bicarbonate are readily available and this is the usual basic solution used.

Alkalinisation has potential advantages. Firstly, the higher pH of the solution may result in less stinging pain being experienced by the patient. Secondly, after injection, the pH of the injected solution may more quickly approach that of the normal tissue pH. The faster formation of a mixture with charged and uncharged forms may then result in more rapid drug diffusion and a quicker onset of nerve blocking. This could be particularly useful in body sites with low tissue buffering capacity where there can be a delay in the rise of pH after injection.

The practice of adding a basic solution to the local anaesthetic solution is sometimes referred to as buffering. This terminology is wrong. Alkalinisation is a more accurate term. A buffer is a solution that tends to resist a change in its pH whether an acid or a base is added to it. The aim of adding a basic solution to the local anaesthetic solution is to raise the pH, not to resist the change in pH, so this practice is not buffering. In contrast, after injection of the local anaesthetic solution the tissues function as buffers as they tend to minimise the change in tissue pH which occurs when an acidic local anaesthetic solution is injected.

The basic solution that is added has to be carefully specified and mixed (Table 1). If too much is added then the pH rises too far and the non-charged basic form will precipitate out of solution. This will be detected as a white clouding of the solution.

Provided precipitation does not occur, alkalinisation does not adversely affect the efficacy of the local anaesthetic solution.[2] As precipitation increases with time, alkalinised local anaesthetic solutions should generally be freshly prepared and used promptly. They should not be used for infusions.[3]

Reduction of pain on injection

A literature review on whether adding sodium bicarbonate to a local anaesthetic solution reduced the pain of injection found 22 human randomised controlled trials. The evidence was 'overwhelming' that pain on injection was reduced. The reason for this reduction may be the more rapid onset of action of the alkalinised local anaesthetic, rather than the change in pH.[2]

A systematic review similarly found that the pain of intradermal injection of alkalinised local anaesthetics was decreased as compared to 'unbuffered' local anaesthetics.[4]

Pain reduction is a worthy goal and painless infiltration may be achievable in some cases. The reduction of this stinging pain due to infiltration anaesthesia and the block of small peripheral nerves is the major advantage of alkalinisation of local anaesthetic solutions.

The reduction of pain of infiltration by alkalinisation of the local anaesthetic solution is significant and so is likely to be useful in general practices and emergency departments where many such blocks are done, and particularly in children. Alternative methods may be a better approach in some situations, for example the use of local anaesthetic cream before intravenous cannulation in children.

Alkalinisation to reduce onset time

For epidural anaesthesia, pain on injection of the local anaesthetic is not a major issue, but time to achieve surgical anaesthesia is important. Onset of epidural anaesthesia is quicker with alkalinised local anaesthetic solutions, but only by a few minutes.[5] More time is taken up in preparing the modified solution than is gained by using it. Onset time can be

Table 1

Alkalinisation of local anaesthetic solutions [2]

Anaesthetic solution	Volume of 8.4% sodium bicarbonate to be added to 20 mL
Lignocaine 1% or 2%	2 mL
Bupivacaine 0.25% or 0.5%	0.1 mL*
Ropivacaine 0.2%†	0.1 mL* (must be used within 5–10 minutes)

* The small volume of 8.4% sodium bicarbonate to be added requires great care as adding too much will cause precipitation

† Higher concentrations of ropivacaine (for example 0.75%) precipitate at a pH greater than 6 so are not suitable for alkalinisation[6]

decreased by using a faster acting drug, such as lignocaine, in a suitable concentration rather than a slower onset drug such as bupivacaine.

The onset of spinal anaesthesia is rapid. There is no advantage in using alkalinised solutions.

Alkalinisation of the solution does not provide any practical advantage in plexus blocks,[1,7] or intravenous regional anaesthesia.[8] With blocks of larger peripheral nerves, onset time is decreased and the quality of the block improved by minimising the diffusion distance by injecting the local anaesthetic solution close to the nerve. This can be achieved by using peripheral nerve stimulation, ultrasound guidance or other techniques to accurately position the needle tip.

In infiltration anaesthesia, the onset of the block is generally rapid so there is minimal time to be gained.

Alkalinisation of local anaesthetics to reduce the onset time of regional anaesthesia or major nerve blocks is not useful.

Conclusion

Alkalinisation of local anaesthetic solutions reduces the pain of infiltration. It also reduces the onset of anaesthesia, but the time saved is small.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 195)

3. Injections of lignocaine with adrenaline are less painful if sodium bicarbonate is added to the local anaesthetic solution.
4. Alkalinisation of the solution delays the onset of action of local anaesthetics.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

Local anaesthetic solutions

Dental local anaesthetic solutions are usually contained in premade cartridges, designed for injection without any further mixing or addition. The only exception is 0.5% bupivacaine, with or without adrenaline. It is supplied in vials and so requires the use of a separate syringe. This type of anaesthetic is used by oral and maxillofacial surgeons for pain control after removal of impacted teeth.

There has been at least one incident where a dentist used an injection of local anaesthetic from a cartridge and then separately injected sodium bicarbonate in an effort to counteract the acidic pH in an area of acute inflammation. This resulted in a permanent nerve injury with adverse medico-legal consequences for the dentist.

It is therefore recommended that dentists do not inject other solutions when using local anaesthetic cartridges.

New drugs for osteoporosis

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Summary

Despite numerous treatments, the majority of Australians with osteoporosis remain untreated. The newer parenteral treatments, intravenous zoledronic acid and subcutaneous denosumab injections, are administered less frequently (annually or six monthly, respectively) than the oral bisphosphonates, potentially overcoming compliance issues. Two other daily treatments – strontium ranelate and teriparatide – do not have major inhibitory effects on bone resorption (anti-catabolic), and teriparatide stimulates new bone formation (anabolic). With the exception of teriparatide, which is reserved for women and men with the most severe osteoporosis, all of these newer drugs are first-line therapy for osteoporosis in postmenopausal women. However, only bisphosphonates are also currently approved for this indication in men and in patients with corticosteroid-induced osteoporosis.

Key words: bone diseases, denosumab, strontium ranelate, teriparatide, zoledronic acid.

(Aust Prescr 2011;34:176–81)

Introduction

Osteoporosis results from reduced bone strength and predisposes patients to an increased risk of fracture. Bone strength is determined by both bone density and bone quality. All fractures due to osteoporosis reduce the quality of life and increase mortality. The most common sites of minimal trauma fractures are the hip and pelvis (40.5%) and wrist and forearm (17.1%). Hip fracture is the most catastrophic of osteoporotic fractures resulting in chronic pain, disability and increased mortality in up to 35% of patients within 12 months.[1,2] Conservative estimates indicate that 692 300 Australians had diagnosed osteoporosis in 2007–08. The annual cost of osteoporosis remains very high at $1.9 billion for direct costs alone.

Despite the public health burden, only 20–30% of Australians with fragility fractures due to osteoporosis are being treated. The causes for this are multifactorial, but include a low awareness of the importance and common nature of osteoporosis among both family doctors and patients.

The most commonly prescribed medications for osteoporosis are the oral bisphosphonates, risedronate (daily, weekly or monthly dose) or alendronate (weekly dose). Weekly risedronate is available with calcium and colecalciferol supplements. Alendronate is available either alone or in combination with 5600 IU colecalciferol (vitamin D_3). Other medicines are raloxifene (a selective oestrogen receptor modulator), etidronate and calcitriol, although the latter two medications have largely been superseded.

For osteoporosis treatments to act optimally on bone, adequate calcium and vitamin D are required. The average diet contains only small amounts of vitamin D, and safe sunlight exposure (ultraviolet index <3) is required to generate adequate serum levels (>50 nmol/L in winter/early spring) of 25-hydroxyvitamin D (25(OH)D). When this is not possible, vitamin D supplements (colecalciferol) may be used, with a dose of 800–2000 IU per day being effective in most people. Regular weight-bearing exercise is also recommended.

There are several new Pharmaceutical Benefits Scheme (PBS)-listed drugs for osteoporosis (Table 1). A summary of their safety and efficacy is shown in Table 2.

Zoledronic acid

Bisphosphonates are synthetic analogues of pyrophosphate and bind to bone mineral with high affinity. They are taken up by osteoclasts during bone resorption and either inhibit the adenosine triphosphate (etidronate or clodronate) or farnesyl pyrophosphate synthase (aminobisphosphonates) pathways.[3] This inhibits bone resorption through reduced recruitment of osteoclasts and decreased osteoclast activity, with formation of giant dysfunctional osteoclasts.[4]

Zoledronic acid is the most potent bisphosphonate and has the longest skeletal half-life. It is administered as an intravenous infusion (5 mg in 100 mL) over at least 15 minutes once per year, for a maximum of three years. Patients must be appropriately hydrated before the infusion, especially the elderly and those with renal impairment or receiving diuretic therapy. Treatment is contraindicated when creatinine clearance is less than 35 mL/minute. Hypocalcaemia and vitamin D deficiency (25(OH)D <50 nmol/L) should be corrected before the infusion. Adequate calcium and vitamin D supplementation should also be recommended after starting therapy.

Table 1

Pharmaceutical Benefits Scheme-listed indications for osteoporosis drugs

Drug	Indication
Zoledronic acid, risedronate, alendronate	Established osteoporosis in women and men with fractures due to minimal trauma, and for the treatment of osteoporosis in women and men aged 70 years or older with a bone mineral density T-score of ≤–3.0 at the femoral neck or lumbar spine People on long-term high-dose corticosteroid therapy (at least 3 months at ≥7.5 mg daily prednisolone or equivalent) and with a bone mineral density T-score of –1.5 or less
Denosumab, strontium ranelate*	Women aged 70 years of age or older with a bone mineral density T-score of –3.0 or less, or established postmenopausal osteoporosis with a fracture due to minimal trauma
Teriparatide	Severe osteoporosis in patients with a bone mineral density T-score of –3.0 or less, and at least two minimal trauma fractures, one of which occurred after 12 months of first-line therapy, or for severe osteoporosis when first-line therapy cannot be tolerated

* Strontium ranelate is not approved for osteoporosis in men, but can be obtained through the Repatriation Pharmaceutical Benefits Scheme

Table 2

New drugs for the treatment of osteoporosis

	Denosumab	Strontium ranelate	Zoledronic acid	Teriparatide
Administration	60 mg SC every six months	2 g daily as oral powder	5 mg IV yearly	20 microgram SC daily
Limitations	Lacks long-term data	Increased DVTs, rash Compliance	Must be given IV Lacks long-term data	Restricted use Lacks long-term data
Advantages	Compliance	Long-term data are available	Compliance	Anabolic effects
Fracture risk reduction in postmenopausal women	Vertebral, non-vertebral, hip	Vertebral, non-vertebral, hip (age ≥74, T-score –3 or less)	Vertebral, non-vertebral, hip	Vertebral, non-vertebral
Fracture risk reduction in men	No data	No data	Clinical vertebral, non-vertebral fractures, clinical fractures	Vertebral
Mortality reduction	No	No	Yes (post-hip fracture)	No

SC subcutaneous IV intravenous DVT deep vein thrombosis

Efficacy

In a large placebo-controlled clinical trial, zoledronic acid treatment reduced vertebral fractures by 70% (10.9% vs 3.3%, p<0.001), non-vertebral fractures by 25% (10.7% vs 8.0%, p<0.001) and hip fractures by 41% (2.5% vs 1.4%, p=0.002) over three years in postmenopausal women with osteoporosis.[5] All-cause mortality decreased by 28% (13.3% vs 9.6%, p=0.01) and all clinical fractures by 35% (13.9% vs 8.6%, p=0.001) in older men and women who received zoledronic acid 5 mg versus placebo within three months of sustaining a hip fracture.[6] The mechanisms responsible for mortality reduction in patients treated with zoledronic acid remain unclear, but may be related to an effect on reducing cardiovascular events and pneumonia.[7] If treatment was deferred for two weeks after the fracture, the improvements in bone mineral density and reductions in mortality and re-fracture rate were greater.[8]

Adverse effects

Infusion-related acute-phase reactions are common, occurring in about a third of patients after the first infusion, and only 7% and 3% of patients after the second and third infusion, respectively.[5] Symptoms including fever, myalgia, influenza-like symptoms, headache, nausea and arthralgia occur for 1–3 days. Giving paracetamol shortly after the infusion reduces these

symptoms. Zoledronic acid may also increase serum creatinine concentrations, particularly in patients with pre-existing renal impairment.

In postmenopausal women with osteoporosis, the incidence of serious atrial fibrillation was increased versus placebo (1.3% vs 0.5%, p<0.001).[5] However, as this was not found in the other zoledronic acid trials, the association remains uncertain and a report from the Food and Drug Administration found no association between bisphosphonates and atrial fibrillation. Rare events reported with both oral and intravenous bisphosphonates include severe ocular inflammation, and severe and incapacitating musculoskeletal pain. In this trial, atypical femoral fractures did not occur.[5]

In osteoporosis trials of zoledronic acid, there was only one case of osteonecrosis of the jaw reported in each of the treatment and placebo groups. The risk is estimated to be very low (about 1:10 000) and is most strongly associated with high cumulative intravenous bisphosphonate doses in patients with malignancy, rather than in patients with osteoporosis.

Denosumab

Denosumab is a fully human monoclonal antibody to RANKL (receptor activator of nuclear factor-κβ ligand) that prevents its interaction with osteoclasts. It reversibly inhibits bone resorption by reducing both osteoclast formation and differentiation and increasing osteoclast apoptosis (New drugs, Aust Prescr 2010;33:193-8).

The potential benefits of denosumab include the absence of gastrointestinal adverse effects that may limit oral bisphosphonate use, and the ease of administration by family doctors, which may lead to improved adherence. Also dose adjustment is not necessary in patients with renal impairment.

Vitamin D deficiency should be corrected before initiating denosumab therapy. Adequate calcium and vitamin D supplementation should also be recommended after starting therapy. As hypocalcaemia may be exacerbated by denosumab, patients with conditions that predispose them to hypocalcaemia (such as hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, severe renal impairment – creatinine clearance <30 mL/min, or renal dialysis) should be aware of the symptoms of hypocalcaemia and be monitored regularly.

Efficacy

When given as a 60 mg subcutaneous injection every six months, compared with placebo, denosumab increases the bone mineral density at the lumbar spine and hip, with associated relative risk reductions of 68% (7.2% vs 2.3%, p<0.001) for vertebral fractures, 20% (8.0% vs 6.5%, p=0.01) for non-vertebral fractures and 40% (1.2% vs 0.7%, p=0.04) for hip fractures.[9,10] Additionally, comparison trials with alendronate, either in treatment-naïve patients or in patients pre-treated with alendronate, have shown non-inferiority in bone mineral density increases at all sites compared with denosumab.[10-12] No head-to-head studies with primary fracture outcomes have been performed.

Adverse effects

Denosumab is well tolerated with adverse effect rates generally similar to placebo.[9,11-16] The most common adverse reactions include musculoskeletal pain, hypercholesterolaemia and eczema, and discontinuation should be considered if the latter is severe.[13] Hypocalcaemia may rarely occur, especially in patients with stage 5 chronic kidney disease. Pancreatitis has also been reported. Denosumab has the potential to increase the risk of infection and neoplasia. Increased rates of serious skin infections, predominantly cellulitis, have been observed in trials and patients should seek prompt medical attention if they develop signs and symptoms of infection. No significant increases in malignancy rates have been noted to date. Atypical fractures and delayed fracture healing have not been observed in trials.

Osteonecrosis of the jaw has rarely been reported (two cases) and a routine oral examination is recommended before starting treatment.[17] In patients with bone metastases from breast or prostate cancer, osteonecrosis of the jaw may be associated with denosumab treatment, suggesting decreased bone turnover may be an important contributing factor.

Strontium ranelate

Although the mechanism of action of strontium is unclear, this orally administered daily treatment decreases bone resorption, increases bone formation markers and maintains bone microarchitecture. It should be administered two hours after the evening meal for optimal absorption and should not be taken at the same time as calcium supplements.

Efficacy

Strontium increased spinal and hip bone density and reduced vertebral fractures by 41% (32.8% vs 20.9%, p<0.001) and nonvertebral fractures by 16% (12.9% vs 11.2%, p=0.04) in postmenopausal women with osteoporosis over three years in the SOTI trial,[18] and for up to five years in the TROPOS trial.[19] A *post hoc* analysis showed it also reduces hip fractures in women aged 74 years and over with a T-score of –3.0 or less.[19] Strontium also reduces vertebral and non-vertebral fractures and improves quality of life in women aged over 80 years[20,21] and reduces vertebral fractures in postmenopausal women with or without prevalent fractures and osteopenia.[22] Although the increases of spinal and hip bone mineral density appear to be greater than for other osteoporosis treatments, just under 50% of the increase in spinal bone mineral density is artefactual and is related to the substitution of strontium, a heavier element, for calcium in hydroxyapatite crystals in bone. Nevertheless,

increases in bone mineral density after strontium treatment are related to fracture risk reduction.

Adverse effects

The annual incidence of venous thromboembolism over five years was 0.9% with strontium ranelate versus 0.6% with placebo (relative risk of 1.4).[23] Strontium has also been associated with rare and potentially fatal cases of hypersensitivity reactions with eosinophilia and systemic symptoms. The incidence of this adverse reaction is extremely low, estimated at 1:54 000 patient-years of treatment. Patients should be warned of the possibility of a rash and it may be prudent to stop strontium if this occurs within the first 6–8 weeks of treatment. Diarrhoea and nausea also occur. Initiating treatment every second day for one month may reduce these adverse effects.

Teriparatide

Anti-catabolic therapies like zoledronic acid and denosumab prevent bone loss but do not add new bone, nor do they restore disrupted bone microarchitecture. In severe osteoporosis, preventing further bone loss may not be enough to stop further fractures. In these cases, treatments that stimulate bone formation and reverse skeletal deterioration may be a valuable option. Teriparatide or human parathyroid hormone (1–34) is the only anabolic drug currently approved for treatment of osteoporosis in Australia.

Continuous high circulating parathyroid hormone has catabolic effects on bone as seen in people with primary hyperparathyroidism. However, low-dose intermittent parathyroid hormone (20 microgram per day subcutaneously) has an anabolic effect.[24] Based on bone marker studies, teriparatide increases both bone formation and resorption. However, during the first three months of treatment parathyroid hormone stimulates bone formation to a greater extent than bone resorption, suggesting that teriparatide could initially induce bone apposition without previous bone resorption through modelling-based formation.[25,26] After 3–6 months of teriparatide treatment, the bone remodelling rate is globally increased, with bone formation favoured over bone resorption resulting in a net gain of bone deposited in each basic multicellular unit.

Treatment needs to be initiated by a specialist and treatment duration is limited to 18 months.

Efficacy

Teriparatide therapy increases spine and hip bone mineral density and reduces vertebral and non-vertebral fractures in postmenopausal women.[27] It has similar effects in men but there are no data on non-vertebral fractures.[28,29] The effect of teriparatide on hip fracture reduction has not been reported for men or women. Decreases in vertebral fractures of 65% (14% vs 5%, p<0.001) and non-vertebral fractures by 53% (6% vs 3%, p=0.02) compared with placebo in postmenopausal women are similar to those seen with zoledronic acid and denosumab. A meta-analysis has shown that severe back pain was reduced by 61% with teriparatide compared to the comparators (placebo, alendronate or hormonal therapy).[30] The risk reduction for back pain was evident after only six months of teriparatide.

Adverse effects

Adverse reactions reported during phase III trials with teriparatide generally have been mild. The most frequent events were dizziness, headache and leg cramps in fewer than 10% of patients. Injection site hypersensitivity occurred in a small number of patients. Allergic reactions, including dyspnoea, urticaria and chest pain, occurred in less than one in 1000 patients.[31] About 5% of recipients experienced mild transient hypercalcaemia which resolved within 24 hours. If hypercalcaemia occurs, it is generally recommended to reduce calcium intake to 1000 mg daily or less or to decrease the frequency of injections. Monitoring of serum calcium is not routinely needed, however it may be worth measuring serum calcium at baseline and after a month of therapy. A recent study evaluating the effect of teriparatide on urinary calcium at one, six and 12 months[27,28] showed small increases in urinary calcium excretion, with less than 1% of the participants requiring a dose change in calcium or teriparatide due to hypercalciuria.

Osteosarcoma was reported in a rat oncogenicity model. However, only two cases have been reported in patients during postmarketing studies of approximately one million patients to date. This frequency is less than anticipated for people aged over 60 years. Each patient commencing teriparatide must sign a consent form acknowledging they are aware of this risk and treatment should be avoided in patients at increased baseline risk for osteosarcoma, such as children, and those with Paget's disease, unexplained elevations in alkaline phosphatase, or prior radiation therapy involving the skeleton.

Conclusion

New treatments for osteoporosis may offer advantages over existing oral bisphosphonates, particularly regarding compliance. Although there are no direct head-to-head studies, relative risk reductions in vertebral fractures may be greater for zoledronic acid, denosumab and teriparatide than for oral bisphosphonates. However, reductions in non-vertebral fractures appear similar for zoledronic acid, denosumab, strontium ranelate and oral bisphosphonates. A comparison of absolute risk reductions (and the number needed to treat) is confounded by baseline differences in the severity of osteoporosis. Each class of drug has potential adverse effects.

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Professor Ebeling has received research funding from Novartis, Amgen and Servier. His institution has received honoraria from Amgen and Novartis.

Self-test questions

The following statements are either true or false (answers on page 195)

5. Zoledronic acid reduces mortality after hip fracture.
6. Denosumab can exacerbate hypocalcaemia in patients with hypoparathyroidism.

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

New drugs for osteoporosis

The newer drugs for the management of osteoporosis widen the range of treatment options, but are not without risk. The main dental concern is bisphosphonate-related osteonecrosis of the jaw. It took several years before the true relation and incidence of bisphosphonate-related osteonecrosis was established and accepted. Multiple independent studies have shown a relation between osteonecrosis after dental extraction and bisphosphonate use. The incidence is approximately 1/500 to 1/1500. For patients taking intravenous bisphosphonates for cancer who have dental extractions the incidence is much higher at 1/10–15.[1]

At present, the incidence of osteonecrosis of the jaw for patients on intravenous zoledronic acid and subcutaneous denosumab for osteoporosis is unknown, but is probably low. These are potent drugs and it is even more important that patients have their oral health checked before treatment, as immediately post-infusion their bone turnover is markedly suppressed. Post-infusion extractions are probably best avoided for at least several months if possible.

Strontium ranelate and teriparatide have different mechanisms of action and osteonecrosis of the jaw is not a risk. Indeed initial reports have shown that teriparatide may be a good potential treatment for established bisphosphonate-related osteonecrosis of the jaw.[2,3]

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NPS is now inviting abstract submissions. To view the preliminary program, register your interest, or submit an abstract, visit **www.nps.org.au/nms2012**

Deprescribing

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Summary

Medicines have adverse effects and the use of multiple medicines, polypharmacy, can be associated with poorer outcomes. Health professionals need to recognise when medicines should be ceased and how to deprescribe. Deprescribing could be considered when there is polypharmacy, adverse drug reactions, ineffective treatment, falls or when treatment goals have changed. If patients are slowly weaned off their medicines, withdrawal and rebound syndromes are usually not serious. A cautious approach to deprescribing includes two principles – stop one drug at a time and wean doses slowly over weeks and months.

Key words: drug withdrawal, falls, polypharmacy.

(Aust Prescr 2011;34:182–5)

Introduction

There are many evidence-based guidelines to help clinicians start drug treatment. There is much less evidence to guide clinicians about withdrawing medicines. Several terms have been used for ceasing medicines including deprescribing, withdrawal, discontinuation, pharmacolysis, untrials and prescription pruning. Here deprescribing is used to define the cessation of long-term therapy, supervised by a clinician.

When should deprescribing be considered?

Good practice requires a regular review of a patient's medicines. These reviews are a good time to consider deprescribing.

Polypharmacy

The use of multiple medicines is termed polypharmacy. In older people it is associated with an increased risk of impaired physical and cognitive function, institutionalisation, hospitalisation and death. These associations appear to be independent of the underlying diseases.[1] Moreover, studies show that reducing the number of drugs has positive outcomes in older people. A feasibility study to reduce polypharmacy in people over 70 years of age suggested that over half of their medicines could be discontinued. Only 2% of the drugs needed to be restarted because the original indication re-emerged. Overall there was improvement in cognition and the patients' global health.[2] A review of medicine withdrawal studies in older people found that withdrawal was rarely associated with adverse effects.[3] After withdrawal of antihypertensive therapy, many patients (20–85%) remained normotensive and withdrawal of psychotropic drugs was associated with a reduction in falls and improved cognition.[3] This is further supported by a recent Australian pilot study which confirmed the feasibility of deprescribing in polypharmacy.[4]

Adverse drug reactions

It is common sense to stop a drug, or to reconsider its benefit:harm ratio, if it causes a significant adverse reaction. For example, in secondary stroke prevention trials of antiplatelet drugs, up to one in five patients stopped treatment because of adverse drug reactions. Given that clinical trial participants do not always reflect real-life patients, it is likely that a greater number of patients in everyday practice will be unable to tolerate their medicines. Health professionals often have difficulty recognising adverse drug reactions, partly because they are reluctant and unwilling to recognise them and partly because the reactions can be mistaken for symptoms of disease. Falls and cognitive impairment are frequently secondary to adverse drug reactions in older people, yet are often overlooked as simply part of the ageing process.[5]

Lack of effectiveness

For many drugs it is not possible for any individual clinician to assess effectiveness. This is because many drugs are used to prevent illness or because the number of patients who need to be treated for one to benefit is too large for the effect to be perceptible.[6] However, if a drug has no effect on a surrogate outcome (for example blood pressure, cholesterol) or symptoms, then it is pointless to continue therapy because it accrues cost and the risk of harm without any benefit.

Falls

Polypharmacy and drugs acting on the central nervous system are important risk factors for falls, increasing the risk by around 50%.[7] A placebo-controlled clinical trial of withdrawing psychotropic drugs showed that falls were reduced by 66%.[8] The number of hip fractures in Australia could be reduced by 10% simply by avoiding the use of benzodiazepines in older people.[9]

The relationship between cardiovascular drugs and falls is less clear. Antihypertensive drugs are often ceased in older people with orthostatic hypotension and recurrent falls.

Terminal illness, dementia or frailty

It is important to re-evaluate the role of medicines once a patient has entered the terminal phases of an illness, become frail or developed disabling dementia, as there should be a shift in treatment goals. Many preventive therapies such as medicines used to treat hypertension, osteoporosis and hyperlipidaemia take many months and even years before their benefit is established. They have limited value in patients with a short life expectancy. Furthermore the pharmacokinetics and pharmacodynamics of many medicines change with frailty or terminal illness and this impacts on their harm:benefit ratio. Deprescribing will reduce the medicine load and potential adverse effects, while shifting the therapeutic focus to end-of-life issues that are important to the patient.[10]

What are the consequences of deprescribing?

Like all medical interventions, including starting medicines, there are potential harms and benefits in deprescribing. There are several possible outcomes following deprescribing.

No obvious change in clinical status

In many cases there may be no obvious change in the patient after deprescribing. However, patient satisfaction is often increased, the financial cost to the patient and the community is reduced and the risk of future adverse drug reactions and interactions is removed.

Resolution of specific adverse drug reactions

For dose-dependent adverse drug reactions, resolution of the adverse effect will usually coincide with the disappearance of the drug from the blood (3–5 half-lives). However, in some situations, such as delirium, resolution may take much longer than expected on pharmacokinetic grounds.

Improvement in function and quality of life

In a clinical trial to reduce polypharmacy in older people, the patients' global assessment scale improved in 88% and in most patients cognitive function improved.[2] A systematic review concluded that deprescribing can be associated with improvements in cognition and behaviour in patients with dementia, and a reduction in falls.[3] Simplification of drug regimens might also improve adherence and reduce medication errors.

Withdrawal syndromes

When deprescribing is undertaken slowly and under medical supervision, clinically significant adverse withdrawal reactions are rare.[2,3] Even so, clinicians should be aware of potential problems.

Withdrawal and discontinuation syndromes

The most common cause of discontinuation syndromes is the withdrawal of drugs acting on the central nervous system. Most general practitioners will be familiar with the antidepressant discontinuation syndrome commonly seen after ceasing selective serotonin reuptake inhibitors. The symptoms typically occur within one week of ceasing the drug. They are usually mild, and resolve over ten days or less. The abrupt withdrawal of benzodiazepines is associated with a much more serious withdrawal syndrome with confusion, hallucinations and seizures. Abrupt cessation of levodopa is associated with a serious withdrawal syndrome with features of the neuroleptic malignant syndrome, including severe muscle stiffness, autonomic instability and impaired consciousness. In patients who have been taking systemic corticosteroids for more than a few weeks, sudden cessation may sometimes lead to an Addisonian crisis secondary to suppression of the hypothalamic-pituitary-adrenal axis.[11,12]

Rebound syndromes

Stopping a beta blocker can be associated with rebound tachycardia and hypertension which may aggravate heart failure or ischaemic heart disease. Stopping proton pump inhibitors is associated with hypersecretion of acid and aggravation of gastrointestinal symptoms. Simple analgesics and nasal drops can be obtained without a prescription, but cessation can be respectively associated with rebound headaches and rhinorrhoea.[12] Rebound insomnia is common after stopping hypnotic drugs.

Unmasking drug interactions

Pharmacokinetic interactions should be considered when undertaking deprescribing. For example, if omeprazole is ceased by a patient on a stable dose of warfarin, the INR may decrease because omeprazole had been inhibiting the metabolism of warfarin.

Reappearance of symptoms of original disease or risk factor

It is important not to misinterpret a rebound or withdrawal syndrome as a recurrence of the symptoms of the original disease. Surprisingly, clinical trials of drug withdrawal do not

show a high incidence of symptoms of the original disease or risk factor reappearing after treatment stops.[3] However, if some drugs, for example immunosuppressants, are stopped abruptly the underlying condition may flare up.

What is the approach to deprescribing?

There is limited clinical evidence to guide deprescribing, but some broad principles can be applied (Fig. 1).[2,4,11,12]

Prepare the patient for deprescribing

When starting a drug, explain to the patient that the outcome will be monitored and the drug might be ceased if there is no beneficial effect or a significant adverse effect occurs. Patient expectations can be discussed and managed at this time. This is particularly important for drugs which have Pharmaceutical Benefits Scheme (PBS) continuation criteria (for example cholinesterase inhibitors for Alzheimer's disease), as the clinician must confirm that there has been clinical improvement in order for PBS funding to continue.

Recognise the need for deprescribing

The main clues that deprescribing might be useful are polypharmacy, adverse drug reactions (for example falls in older people), lack of efficacy and changes in treatment goals which may be secondary to the onset of terminal illness, dementia or frailty.

Prioritise medicines to cease or doses to reduce

A cautious approach is to stop or reduce the dose of one drug at a time. This helps to identify which drug might have been causing harm or, if withdrawal symptoms occur, to provide a guide for which drug to consider recommencing. If an adverse drug reaction is suspected, then the implicated drug should obviously be stopped first.

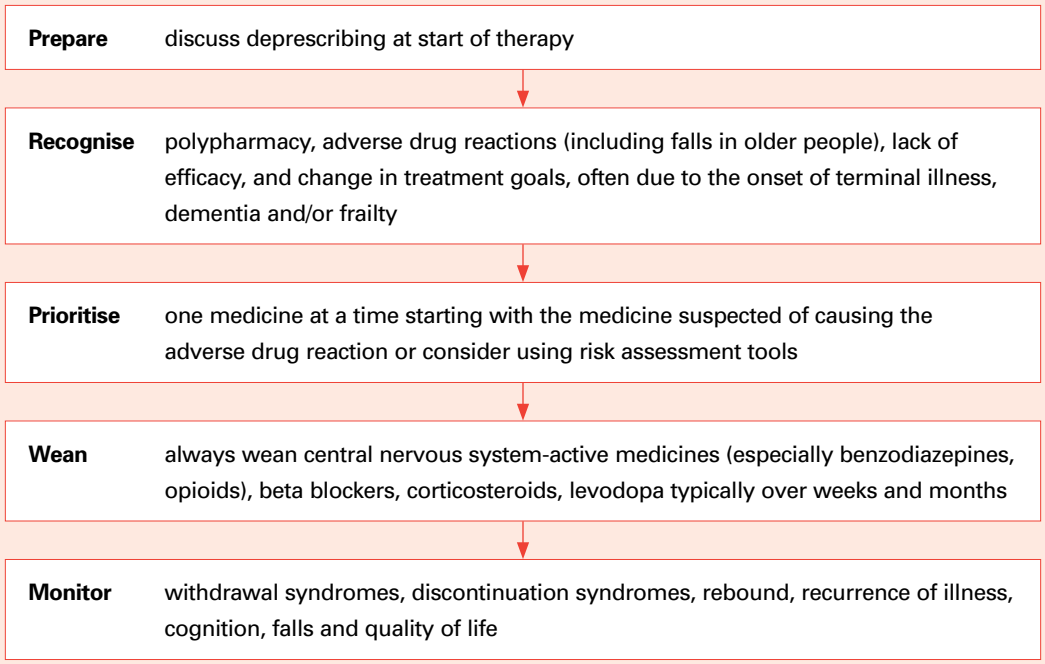
If the patient is elderly and taking multiple medicines then there are several possible approaches to identifying the drugs which are suitable for deprescribing, in particular focussing on anticholinergic and sedating drugs.[2,13,14] Reducing the dose of a medicine or changing it from regular to 'as needed' might also be an appropriate goal.

Wean or taper the dose

In many cases, medicines can be ceased abruptly, while for others (beta blockers, benzodiazepines, corticosteroids, opioids, levodopa) sudden cessation can generate serious withdrawal and rebound syndromes. The duration of weaning can vary from days to months and is influenced by factors such as the drug's half-life, the availability of different dose form sizes and scored tablets, as well as the physiological and psychological responses of the patient. For psychotropic medicines, the overall aim might be to reduce the dose by 25% each month, adjusting this according to the patient's response.[12,15,16] This

Fig. 1

General approach to deprescribing



is a reasonably conservative regimen that would be suitable for most other prescription drugs if there was concern about withdrawal or rebound. For patients who have taken benzodiazepines for a long time, there might also be a benefit in transferring the patient to an equivalent dose of diazepam, because of its long half-life, then commencing withdrawal. However, for patients who have had a serious adverse drug reaction, then usually the drug should be stopped immediately.

Monitor outcomes

If a significant withdrawal syndrome or rebound occurs, then the drug could be resumed. Withdrawal could be attempted later at a slower rate.

Assess patients for positive outcomes of deprescribing, such as decreased adverse effects and improved function. These benefits will be important for continuing compliance with deprescribing.

Conclusion

Recognising adverse outcomes or a lack of efficacy requires skill and diligence, particularly in older people taking multiple medications. However, good patient care depends upon the ability of prescribers to evaluate the clinical need for deprescribing and then undertake supervised withdrawal of medicines when appropriate.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 195)

7. Antihypertensive drugs are not suitable for deprescribing because of the risk of rebound hypertension.
8. Sudden cessation of long-term use of benzodiazepines may cause hallucinations.

RADAR
Rational Assessment of Drugs and Research

The December issue of NPS RADAR reviews the evidence and place in therapy for:

- asenapine (Saphris) for schizophrenia or bipolar 1 disorder (acute mania or maintenance)
- indacaterol (Onbrez), a once daily beta$_2$-agonist for chronic obstructive pulmonary disease
- ticagrelor (Brilanta), an oral antiplatet for acute coronary syndrome
- oxycodone-with-naloxone controlled-release tablets (Targin) for chronic severe pain.

Read the full reviews at www.nps.org.au/radar

Prostate specific antigen

***Ken Sikaris**, Chemical pathologist, Melbourne Pathology, Collingwood, Victoria*

Summary

The concentration of prostate specific antigen in the blood can help in the assessment and management of early prostate cancer. However, it is important to understand the biology underlying the test. Recent refinements have addressed some of the weaknesses of the test. These include age-related prostate specific antigen reference limits, the free to total prostate specific antigen ratio and prostate specific antigen rates of change including velocity or doubling time. Measuring prostate specific antigen without understanding the underlying biology or without applying these refinements may result in more harm than good.

Key words: prostate cancer.

(Aust Prescr 2011;34:186–8)

Introduction

Prostate specific antigen (PSA) is the name commonly used for a protein that is normally secreted by the healthy prostate gland into semen. PSA is a kallikrein protease whose biological role in semen is to hydrolyse the high molecular weight proteins secreted by the seminal vesicles. This converts the seminal gel to its fluid form to enable spermatozoa to swim free. PSA occurs naturally in semen, but the occasional molecule escapes into the interstitium of the prostate gland and then via the lymphatics to the blood. The PSA concentration in blood is a million times lower than in semen.

The test

A sample of venous blood is needed to measure the concentration of PSA. The result may be affected by mechanical disturbance of the gland such as digital rectal examination, exercise or ejaculation which ideally should be avoided for a day or two before the test. Samples should also be analysed within 24 hours as PSA (especially free PSA) decays *in vitro*. Although PSA concentrations measured by different laboratory methods are far more comparable today than even five years ago, it is unwise to compare results between laboratories as important differences may still exist.

Age-related PSA reference limits

As the prostate gland typically enlarges with ageing, the larger gland will expectedly release more PSA. This leads to a normal age-related rise in serum PSA concentrations.

There is an age-related rise in the upper reference limit from 2 microgram/L in young men to up to 9 microgram/L in the very old (Fig. 1). The age-related upper reference limit of PSA maintains a 95% specificity across all age groups. However, just as important is the age-related rise in the median PSA with age.

When a man consents to have a PSA test to ascertain his risk of prostate cancer, there are two important limits to consider. Firstly, if his PSA concentration is above the median, his probability of prostate cancer is above average. Secondly, if his PSA is above the upper limit of the age-related reference range, it is unlikely to be due to chance alone. For example, a man in his early 60's with a PSA above 4.5 microgram/L has about a 25–30% chance of prostate cancer being found at biopsy – indicating a high **absolute risk**.[1]

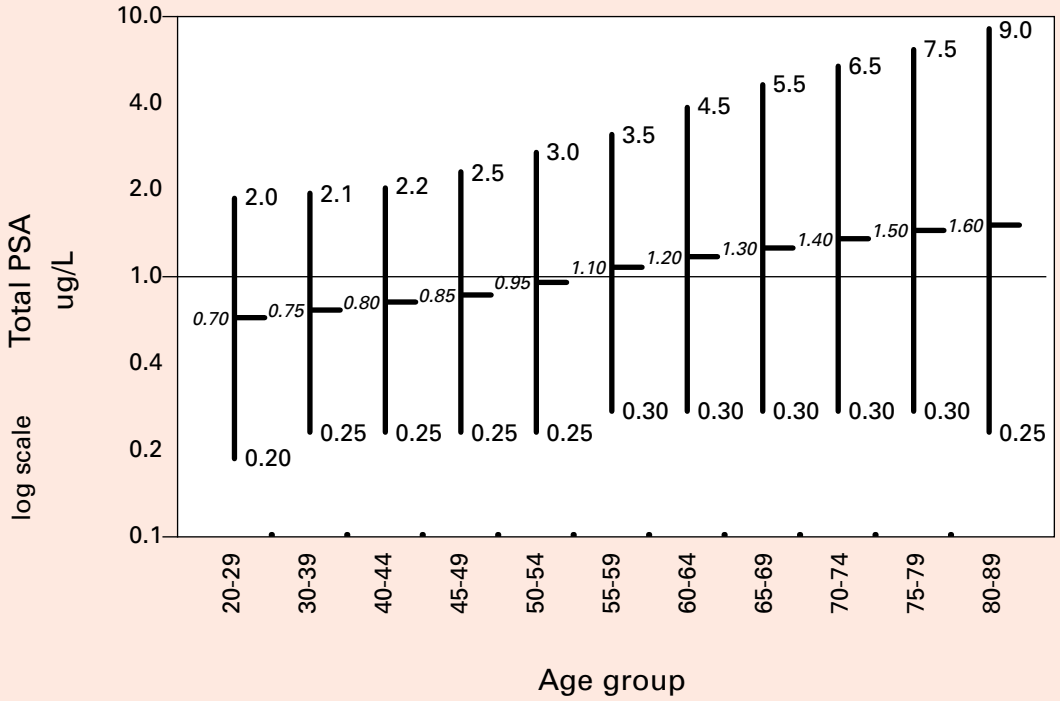
Results above the age-related upper reference limit

When the PSA exceeds the reference interval, the absolute risk of prostate cancer seems high (for example 30%), but it is still more likely that the cause is not prostate cancer. It is usually due to benign hyperplasia or prostatitis. However, a very high PSA level (above 10 microgram/L) is unlikely to be due to hyperplasia in asymptomatic men under 70 years of age. It is probably due to prostate cancer so referral to a urologist is appropriate. Clinically evident prostatitis is usually associated with PSA concentrations over 20 microgram/L so the risk of prostate cancer cannot be determined until this has fully resolved which may take one month.[2]

The most common challenge occurs when the PSA is abnormal (above the age-related upper reference limit) but not above 10 microgram/L. We need more specific approaches to reduce the false alarm caused by concentrations transiently in this range. The simplest approach is to repeat the test after two weeks. If the concentration falls it is less likely that there is a prostate cancer, and the patient may have intermittent subclinical prostatitis.

Fig. 1

Age-related rise in prostate specific antigen [3]



The central value is the median. The upper and lower values represent the 95% 'normal' range or reference interval. While these results refer to the Abbott Architect method and an Australian population, the values will be similar for any internationally calibrated (WHO standard) PSA assay on Caucasian men.

Free to total PSA ratio

The PSA in the blood is either free or bound to protein. As PSA is a protease, the anti-protease proteins of the blood will identify the molecule and bind to it inactivating its potential proteolytic actions within the body. Bound PSA is therefore active PSA molecules which have escaped from the prostate gland, but have been bound to antiproteases such as alpha-2-macroglobulin and alpha-1-antichymotrypsin. Molecules of free PSA are not bound to protein, and are not active. Free PSA is inactive because these molecules were either immature (pro-PSA) or inactivated (nicked PSA) when they escaped from the prostate gland.

The clinically important difference in these two forms of PSA is that free PSA has a short half-life (2–3 hours) whereas bound PSA has a long half-life (2–3 days). Patients who have diseases that cause intermittent 'showers' of PSA to appear in the blood will have both free and bound PSA, whereas in diseases that cause chronic release of PSA, bound PSA will accumulate in the blood due to its longer half-life compared to free PSA. Benign prostatic hyperplasia is characterised by highly variable PSA concentrations due to the intermittent physical disturbance of the enlarged gland or the increased risk of intermittent subclinical prostatitis. Cancer is the only continuously progressive disease of the prostate that constantly increases PSA release and most patients with low free to total PSA ratios (less than 10% free PSA, more than 90% bound PSA) will have prostate cancer.

Men with constantly elevated PSA concentrations (but below 10 microgram/L) should have the free to total PSA ratio estimated. If the free to total PSA ratio is below 8%, the risk of prostate cancer is almost 80%.[4] The only problem with this test is that free PSA is short-lived not only *in vivo* but also *in vitro*, so it must be measured within 24 hours of collecting the blood sample. Delay will falsely lower free to total PSA ratios which could be misinterpreted as an increased risk of cancer.

Results above the age-related median

The PSA test has 60% sensitivity using the upper reference limit, so we would miss the 40% of prostate cancers that occur in men with 'normal' concentrations. These cancers are also usually organ-confined and 'treatable'. By definition, the 50% of men with 'normal' PSA (below the age-related upper reference limit) but above the age-related median will have an above average risk of prostate cancer, but that risk is not high enough to warrant prostate biopsy. In these men with above average risk, continued monitoring with yearly measurements of PSA and digital rectal examination should be offered.

More frequent monitoring may be warranted in a man whose pre-test likelihood of prostate cancer is already high and who has a PSA above the age-related median, for example men with a family history of prostate cancer in a close relative (especially a brother). When both family history and PSA concentration suggest an increased risk, the test could be repeated within 3–6 months with a free to total PSA ratio.[5]

Results below the age-related median

If a man's PSA concentration is below the age-related median, his probability of prostate cancer is below average. Most researchers suggest that no further testing is justified for at least 3–5 years, as several studies have shown the absolute risk of prostate cancer in these men is very low (less than 1%). A man over 70 years of age is unlikely to benefit from further testing.

The rate of PSA changes

A useful refinement in predicting the clinical significance of any prostate cancer is the measurement of the rate of change of PSA concentrations. This is usually referred to as PSA 'velocity', but the 'doubling time' of PSA may be the more appropriate way to assess malignant potential.[6]

PSA concentrations may double every five years in the early stages of benign prostatic hyperplasia. If the PSA concentration is doubling faster (for example every three years or faster), this is more likely to be due to prostate cancer. When a man has had at least three PSA concentrations, several months apart and they show a rising trend, PSA doubling time can be calculated (see www.mskcc.org/applications/nomograms/prostate/). Estimating the rate of change of PSA applies both to PSA 'screening' or monitoring a known cancer.

PSA monitoring in known malignancy

A rising concentration of PSA in a man with prostate cancer suggests that the cancer is progressing.

PSA production is typically reduced by prostate cancer treatment (for example antiandrogen therapy), and the nadir can predict clinical outcome. PSA concentrations are ideally undetectable after radical prostatectomy, however men with 'biochemical recurrence' may still not have anything to worry about as a slowly rising PSA indicates their residual tissue may not be an aggressive cancer.[7] Watchful waiting should be reserved for men who are not at high risk. Men with low free to total PSA ratios or fast doubling times are at risk and should be considering treatment.[8]

Medicare Benefits Schedule

All the suggestions made in this article are currently supported by the Medicare Benefits Schedule. At least one free to total PSA ratio can be requested each year when the PSA is above the median. Should the PSA concentrations be above the age-related upper limit, several PSA tests and up to four free to total PSA ratios can be requested within each year.

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Further reading

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Conflict of interest: none declared

Medicines Australia Code of Conduct: breaches

(Aust Prescr 2011;34:189)

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

Considering all the advertising and the thousands of educational events sponsored by the pharmaceutical industry, complaints are uncommon. Of the 24 complaints considered in 2010–11, 14 were found in breach of the code. Only four of these breaches were identified from complaints made by health professionals. One of these resulted in a fine of $200 000 after a company offered funding to an area health service contingent on the number of patients treated with its products. Table 1 shows the complaints where at least one breach was identified, and more details can be found in the full report.[2]

References

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Table 1

Breaches of the Code of Conduct July 2010 – June 2011

Company	Brand (generic) name	Material or activity	Sanction
Alcon Laboratories Australia	–	Disease education booklet	$5 000 fine Withdraw glaucoma information booklet and do not use it again in the same or similar form
AstraZeneca	Nexium (esomeprazole)	Media release	$75 000 fine Do not distribute the media release again in the same or similar form
	–	Educational event	$15 000 fine
Bayer Australia	–	Advertising campaign to the general public	$10 000 fine
Janssen-Cilag	Concerta (methylphenidate)	Media release	$15 000 fine Do not distribute the media release again
Merck Serono Australia	Movectro (cladribine)	News item	$20 000 fine
Novartis Pharmaceuticals	Exforge and Exforge HCT (amlodipine combinations)	Advertising campaign	$50 000 fine Cease using misleading claim in advertising
Pfizer	Lipitor (atorvastatin)	Advertisement	$20 000 fine Cease publication of advertisements
Roche Products	MabThera (rituximab)	Media release	$30 000 fine
	Pegasys (peginterferon alfa-2a)	Financial support for medical practice activities	$200 000 fine
	Mircera (methoxy polyethylene glycol-epoetin beta)	Posters, website, dosing card	$200 000 fine Cease use of all materials and website Send a corrective letter to healthcare professionals Place the corrective letter on the website
Sanofi-aventis	Actonel (risedronate)	Media release	$20 000 fine Do not distribute the media release again
Sanofi Pasteur	Adacel and Acel (diphtheria, tetanus, pertussis vaccines)	Advertising campaign	$50 000 fine
Schering Plough (subsidiary of Merck Sharp & Dohme Australia)	Simponi (golimumab)	Promotional material	Send a corrective letter to all rheumatologists in Australia Publish corrective advertisement

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

Medicines Safety Update Volume 2, Number 6, December 2011

Medicines Safety Update is the drug safety bulletin of the Therapeutic Goods Administration (TGA). It is published in each issue of *Australian Prescriber*. You can also read it and sign up for free Medicines Safety Update email alerts on the TGA website at www.tga.gov.au/hp/msu.htm

In this issue:

Proton pump inhibitors and acute interstitial nephritis

Summary

The incidence of acute interstitial nephritis caused by proton pump inhibitors (PPIs) is unknown. Given the widespread and growing use of PPIs and the consequences of acute interstitial nephritis, the potential for this adverse reaction should not be forgotten.

PPIs are a leading cause of drug-induced acute interstitial nephritis (AIN), which may cause acute kidney injury and sometimes long-term damage.[1] The association between PPIs and interstitial nephritis was reported by the TGA in the Australian Adverse Drug Reactions Bulletin in 1995 and 2003.[2,3]

Reports continue to be received of interstitial nephritis with PPI use. The table below shows reports to the TGA and the World Health Organization's (WHO) Program for International Drug Monitoring* to July 2011 of suspected cases of interstitial nephritis in which a PPI was suspected. These data should not be taken to reflect incidence rates.

The total number of PBS/RPBS prescriptions dispensed since 1992 for each PPI have been: omeprazole 50.1 million; lansoprazole 10.2 million; pantoprazole 29.6 million; rabeprazole 15.3 million; and esomeprazole 38.2 million. PPIs are also available for direct purchase by consumers.

Product Information documents for PPIs mention interstitial nephritis as a very rarely or rarely reported event in the postmarketing experience with these drugs. Fever and skin rash are also sometimes mentioned but patients with PPI-induced AIN rarely present with the classic hypersensitivity syndrome of fever, skin rash and eosinophilia in the context of renal impairment.[4] Non-specific symptoms such as fever, anorexia, weight loss, fatigue, lethargy, nausea, vomiting and malaise predominate. Laboratory findings include pyuria, proteinuria and/or haematuria.[1]

While AIN is considered a class effect of PPIs, the TGA has received no reports of interstitial nephritis with lansoprazole. The lack of reports may reflect the lower use of lansoprazole compared with other PPIs, but could possibly reflect variation in the incidence of rare adverse reactions within a class. Prescribers should be aware of the possibility of AIN with this class of medicine. If cases are suspected, please report them to the TGA – see 'What to report' on page 193.

* Adverse drug reaction information from this Program is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction and the information does not represent the opinion of the World Health Organization

References

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Reports to the TGA and WHO to July 2011 of interstitial nephritis in patients taking a PPI

	TGA	WHO
omeprazole	54 (from 1990)	293 (from 1993)
lansoprazole	0 (from 1994)	23 (from 1996)
pantoprazole	21 (from 1995)	84 (from 1998)
rabeprazole	28 (from 2001)	54 (from 2000)
esomeprazole	28 (from 2002)	44 (from 2002)

Dabigatran (Pradaxa) and the risk of bleeding

Summary

Dabigatran (Pradaxa) is a potent short-acting anticoagulant for which there is no antidote or reversal agent. As with warfarin, bleeding events can occur. Clinicians are urged to give careful consideration to the suitability of their patients for dabigatran particularly with regard to recognised risks of bleeding.

Dabigatran (Pradaxa) is a potent oral anticoagulant. It is a direct thrombin inhibitor that inhibits free and clot-bound thrombin. It has a mean half-life of 12–17 hours. It is renally excreted and the rate of elimination is related to renal function. There is a close correlation between plasma dabigatran levels and anticoagulant effect.

Dabigatran may be considered an alternative to warfarin and it carries similar risks of bleeding. In clinical trials the risk of bleeding per year of treatment with dabigatran was 16.6% (1 in 6 patients) when taking 150 mg twice daily, and 14.7% (1 in 6.8 patients) taking 110 mg twice daily compared with 18.4% (1 in 5.4 patients) for warfarin.

Bleeding adverse events with dabigatran

In April 2011 the TGA approved dabigatran for use for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor for stroke. Since then, the TGA has received an increase in the number of bleeding-related adverse events reports for dabigatran (see table).

The analysis of these reports shows that some of the bleeding adverse events occurred during the transition from warfarin to dabigatran; many of the adverse events are occurring in patients on the reduced dosage regimen; and the most common site of serious bleeding for dabigatran is the gastrointestinal tract, whereas for warfarin it is intracranial.

Adverse events reported to the TGA for dabigatran June 2009 – Oct 2011

Type of adverse event	Number
Total adverse events	297
Serious adverse events	196
Serious bleeding adverse events	70
Serious gastrointestinal bleeding	48
Serious intracranial bleeding	6
Events in patients aged 75 years or older	
Total adverse events	166
Serious adverse events	108

Risk factors for bleeding

- Age ≥ 75 years
- Moderate renal impairment (30–50 mL/min) – severe renal impairment is a contraindication
- Concomitant use of aspirin (approximately twice the risk), clopidogrel (approximately twice the risk), non-steroidal anti-inflammatory drugs including COX-2 inhibitors

Monitoring renal function

New recommendations for assessing renal function before starting dabigatran and during its use are now in place. See information on the TGA website at www.tga.gov.au/safety/alerts-current.htm

Coagulation testing

In bleeding patients Thrombin Time is the most readily available clotting test reflective of the relationship between dabigatran concentration and clotting time. Although there is not a direct linear relationship, activated Partial Thromboplastin Time (aPTT) >80 seconds is associated with a higher bleeding risk. Prothrombin time (INR) should not be used.

Guidelines for managing bleeding patients

Australian experts are currently developing Australian guidelines for the management of bleeding in patients taking dabigatran. In the meantime clinicians are referred to the New Zealand guidelines.[1]

It is strongly recommended that clinicians read the Product Information **before** prescribing dabigatran. The Product Information is available from the TGA website.[2] For more detailed information regarding the considerations of the TGA in approving dabigatran please see the Australian Public Assessment Report (AusPAR).[3]

Reporting adverse events

Health professionals are requested to report adverse events associated with dabigatran to the TGA via the TGA website.

References

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Risk of myopathy and rhabdomyolysis with simvastatin – new dosage recommendations and contraindications

Summary

To reduce the risk of myopathy and rhabdomyolysis, health professionals are advised of new recommendations to limit the use of high dose simvastatin (80 mg/day) and of new contraindications for the use of simvastatin with potent CYP3A4 inhibitors, gemfibrozil, cyclosporin or danazol (see box). They are also reminded of the need for lower doses when simvastatin is used concomitantly with drugs that interact with simvastatin and increase its absorption.

Simvastatin, like other inhibitors of HMG-CoA reductase, is known to cause myopathy and more rarely rhabdomyolysis. The risk of myopathy is dose related and is more likely to occur in the first year of treatment. Other risk factors include age ≥65 years, female gender, uncontrolled hypothyroidism and renal impairment. Myopathy can be the result of interactions with other drugs. Many cases may be associated with a genetic variant which results in reduced uptake of simvastatin by the liver.

A recent re-analysis by the US Food and Drug Administration of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial has confirmed the increased risk of myopathy and rhabdomyolysis with

Key safety related updates for simvastatin *

Risk of myopathy/rhabdomyolysis

The risk of myopathy is greater in patients on simvastatin 80 mg compared with other statin-based therapies with similar LDL-C lowering efficacy

New dose recommendation

The 80 mg/day dose of simvastatin should only be used in patients at high risk of cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks

New contraindications

Concomitant administration of potent CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone). If treatment with these medicines is unavoidable, simvastatin should be suspended during the course of treatment.

Concomitant administration of gemfibrozil, cyclosporin or danazol

Precautions – interactions with other medicines

Amiodarone: the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with amiodarone

Calcium channel blockers:

– **Verapamil or diltiazem**: the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with verapamil or diltiazem

– **Amlodipine**: the dose of simvastatin should not exceed 40 mg daily in patients receiving concomitant medication with amlodipine

Moderate inhibitors of CYP3A4: patients taking other medicines labelled as having a moderate inhibitor effect on CYP3A4 concomitantly with simvastatin, particularly higher simvastatin doses, may have an increased risk of myopathy

Other fibrates: concomitant use of gemfibrozil is contraindicated. The concomitant use of simvastatin and other fibrates should be avoided.

Niacin (≥1 g/day): the dose of simvastatin should not exceed 20 mg daily in patients receiving concomitant medication with niacin (nicotinic acid) ≥1 g/day

Colchicine: there have been reports of myopathy and rhabdomyolysis with the concomitant administration of colchicine and simvastatin in patients with renal insufficiency. Close clinical monitoring of patients taking this combination is advised.

* These updates provide information on changes to the recommendations for simvastatin. For full prescribing information, see the Zocor Product Information available on the TGA website.

increasing doses of simvastatin.[1] In the trial the incidence of myopathy increased from 0.02% among patients taking 20 mg of simvastatin daily to 0.9% among those taking 80 mg daily. The trial also found only a limited increase in benefit from the 80 mg dose compared with lower doses.

Following a review of these findings, the TGA is recommending limitations to the use of high dose simvastatin (80 mg/day) and changes to the contraindications. The TGA is working with the sponsors of simvastatin and simvastatin-containing medications to update the Product Information to provide increased warnings regarding the risk of myopathy associated with high doses of simvastatin, and to detail the new dosage recommendations and contraindications.

Important information for health professionals

The 80 mg/day dose of simvastatin should only be used in patients at high risk of cardiovascular complications who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks.

Concomitant administration of simvastatin with potent CYP3A4 inhibitors, gemfibrozil, cyclosporin, or danazol is now contraindicated (see box for details).

Simvastatin is contraindicated in patients who have previously experienced myopathy secondary to other lipid lowering agents.

In patients taking simvastatin for whom an interacting agent is needed, a lower dose of simvastatin or an alternative statin with less potential for drug-drug interactions should be used.

Health professionals should advise patients who are commencing simvastatin therapy or whose dose is being increased, of the risk of myopathy and remind patients to report any unexplained muscle pain, tenderness or weakness to a health professional promptly.

Simvastatin therapy should be discontinued immediately if myopathy is suspected.

Health professionals are asked to report any suspected cases of myopathy to the TGA.

Reference

1. Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. US Food and Drug Administration. 8 June 2011. www.fda.gov/Drugs/DrugSafety/ucm256581.htm#Simvastatin_Dose_ Limitations [cited 2011 Nov 8]

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What to report? You do not need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** on the TGA website
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

New drugs

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

Nomegestrol/oestradiol

Zoely (Merck Sharp and Dohme)

24 white active tablets and 4 yellow placebo tablets

Approved indication: contraception

Australian Medicines Handbook section 7.1.1

This new oral contraceptive contains the progestogen nomegestrol (2.5 mg) combined with the endogenous oestrogen 17β-oestradiol (1.5 mg). Nomegestrol is similar to endogenous progesterone and has a strong affinity for the human progesterone receptor. It also has strong anti-gonadotropic activity and moderate antiandrogenic activity.

The contraceptive efficacy of this new combination has been compared to drospirenone 3 mg/ethinyloestradiol 30 microgram (21 active and 7 placebo tablets) for 13 menstrual cycles in women aged 18–50 years.[1] In this open-label trial, there were 4 pregnancies in the 1587 women who took the nomegestrol combination pill and 3 pregnancies in the 534 women who took the comparator pill (estimated Pearl Index in women aged ≤35 years = 0.38 vs 0.81). Most pregnancies were thought to be related to missed pills or conditions that affect contraceptive efficacy, such as diarrhoea or vomiting. However the reason for contraceptive failure was not identified for one pregnancy in the nomegestrol/oestradiol group. There were no pregnancies in women aged 36 and over.

The incidence of breakthrough bleeding or spotting in the trial was slightly higher with the nomegestrol combination pill than with the comparator during most cycles (14–20% vs 11–17%). However, this decreased over time in both groups. Periods were shorter and lighter with nomegestrol/oestradiol and missed periods were more common. This may have been because there were only four placebo pills with nomegestrol/oestradiol compared to seven with the comparator. One-third of women had acne at baseline. By cycle 13, this had decreased to 24% in the nomegestrol/oestradiol group and 16% in the comparator group.[1]

The contraindications and precautions for nomegestrol/oestradiol are similar to other combined pills, as are the adverse effects. Acne (15.3% vs 7.1%), irregular withdrawal bleeding (11.7% vs 0.4%), weight gain (7.9% vs 6.2%) and headache (6.6% vs 6.2%) were more common with nomegestrol/oestradiol than with drospirenone/ethinyloestradiol. These events led to discontinuation in some women. There were three serious adverse events possibly related to treatment. These were menorrhagia in the nomegestrol/oestradiol group, and deep vein thrombosis and systemic lupus erythematosus in the comparator group.[1]

The combination of nomegestrol and oestradiol proved to be an effective contraceptive compared with drospirenone/ethinyloestradiol. It is unclear if it will have any advantages over currently approved contraceptive pills, however periods may be shorter and lighter.

[T][T] manufacturer provided additional useful information

Reference [A]

1. Mansour D, Verhoeven C, Sommer W, Weisberg E, Taneepanichskul S, Melis GB, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinyloestradiol and drospirenone in a 21/7 regimen. Eur J Contracept Reprod Health Care 2011 Oct 13. [Epub ahead of print]

The T-score ([T]) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

[A] At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

Book review

Martindale: The complete drug reference. 37th ed.

UK: Pharmaceutical Press. 4142 pages.

***Helen Trenerry**, Director of Queensland Drug Information Centre, Royal Brisbane and Women's Hospital, Herston, Queensland*

This edition, published two years since the last, continues the tradition of previous Martindales in providing health professionals with unbiased, evaluated information on drugs used worldwide.

It follows the same format as the last two editions and is published as two volumes. Volume A contains drug monographs while Volume B contains a list of worldwide proprietary preparations, a directory of manufacturers and the indexes. The volumes have been clearly labelled on the spines to indicate their content. There are 5930 drug monographs in total – 240 are new and 171 old ones have been removed. They are grouped in chapters according to their action, for example antibacterials, cardiovascular drugs. The start of each chapter provides a review of the disease and treatment followed by the individual monographs listed alphabetically. Each monograph contains the drug name, chemical structure, information on adverse effects, drug interactions, pharmacokinetics, uses and administration, available preparations and references.

Martindale provides information and monographs on herbal medicines, diagnostic agents, radiopharmaceuticals, toxins and poisons, which is unlikely to be included in other pharmaceutical references making it a unique resource. There is a new chapter on pharmaceutical excipients which has combined and expanded on the chapters in the last edition. It covers colouring agents, non-ionic surfactants, organic solvents, paraffins, soaps and other anionic surfactants, and stabilising and suspending agents.

Volume B has expanded the list of proprietary preparations to 41 countries and regions including Ukraine, and has over 161 000 preparations. The list of manufacturers extends to over 15 000.

Martindale is also available electronically. It remains a valuable resource of current, unbiased information on pharmaceuticals for pharmacists and other health professionals.

Answers to self-test questions

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

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