Australian Prescriber

VOLUME 30 | NUMBER 4 | AN INDEPENDENT REVIEW | AUGUST 2007

CONTENTS

Dealing with depression and medical illness

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Summary

Depressive illness in the presence of medical illness is common and the relationship between them is complex. Often the medical illness can cause the depression. However, in some illnesses depression may be the primary presentation. Depression in medically ill patients may be difficult to diagnose. The assessment of both conditions and the interaction between them is critical in managing these patients. A review of the medical disorder and the patient's medications is important. Psychotherapy may be sufficient to treat mild depression. However, for more severe depression antidepressants may be required, or referral to a psychiatrist. The patient and their family are likely to need long-term support.

Key words: antidepressant drugs, cognitive behaviour therapy, drug interactions.

(Aust Prescr 2007;30:86–8)

Introduction

Depressive illness in patients with medical illness is common and has extensive implications for the patient and their family, and the treating doctor. The co-occurrence of these disorders results in amplification of suffering, increased morbidity and mortality, prolonged hospital stays and increased utilisation of healthcare services.

Unfortunately, the diagnosis of depression in the presence of medical illness is frequently missed, often resulting in unnecessary investigations and procedures, increased disability and increased costs to the community. The main issues in dealing with depression in this context are making an accurate diagnosis, teasing out the complexity of the interaction between the depression and the medical illness and establishing an appropriate management plan that addresses both problems and the interactions between them.

The extent of the problem

Rates of depression vary with the nature of the medical disorder. The most common associations are found in neurological, cardiovascular, endocrine and oncological illnesses, but can occur in almost any disorder. It has been reported that around 30% of patients attending a neurological clinic had significant symptoms of depressive illness and in up to 72% of these patients the depression was unrecognised by the physician.[1] The prevalence of depression following acute ischaemic heart disease may be as high as 30% and the risk persists for 12 months following myocardial infarction. After stroke the prevalence of depression may be as high as 31% at three months.[2] In cancer patients after the diagnosis, the risk of depression is as high as 55%.

Comorbid depression has been suggested to increase the death rate of the underlying illness by as much as 4.3 times regardless of whether the patient was previously healthy or not.[3] In haemodialysis patients, depression predicted mortality after adjusting for age, gender, race, medical comorbidity and several biochemical markers.[4] Depression was also found to be a significant predictor of cardiac mortality in patients with recent myocardial infarction.[5] There is some evidence that treating depression in cardiac patients following myocardial infarction or those with unstable angina may reduce subsequent cardiac events.[6] This may be due to antiplatelet aggregation effects that have so far been documented following treatment with the selective serotonin reuptake inhibitors sertraline, paroxetine and escitalopram.[7,8]

Compared with non-depressed patients, those with comorbid depression have increased mortality, prolonged length of hospital stay and greater number of days in hospital on follow-up.[9]

In this issue…

Thanks to some of the interventions described by Andrew McCann the outlook for patients with coronary occlusion has improved. Survivors may, however, become depressed and James Olver and Graham Burrows say that depression often co-exists with medical illness. If antidepressants are prescribed they may cause the patient unexpected consequences such as the dental problems discussed by Michael Page and Luke Somerville-Brown.

Osteonecrosis of the jaws is another example of a drug treatment causing a dental problem. Alastair Goss and Patricia Backhouse describe this uncommon adverse effect of bisphosphonates.

The relationship between depression and medical illness

The association between depression and medical disorders is complex. The depressive illness may be a consequence of the medical illness or may be a primary issue. For example, depressive symptoms frequently present in Parkinson's disease, stroke, space-occupying lesions of the central nervous system, and endocrinopathies such as Cushing's syndrome and thyroid disorders. Depressive symptoms may precede the onset of some disorders including hypothyroidism, ischaemic heart disease and stroke and may even contribute to their causation through alterations in platelet adhesion and immunological changes.

The exact biological mechanisms by which these illnesses may cause depression are yet to be determined. However, reduced dopamine availability has been suggested in illnesses such as Parkinson's disease. Destruction of central nervous system pathways have been implicated in depression, especially in patients with central nervous system lesions. Hormonal modulation of central monoamine receptors may explain some depression in the endocrinopathies.

Finally, the association between depression and medical illness may be explained by factors that can lead to both disorders. For example, stress and substance abuse may lead to the development of stress-related and substance-related medical disorders and depression.

Making the diagnosis

A careful history of the onset, course and severity of the depressive symptoms is required. This may help tease out whether the depression is primary or secondary and also the relationship between the severity of physical symptoms of illness and degree of depression. Risk factors, such as those for suicidality, should always be assessed.

Appropriate investigations (for example thyroid, blood, liver and renal function screen and neuroimaging) are needed to exclude an organic cause of depression and to assess the status of the medical illness. Specific metabolic investigations may be needed depending on the medical disorder, for example calcium concentrations in patients with metastatic cancer.

Depression in medically ill patients may be overlooked by the busy medical practitioner. This is partly due to the 'understandability' of the depressive symptoms and the dominance of the physical presentation of the disorder. However, the constellation of the depressive symptoms may also be difficult to recognise in the presence of a major medical disorder.

Depressive symptoms can be grouped into biological (e.g. sleep, appetite), psychological (e.g. preoccupations with guilt, failure) and social (e.g. withdrawal, loss of role). Psychologically-based symptoms such as dissatisfaction, a sense of failure, feeling the illness was punishment, suicidal thoughts, crying and loss of social interest in family and friends are the most discriminating symptoms of depression in medically ill patients.[10] When sleep disturbance is unexplained by the medical disorder and is accompanied by ruminatory thoughts of guilt, failure and hopelessness, it may also help in the diagnosis. This is also true for unexplained weight loss.

The diagnosis may be complicated by substance abuse. Depression and substance abuse may frequently coexist and contribute to the expression of either disorder. Alcohol, cannabis and amphetamines have been directly implicated in the cause of depression.

Managing the medical illness

A review of the medical disorder is important. This may include minimising unnecessary medication and maximising the treatment of the medical condition. Rehabilitation approaches to chronic problems such as pain, neurological disorders, arthritis and some cancers should be considered. It can be helpful to give advice regarding a healthy lifestyle including diet, sleeping habits, substance misuse and regular exercise within the constraints of the medical problem. Improvements in the individual's functioning can have considerable benefit in terms of self-esteem and mood.

> Depression in medically ill patients may be overlooked

Managing the depression

Although optimising the management of the medical illness may improve the patient's mood, the depression may still require specific management. This includes psychotherapeutic techniques and antidepressant medications.

When the symptoms are mild to moderate, psychotherapy is indicated. Cognitive behaviour therapy is often well suited for these patients. Standard elements may include challenging negative thinking and catastrophisation, relaxation techniques, behavioural scheduling which may include regular exercise and socialisation and problem solving techniques.

When the depressive disorder is moderate to severe, medications may be required. Older tricyclic antidepressants and monoamine oxidase inhibitors should be avoided as first-line drugs since they may interact and worsen the underlying medical disorder due to anticholinergic, anti-adrenergic and cardiac effects. As many patients will be on multiple medications for their underlying physical disorder, care should be taken to avoid drug interactions. In order to counter altered metabolism and minimise adverse effects, medications should be started at low doses and adjusted slowly.

When the depression is severe with suicidal ideation or the interaction with the medical disorder is complex, referral to a psychiatrist may be indicated. Electroconvulsive therapy (ECT) can be used when the depression is severe. However,

caution is required and ECT is contraindicated in patients with uncontrolled hypertension or raised intracranial pressure.

In all cases, frequent liaison with other professionals involved with the management of the patient is essential. In some disorders such as chronic pain, the interactions between illness and depression are so complex the patient is best managed in a multidisciplinary rehabilitation program where physician, psychiatrists, psychologists and physical therapists meet regularly and address the issues in a co-ordinated approach. Changes to the Medicare Benefits Schedule may make it easier for patients to access these services.

Patient support

As with all therapeutic interactions, and in particular when they are complex and likely to be prolonged as in the case of comorbid depression with medical illness, a good rapport with the patient and their family is essential. This will begin with education of the patient and their family about both the medical disorder and the depressive disorder. Often there are negative judgments from family members who may be critical of the patient for not trying or using the symptoms to avoid the usual responsibilities of their role. On the other hand, some families may perpetuate disability and not encourage the patient to maximise their capacity. The patient and their family are likely to need a prolonged period of support which may be best supplied with regular appointments.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 111)

1. Dothiepin is the first treatment of choice for patients with comorbid depression and medical illness.
2. Unexplained weight loss and sleep disturbance should not be considered signs of depression in medically ill patients.

Letters

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

Generic medicines

Editor, –The article, 'Frequently asked questions about generic medicines' (Aust Prescr 2007;30:41–3), provides a clear and useful précis of some of the key issues that can impact on the decision to substitute an equivalent generic medicine.

However, the question of whether or not to substitute a medicine with a narrow therapeutic index with a bioequivalent generic remains open to debate. Perhaps the prescriber and pharmacist could approach this decision with more confidence if we consider the criteria used to define the term narrow therapeutic index, or more correctly narrow therapeutic ratio, by regulatory agencies.

The US code of federal regulations (Part 320.33(c) – Bioavailability and bioequivalence requirements) defines a medicine displaying a narrow therapeutic ratio as follows:

There is less than a 2-fold difference between median lethal dose and median effective dose

OR

There is less than a 2-fold difference between minimum toxic concentrations and minimum effective concentrations in the blood

AND

Safe and effective use of the drug products requires careful dosage titration and patient monitoring.[1]

The US Food and Drug Administration (FDA) specifically mentions only five medicines falling into this category, namely digoxin, lithium, phenytoin, theophylline and warfarin. However, the FDA recommends that even medicines with narrow therapeutic indices may be evaluated for bioequivalence using the conventional confidence interval limits of 0.80 to 1.25.[2]

In reality, the number of medicines matching the definition of narrow therapeutic ratio is very small indeed. In clinical practice, the dosage and plasma concentration of these medicines is usually carefully titrated and monitored.

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Professors AJ McLachlan, I Ramzan and RW Milne, authors of the article, comment:

We agree with the issues that Dr Pearce raises and add a further comment. We would suggest that the list of narrow safety margin medicines (and the criteria listed) also includes immunosuppressants (such as cyclosporin) and many anticancer medicines. A useful commentary on this issue makes the critical point that inter-subject (between people) variability in the pharmacokinetics of narrow safety margin medicines is considerably higher than intra-subject (within the same person on any given day) variability in pharmacokinetics.[1] This means that for many of these drugs careful monitoring of a patient's therapeutic response (or some surrogate of that response) can facilitate dose individualisation and that once that dose is selected, therapy can generally continue uneventfully with appropriate monitoring.

In our article we also highlighted the importance of separating the scientific (which remain unchallenged) from the clinical (which remain in the purview of clinical judgement) issues surrounding generic substitution of medicines. The latter point being that the potential for confusion around the issues of brand substitution can be managed by effective communication and clinical judgement. Obviously the potential for problems increases significantly when people are confused about their medicines and are taking medicines with a narrow safety margin.

In summary, Australian prescribers, pharmacists, other healthcare providers and patients should have full confidence in the Australian system used to establish and evaluate bioequivalence of drug products which applies to all medicines independent of their safety margin. Effective communication of all these issues is a central component of brand substitution.

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Editor, – I note that the problem of generic medicines has been mentioned again in your April edition (Aust Prescr 2007;30:41–3).

I am a firm believer in not using generic names – not from habit, but from practicality. When a drug is marketed the makers go to a lot of trouble to find a name that is easily recognised and remembered and unlikely to be confused with other drugs. The same cannot be said about generic names which are often complicated chemical names and the possibility of confusion arises.

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Response:

The Editorial Executive Committee believes that the use of generic names in *Australian Prescriber* is appropriate. There are several reasons for this.

1. Medical students are not taught brand names, so it is appropriate that educational material uses generic names.
2. There are many different brand names for commonly prescribed drugs. It would be impractical to include all the brand names of each drug mentioned in *Australian Prescriber.*
3. The variety of brand names can cause confusion. There is a possibility of medication error with badly written prescriptions for drugs such as Losec and Lasix, Mobilis and Movalis, MS Contin and Oxycontin, Provera and Proviron.

4. The brand names are devised as part of a drug company's marketing strategy. As *Australian Prescriber* is independent of the pharmaceutical industry it avoids brand names.
5. Many thousands of people overseas visit the *Australian Prescriber* website (www.australianprescriber.com). As brand names vary from country to country it is helpful if the articles use internationally approved names.

While the Editorial Executive Committee appreciates other views, generic names will continue to be used in *Australian Prescriber.*

Nurse prescribing

Editor, – It was with interest that I read the editorial 'Nurse prescribing: adding value to the consumer experience' (Aust Prescr 2007;30:2–3). As Australia finds itself in the midst of a health workforce crisis, there is pressure to allow health professionals other than doctors to prescribe.

The strength of medical practitioner training means doctors are the health professionals most qualified to understand the risks and benefits inherent in prescribing, and to make a complete diagnosis. Patients have confidence in a doctor's ability and knowledge. We should not substitute doctors with lesser-trained health professionals simply to ease an acute political problem with little acknowledgement of the effect it will have on fragmentation of care, patient outcomes and the quality of prescribing. Where there is no other choice, an alternative must be sought in the best interests of patient care, but such a compromise should not become the standard.

Non-medical practitioners are able to prescribe from a broad range of S3 medications. The remaining S4 prescription-only medicines should remain as that – doctor prescription-only medications.

The prime consideration should be the safety of patients. The benefit of a degree in medical training as opposed to a short course in prescribing should be paramount to any discussion around prescribing and the quality use of medicines.

The Productivity Commission proposals have the potential to realign healthcare delivery. However, in the words of Martin Van Der Weyden, the Editor of the Medical Journal of Australia, 'It should not be the slippery slope to doctor pretenders'.[1]

John Gullotta
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Reference

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Evidence, risk and the patient

Editor, –The article, 'Evidence, risk and the patient' (Aust Prescr 2007;30:47–50) shows the limitations of statistics in medical decision making. While we would like a p-value to answer the question, 'How likely is it that the results are 'for real' and not just due to chance?' this is not the question that the p-value answers. Instead, it answers the question 'If we wanted to blame chance for the results, what sort of chance would we be blaming?'

Consider a trial of the power of anonymous prayer to improve the recovery of patients in coronary care units.[1] This was summarised in the Australian medical press as concluding that prayer works, but '[t]here was a one in 25 chance that the better outcomes had arisen by chance'.[2] This misinterpretation of a p-value of 4% implies that there is precisely a 96% chance that there is a God responsive to prayers. What has actually been discovered is that the prayed-for group recovered a little faster to an extent which would be explained by atheists as the outcome of a 4% chance and which would be regarded as anything but chance by the religious.

The calculation of the 'number needed to treat' also has its limitations. In chronic conditions, people who receive the additional treatment may all have an event delayed by a few months, but if the data are arbitrarily presented so that we are told that an extra 10% survive for five years, this implies only 1 in 10 has benefited.

Evidence-based medicine has generated a lot of suspicion amongst 'rank and file' doctors. This is understandable, because if statistics are misunderstood and the clinical context is ignored, bizarre assertions can result. For example, the pronouncements that there is no evidence to support cleaning the skin before administering injections.[3]

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A century of concern about complementary medicines

John S Dowden, Editor, Australian Prescriber

In August 1907 the Parliament of the Commonwealth of Australia received the report of the Royal Commission on Secret Drugs, Cures and Foods.[1] This revealed the widespread promotion and purchase of dangerous and useless medicines. Then, as now, there was political concern about Australia's population growth and the report contended that nostrums had brought about a decline in fertility and increased infant mortality.

The declining birth rate of the recently federated country was of particular concern to Octavius Beale, a piano manufacturer from Sydney. He therefore persuaded Prime Minister Alfred Deakin to establish the Royal Commission. The Prime Minister agreed as long as his government did not have to pay anything. Beale therefore funded the inquiry himself. This included travel to Britain, Germany, Canada and the USA.

The 431 page report seems very moralistic, portraying the manufacturers of medicines as 'gilded miscreants' engaged in the 'multifarious evils of the traffic in secret drugs'. These medicines were 'not subject to preliminary examination, license and inspection', so Beale proposed legislation for the compulsory registration of products. He may therefore have begun a process which ultimately led to the foundation of the Therapeutic Goods Administration.

Beale found that newspapers and magazines were publishing stories which were really promotional pieces, in addition to accepting advertising for unproven medicines. Even then the marketing was sophisticated with companies buying and selling the names of pharmacists' customers. Beale therefore proposed a ban on pharmaceutical advertising.

In 1907 little information was disclosed about medicines, particularly their active ingredients. Beale said, 'The preservation of secrecy… is absolutely indispensable to the traders whose traffic is reported upon…'. One hundred years later, 'commercial-in-confidence' is still a barrier to our understanding of complementary medicines.[2]

Acknowledgement: former Editor of Australian Prescriber, Dr John McEwen, for unearthing the report.

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Book review

Therapeutic Guidelines: Neurology. Version 3.

Melbourne: Therapeutic Guidelines Limited; 2007. 273 pages. Price $39, students $30, plus postage

John Casey, Resident Medical Officer, Royal Brisbane Hospital, Brisbane, and Pharmacist

The third edition of Therapeutic Guidelines: Neurology is a timely update to an essential reference for Australian prescribers. This edition is well organised and presents concentrated information that is suitable for readers of all levels – from medical students to specialists.

This edition covers essential subject areas of neurology such as headache, stroke, epilepsy and Parkinson's disease. As a doctor-in-training, I found the headache section useful with concise differential diagnoses and red-flag warnings. The stroke chapter is compact and contains the latest evidence and best practice recommendations. Management of epilepsy and Parkinson's disease can be challenging and, appropriately, these chapters have been expanded to assist practitioners with patients who have treatment-resistant disease or complications.

The redesigned chapter on getting to know your drugs contains detailed practical information that also covers off-label uses. Newly released drugs, such as levetiracetam and pregabalin, have been included and each entry provides an excellent overview for busy practitioners. For pharmacists and specialists, it is sufficiently detailed to include pharmacokinetics and extensive listings of drug interactions and adverse reactions.

While this revision is well written, some sections are overly detailed and wordy which detracts from this book being a quick reference guide. A practical inclusion for future editions would be a tabulated version of driving recommendations for people with epilepsy, rather than a website reference.

I recommend this addition to the Therapeutic Guidelines library. It is a great reference for common neurological conditions and is sure to help most prescribers in their daily practice.

Antiplatelet therapy after coronary occlusion

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Summary

Platelets are pivotal in the pathogenesis of acute coronary syndrome and in the complications following the implantation of coronary stents. Dual antiplatelet therapy with aspirin and clopidogrel is essential to reduce the risk of recurrent ischaemic events. The combination should be taken for up to one year following acute coronary syndrome in patients at high risk of future events. Aspirin should be continued indefinitely. The duration of treatment with clopidogrel depends on the type of stent implanted. Patients with drug-eluting stents require combination therapy for at least one year. Premature withdrawal of antiplatelet therapy carries a risk of thrombosis in the stent. In patients with drug-eluting stents, thrombosis may occur as a late complication of stent implantation. Withdrawal of antiplatelet therapy should be done in consultation with the cardiologist who implanted the drug-eluting stent.

Key words: aspirin, clopidogrel, stents.

(Aust Prescr 2007;30:92–6)

Introduction

The term 'acute coronary syndrome' encompasses the spectrum of unstable angina and myocardial infarction with or without elevation of the ST segment of the ECG. These conditions share a common aetiology, usually rupture of an atherosclerotic plaque, activation of the coagulation cascade with platelet thrombus formation and vessel occlusion possibly with distal embolisation.

Contemporary medical therapy in these patients includes combination antiplatelet therapy, beta blockers, angiotensin converting enzyme inhibitors and cholesterol lowering drugs. Despite optimal medical therapy a significant proportion of patients develop recurrent angina and re-infarction. An 'invasive strategy' has therefore been adopted whereby early coronary angiography is undertaken and in those with suitable coronary anatomy (namely flow limiting coronary stenoses in important sized coronary vessels) coronary revascularisation is performed. This may either be percutaneous coronary intervention (see box) or coronary artery bypass grafting surgery depending on the nature and extent of coronary disease. Such an approach reduces the rates of recurrent angina and myocardial infarction. Both acute coronary syndrome and percutaneous intervention are associated with high levels of platelet activation. Effective antiplatelet therapy is therefore essential to reduce the risk of recurrent vascular events.

Antiplatelet drugs

Platelets are activated by a number of pathways. When there is marked platelet activation, combinations of antiplatelet drugs are required to inhibit platelet function (Fig. 1).

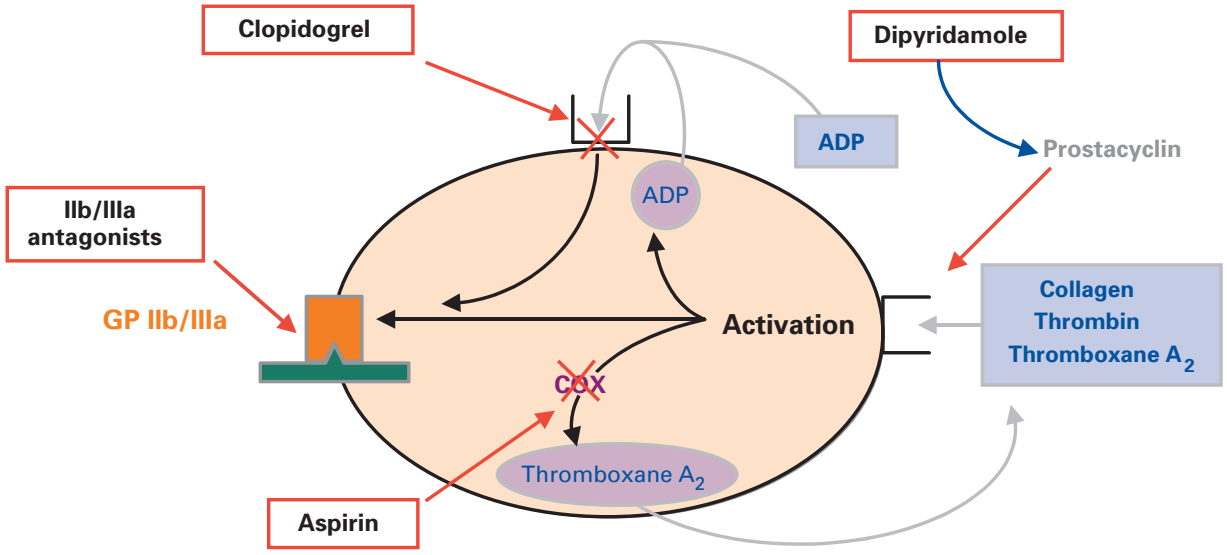
Aspirin

Aspirin acts by irreversibly inactivating platelet cyclo-oxygenase (COX)-1. This stops the synthesis of thromboxane A_2, a known vasoconstrictor and potent platelet aggregator. The antiplatelet effect is relatively weak as aspirin inhibits only one of the pathways of platelet activation. As aspirin irreversibly acetylates

Acute coronary syndrome	A collective term to describe unstable angina, non-ST elevation myocardial infarction, and ST elevation myocardial infarction.
Percutaneous coronary intervention	A collective term for balloon angioplasty, atherectomy and coronary stenting. Nowadays it is usually synonymous with coronary stenting.
Restenosis	Gradual renarrowing within the stent or at the site of angioplasty secondary to neointimal hyperplasia and smooth muscle proliferation. Usually occurs within 2–8 months following stent implantation. Reduced with drug-eluting stents.
Stent thrombosis	Occlusion of the stent with thrombus usually within the first 24–48 hours following stent implantation, but rarely occurring late after stent implantation. There may be higher rates of late thrombosis with drug-eluting stents.
Drug-eluting stent	A tube coated with an antiproliferative drug to prevent restenosis.

Fig. 1

Mechanism of action of antiplatelet drugs



Key

ADP	adenosine diphosphate
GP IIb/IIIa	glycoprotein IIb/IIIa complex
COX	cyclo-oxygenase

Aspirin stops platelet activation by inhibiting the enzyme cyclo-oxygenase 1. This prevents the synthesis of thromboxane A_2 which normally causes platelet aggregation.

Clopidogrel inhibits the activation of the glycoprotein IIb/IIIa complex by preventing adenosine diphosphate binding to a platelet receptor. This inhibits platelet aggregation. Antagonists of the glycoprotein IIb/IIIa receptor stop platelet aggregation by blocking the binding of fibrinogen to the receptor.

Dipyridamole increases the production of prostacyclin, a potent inhibitor of platelet aggregation.

COX-1, full recovery of platelet function requires regeneration of new platelets. This typically occurs about 7–10 days from the last dose.

Clinical data

The Antithrombotic Trialists' Collaboration showed that in patients with acute coronary syndrome aspirin is associated with a relative reduction of recurrent vascular events by about 25%. In patients with unstable angina, without myocardial infarction, the benefit is even greater.[1]

Dose and duration

A dose of 300 mg of soluble aspirin should be given immediately to any patient with suspected acute coronary syndrome. If only enteric-coated aspirin is available then this should be chewed or crushed to ensure rapid absorption.

After the acute event, long-term therapy is with aspirin 75–150 mg/day. Low doses (75–100 mg/day) are just as effective as higher doses and may confer less risk of gastrointestinal bleeding although this remains contentious. Therapy with aspirin should be continued indefinitely following acute coronary syndrome events, percutaneous coronary interventions and coronary artery bypass surgery.

Adverse effects

These include gastrointestinal adverse effects (nausea, dyspepsia, peptic ulcer, bleeding), easy bruising and hypersensitivity reactions (such as exacerbation of asthma in 10% of the population and urticaria in 0.2%). Enteric-coated aspirin may be better tolerated in the event of nausea or dyspepsia but does not confer a lower risk of gastrointestinal bleeding. The absolute increase in risk of gastrointestinal bleeding with low-dose aspirin is less than 1% per year compared with placebo (2.3% vs 1.45% per year in a meta-analysis).[2] In patients with a history of complicated peptic ulcer disease the combination of low-dose aspirin plus a proton pump inhibitor is more effective in reducing a patient's risk of gastrointestinal bleeding than switching the patient to clopidogrel.[3]

Thienopyridines

The thienopyridines (clopidogrel and ticlopidine) prevent adenosine diphosphate from binding to its receptor on platelets. This stops activation of the glycoprotein IIb/IIIa complex and thereby inhibits platelet activation. Both drugs are prodrugs which require metabolism by the cytochrome P450 enzyme system to become active.

Clopidogrel

The maximum effect of clopidogrel occurs within approximately six hours of a loading dose of 300 mg and within approximately two hours of a 600 mg loading dose. Higher loading doses have not conclusively been shown to be of further benefit. Like aspirin the effects are irreversible and full recovery of platelet function takes up to 7–10 days from the last dose.

Clinical data

The combination of clopidogrel with aspirin is synergistic providing more complete platelet inhibition than with either drug alone. After nine months of treatment in patients with non ST elevation acute coronary syndrome, the combination of clopidogrel plus aspirin provided a 20% relative risk reduction in death, myocardial infarction or stroke compared to aspirin alone.[4] The combination was of benefit regardless of whether or not a stent was implanted. In patients with ST elevation myocardial infarction receiving thrombolytic therapy, the combination of clopidogrel and aspirin provided superior outcomes compared with aspirin alone.[5] The optimal duration of combination therapy in this setting is unknown.

Adverse effects

Clopidogrel can cause gastrointestinal symptoms and skin rash. The combination of aspirin and clopidogrel is associated with a 1% absolute increase in major, non-life-threatening bleeding per year compared to aspirin alone.

Ticlopidine

This drug is now rarely used given its adverse effect profile of gastrointestinal upset, neutropenia (in 2.4% of cases) and rare cases of thrombotic thrombocytopenic purpura. It is an alternative in the rare situation of intolerance to clopidogrel. Haematological monitoring should be undertaken every two weeks during the first four months of therapy to watch for neutropenia.

Glycoprotein IIb/IIIa receptor antagonists

The glycoprotein IIb/IIIa receptor located on the platelet surface plays a pivotal role in platelet thrombus formation by binding to fibrinogen thereby facilitating cross linkage of platelets. Tirofiban and abciximab are intravenous drugs used in patients with high risk acute coronary syndromes and patients undergoing high risk percutaneous coronary interventions. Oral glycoprotein IIb/IIIa antagonists have not shown benefit.

Other antiplatelet drugs

Dipyridamole and sulfinpyrazone confer no additional benefit in acute coronary syndrome and are not recommended.

Antiplatelet therapy following acute coronary syndrome (without coronary stent implantation)

In patients with non ST elevation acute coronary syndrome, 12 months of clopidogrel is recommended. In patients with ST elevation myocardial infarction who are not undergoing coronary stenting the optimal duration is unclear.

Antiplatelet therapy after coronary stenting

Coronary stent implantation is associated with two potentially adverse sequelae. The first is stent thrombosis. Coronary stents are inherently thrombogenic and dual antiplatelet therapy is essential to reduce the risk of thrombosis in the stent. This risk is greatest early after implantation when platelet activity is maximal and diminishes once endothelialisation of the stent occurs. The second adverse consequence of stent implantation is restenosis. Restenosis is defined as gradual renarrowing within the stent secondary to neointimal proliferation and usually occurring within 2–8 months of stent implantation. It has been dramatically reduced with the introduction of drug-eluting stents. These stents elute antiproliferative drugs such as sirolimus and paclitaxel which suppress the growth of neointimal tissue (Table 1). As a consequence adequate endothelialisation may be delayed thus the duration of dual antiplatelet therapy needs to be longer than with bare metal stents.

The usual antiplatelet regimen consists of aspirin (at least 75 mg/day) indefinitely and clopidogrel (75 mg/day). If stent implantation was for non ST elevation acute coronary syndrome then combination therapy is beneficial for at least one year.[4] If implantation was elective the duration of clopidogrel therapy depends on the stent type.

Non-drug-eluting stents

Bare metal stents require a shorter duration of combination therapy than drug-eluting stents. Initial data suggested that clopidogrel be prescribed in conjunction with aspirin for a minimum duration of one month. However, data from the

Table 1
Available drug-eluting stents

Stent name	Antiproliferative drug
Cypher	sirolimus
Taxus	paclitaxel
Endeavor	zotarolimus
Xience V	everolimus

CREDO study show a small but definite benefit from one year of dual antiplatelet therapy following elective bare metal stent implantation.[6] One year of therapy may therefore be considered in patients with more extensive vascular disease.

Drug-eluting stents

A longer duration of combination antiplatelet therapy is required because the drug in the stent delays endothelialisation. Initial data from trials suggested clopidogrel be continued for a minimum of 3–6 months following implantation of a stent. However, data are emerging that drug-eluting stents are associated with a slightly increased risk of late stent thrombosis (1 in 500 patient-years increased risk).[7] Incomplete or delayed stent endothelialisation due to drug inhibition of neointimal growth is at least partly responsible for this phenomenon.

Late stent thrombosis is serious and usually presents as myocardial infarction or sudden death with published case fatality rates in the order of 20–45%. Many cases have been associated with the withdrawal of antiplatelet therapy (for example for surgery), or with aspirin monotherapy. The risk is also higher with longer total stent lengths, multiple stents and in patients with diabetes, renal impairment and left ventricular dysfunction. An increasing number of cardiologists therefore recommend at least one year of combination therapy and in some instances indefinite combination therapy for patients with drug-eluting stents.

Recommendations

All patients should take low-dose aspirin indefinitely if possible. The duration of clopidogrel depends on the clinical situation.

One approach to therapy with clopidogrel is:

- minimum of one month of clopidogrel therapy following elective implantation of a bare metal stent. If the bleeding risk is low, consider up to 12 months in patients with more extensive vascular disease or patients with a high risk of coronary artery thrombosis.
- 12 months following implantation of a bare metal stent for acute coronary syndrome
- at least 12 months following implantation of a drug-eluting stent regardless of the clinical context
- indefinite combination therapy if possible following implantation of drug-eluting stents in high-risk patients (for example, left main coronary artery stenting, long total stent length, multivessel stenting or in patients with other risk factors for late stent thrombosis such as diabetes, renal failure, or left ventricular dysfunction).

Antiplatelet therapy and non-cardiac surgery after coronary stenting

Patients taking antiplatelet drugs may need surgery. Unfortunately, some patients may be routinely instructed to stop 'blood thinners' prior to surgery without proper assessment of the risk involved in terms of stent thrombosis (and therefore myocardial infarction or death). The risk of bleeding during surgery needs to be balanced against the risk of stent thrombosis and assessed case by case. The consequences of bleeding are more critical, for example, in neurosurgical cases than in diagnostic endoscopy or following dental procedures. The risk of stent thrombosis is higher soon after implantation but may still occur late (beyond one year) particularly if it is a drug-eluting stent. Certain procedural characteristics (for example, multivessel stenting, longer total stent length, smaller stent diameter) and patient-related characteristics (for example, presence of diabetes, renal failure and left ventricular dysfunction) predispose to a higher likelihood of stent thrombosis. This needs to be factored into the decision-making process.

Elective procedures may be deferred to a period where dual antiplatelet therapy is no longer required. Alternatively, it may be an option to perform the procedure during antiplatelet therapy. For instance, patients undergoing tooth extractions may be able to continue antiplatelet therapy given that local measures during surgery (gelatin sponge and sutures) are often sufficient to control bleeding and the risk of subsequent re-bleeding is low.[8,9]

If clopidogrel must be stopped before major surgery, consider continuing to give aspirin throughout the operation and restarting clopidogrel as soon as possible.

Recommendations

Important questions to ask when a patient who has a stent needs surgery:

- Is the procedure necessary?
- Can the procedure be performed if dual antiplatelet therapy is continued?
- Can the procedure be performed on aspirin monotherapy?
- Can the procedure be delayed to minimise the risk of stent thrombosis?

In the patient who has a bare metal stent implanted, there is an appreciable risk of stent thrombosis if antiplatelet therapy is ceased before six weeks (incidence 3%). Antiplatelet therapy should therefore not be ceased for minor bleeding and elective procedures should be deferred for at least six weeks.

In the patient with a drug-eluting stent, given the concerns regarding late stent thrombosis, we recommend that elective surgery should be delayed for 12 months if possible. As isolated cases of thrombosis following antiplatelet withdrawal have occurred beyond 12 months, we recommend discussion with the cardiologist in all situations requiring cessation of antiplatelet therapy in patients with drug-eluting stents.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 111)

3. Patients with drug-eluting stents only need one antiplatelet drug to prevent stent thrombosis.
4. Dual antiplatelet therapy has to be continued longer in patients with drug-eluting stents than in patients with bare metal stents.

Medicinal mishap

Bisphosphonates and osteonecrosis of the jaws

Prepared by Alastair Goss, Oral and Maxillofacial Surgeon, and Patricia Backhouse, General Practitioner, Adelaide

Case

An otherwise well 66-year-old woman was referred with pain, swelling and numbness of the left mandible with pus discharging from around a dental implant. Her problems had developed over the previous six months.

The patient had undergone dental reconstruction 15–20 years previously. This involved eight titanium implants in both jaws with extensive crown and bridge work. (This work involved a personal cost of approximately $25 000 above insurance benefits.)

The woman had been diagnosed with 'borderline osteoporosis'. Her bone mineral density was –2.42 standard deviations below normal (consistent with a diagnosis of osteopenia). She was prescribed 70 mg alendronate weekly but later developed stress fractures. Over three years she took a total dose of 11.2 g.

A clinical diagnosis of bisphosphonate-associated osteonecrosis of the left mandible was made. A CT scan showed extensive involvement around the infected implant. The right mandible and maxilla were not involved.

Alendronate was ceased and non-surgical treatment commenced with 0.12% chlorhexidine mouth washes, intermittent short courses of cephalosporins for the soft tissue infection, and tramadol or paracetamol with codeine for the pain. This controlled the acute symptoms.

One year after stopping alendronate the symptoms recurred. A repeat CT scan showed extension of the necrosis without bone reformation. The involved implant and soft tissue were curetted under general anaesthesia. The wound healed slowly (see Fig. 1).

Comment

In this case alendronate was commenced before bisphosphonate-associated osteonecrosis of the jaw had been described.[1] Osteonecrosis associated with a previously stable implant was one of the first such presentations in Australia.

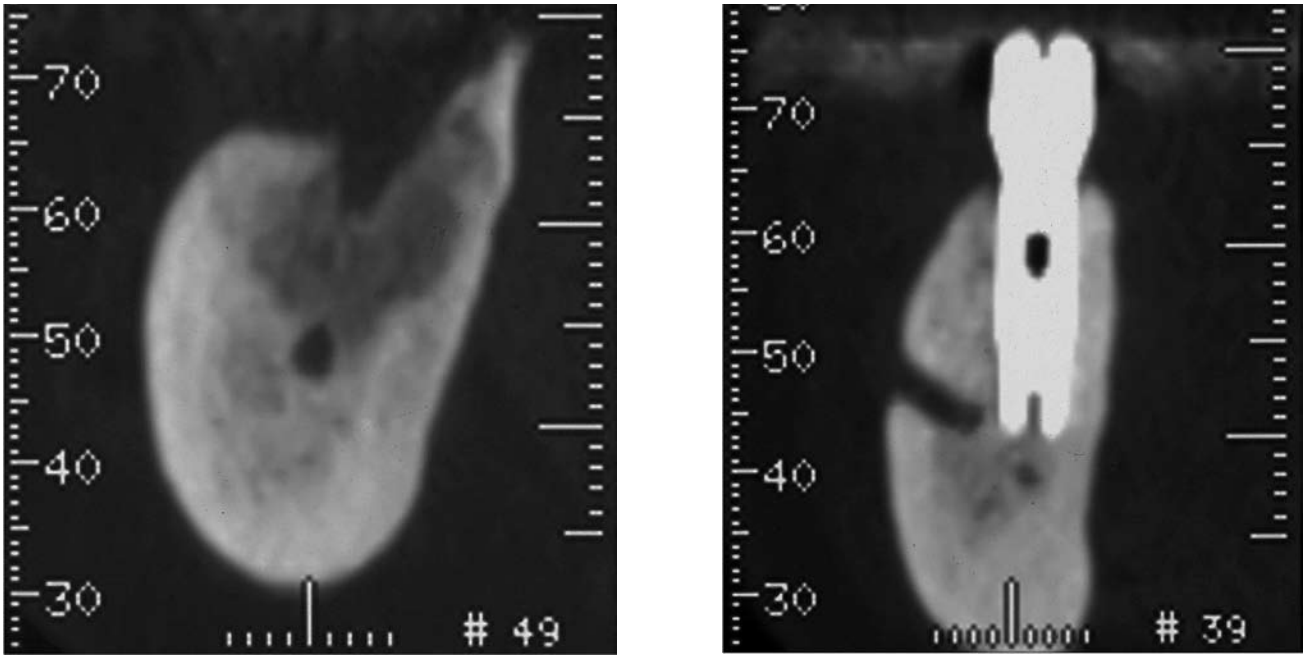
Bisphosphonate-associated osteonecrosis of the jaws is now defined as an area of exposed bone in the jaws which persists for more than eight weeks. Other conditions, including osteoradionecrosis and the presence of tumour, need to be excluded. The first described cases were in older, medically compromised patients treated with intravenous infusions

Fig. 1

CT of mandible

a) Area of osteonecrosis (dark area). Note the loss of the normal compact/cancellous bone with dense mineralisation of the marrow space. The mandibular canal is smaller and has lost its cortical rim.

b) Surviving implant just anterior to the area of osteonecrosis. Dense hypermineralised bone in contact with the implant.



of potent nitrogen containing bisphosphonates for multiple myeloma, breast or prostatic metastasis or malignant hypercalcaemia.[2] The most commonly reported drugs involved were zoledronic acid followed by pamidronate.[3,4] Common triggers for osteonecrosis of the jaws were dental extractions, periodontal disease or oral trauma. The frequency of osteonecrosis of the jaws following dental extractions in oncology patients was 1–10%. It is a painful and persistent condition which represents another difficulty that confronts patients with cancer.

This case shows a different situation as it involved two common benign conditions, osteopenia and dental disease. Approximately three million prescriptions were written for oral bisphosphonates last year, and 10% of all Australians have a dental extraction in any given year. Although the risk of osteonecrosis of the jaws after dental extraction is low (0.1–0.3%) for a patient on oral bisphosphonates for osteoporosis, the potential number of cases is high.[3] It is anticipated that the number will increase as the population ages and the number of prescriptions and duration of bisphosphonate dosage increases. Osteonecrosis of the jaws is uncommon in patients who have taken oral bisphosphonates for less than three years.

Just as an extraction requires bone turnover to heal, dental implants require bone turnover to maintain osseointegration. The frequency of osteonecrosis of the jaws associated with dental implants is unknown.

Strategies to minimise the risk of osteonecrosis of the jaws with bisphosphonates are unclear. It is important to ensure that the patient has good oral health. This should be regularly assessed by a dentist.

Conclusion

Clinicians who treat osteoporosis with bisphosphonates need to balance the known beneficial effects of treatment with the small risk of osteonecrosis of the jaws. This risk can be minimised by ensuring that the patient is dentally fit and, in particular, does not require dental extractions or other jawbone surgery, including dental implants.

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Professor Goss has provided advice on osteonecrosis of the jaws to Merck Sharp & Dohme and Novartis (nationally and internationally).

Psychotropic drugs and dentistry

Michael M Page, Clinical Pharmacist, Graylands Hospital; and Luke M Somerville-Brown, Dental Surgeon, Sir Charles Gairdner Hospital, Perth

Summary

Psychotropic drugs have oral adverse effects such as xerostomia and bruxism. They may also interact with sympathomimetic vasoconstrictors or other drugs used in dentistry but some of these interactions have been overstated. The conscious sedation techniques used by dentists to manage anxiety require caution and must be used in accordance with treatment guidelines.

Key words: bruxism, conscious sedation, vasoconstrictors, xerostomia.

(Aust Prescr 2007;30:98–101)

Introduction

Dental patients may be prescribed psychotropic drugs either for a mental illness (see Table 1) or to manage severe anxiety associated with dental procedures. When psychotropic drugs are used to treat a mental illness, they can cause problems such as xerostomia which need preventive dental care.

Taking a medication history is essential for the safe prescribing of dental drugs for concomitant administration. Particular care is needed if the dentist intends to use sedation in a patient who is anxious about dental treatment.

Dental care for the patient taking psychotropic medication

The adverse effects of psychotropic drugs may cause dental problems.

Xerostomia

The most frequently encountered adverse effect of dental importance in patients taking psychotropic drugs is xerostomia. The patient has a perception of dry mouth and the lack of saliva can lead to dental caries and candidosis.[1]

Most antidepressants can cause xerostomia. Drugs with significant anticholinergic activity such as the tricyclic antidepressants are more likely to lead to oral complications, as the effect on salivary function is often prolonged. Newer antidepressants such as venlafaxine, reboxetine and the selective serotonin reuptake inhibitors (SSRIs) can cause dry mouth, but this is likely to be mild and transient, as would often be the case with the psychostimulants. Other drugs with anticholinergic properties such as antipsychotic drugs and antiparkinsonian drugs used to treat antipsychotic-induced movement disorders may also cause dry mouth.[2]

Patients complaining of a dry mouth while taking lithium may be suffering from dehydration as a result of lithium-induced polyuria. They should be referred for appropriate investigation.[2]

If a change to the patient's treatment is not possible, options for the long-term management of xerostomia include dietary modification, saliva substitutes, regular sipping of water and non-pharmacological salivary flow stimulators such as sugarless chewing gum. Sialogogues such as the cholinergic agonist pilocarpine (as diluted eye drops administered topically in the mouth) can be particularly useful for short-term use, but their utility may be limited by systemic adverse effects such as headache, sweating and diarrhoea.[3]

Dental management of a patient with xerostomia requires increased dental recalls for oral hygiene instruction, fluoride application and early intervention.

Bruxism

Bruxism involves forceful excursive movements of the jaw with grinding of the teeth, and leads to excessive dental attrition with various complications. It is occasionally seen with antipsychotics, antidepressants and psychostimulants though it is rarely prolonged. Bruxism may also occur independently of medication in patients suffering symptoms of anxiety associated with mental illness. The complications of persistent bruxism can be reduced by the use of an occlusal splint.

Surgical bleeding

Sodium valproate, an anticonvulsant used in patients with bipolar disorders, is associated with a relatively high incidence of thrombocytopenia and it impairs platelet aggregation. It has been reported to potentiate surgical bleeding and this may occur in dental patients. It may be prudent to obtain relevant laboratory investigations such as platelet count and function before dental surgery. If a significantly abnormal result is obtained the patient should be referred to their medical practitioner for appropriate management. Some antidepressants, in particular the SSRIs, also impair platelet aggregation due to their effects on platelet serotonin uptake. Compared to valproate, less is known about their effect on surgical bleeding, but some caution may be required.[2]

Drug-induced excess salivation

The atypical antipsychotic clozapine has many adverse effects, including cholinergic agonism which leads to hypersalivation –

Table 1

Drugs commonly used in psychiatry [2]

Therapeutic group	Common drugs
Antidepressants	Selective serotonin reuptake inhibitors – including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
	Tricyclic antidepressants – including amitriptyline, dothiepin, doxepin, imipramine, nortriptyline
	Monoamine oxidase inhibitors – including moclobemide*, phenelzine, tranylcypromine
	Others – including mianserin, mirtazapine, reboxetine, venlafaxine
Antipsychotics	Typical (older type) antipsychotics – including chlorpromazine, flupenthixol, fluphenazine, haloperidol, pericyazine, trifluoperazine, zuclopenthixol
	Atypical (newer type) antipsychotics – including amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone
Anxiolytics/sedatives	Benzodiazepines – including alprazolam, bromazepam, clonazepam, diazepam, flunitrazepam, nitrazepam, oxazepam, temazepam, triazolam
	Beta blockers (used for somatic complaints in anxiety disorders) – particularly propranolol
Psychostimulants	Including atomoxetine, dexamphetamine, methylphenidate
Drugs for bipolar disorders	Including carbamazepine, lamotrigine, lithium, sodium valproate
Anticholinergic antiparkinsonian drugs	Benzhexol, benztropine

* Moclobemide is a selective, reversible inhibitor of monoamine oxidase type A and at standard doses is less susceptible to dietary or drug interactions than the classical monoamine oxidase inhibitors.

often nocturnal, but sometimes continual – in a large proportion of patients. During dental treatment, excess saliva may compromise dental materials, create a difficult working environment for the dentist and pose a risk of aspiration.

Anticholinergic drugs are commonly used for patients suffering clozapine-induced hypersalivation. Hyoscine hydrobromide 300 microgram chewed and swallowed before dental work, in addition to standard measures for maintaining a dry field, may be helpful.[4]

Operative use of vasoconstrictors

Sympathomimetic vasoconstrictors such as adrenaline, used in conjunction with local anaesthetics to prolong anaesthetic effect and control local bleeding, are generally safe, but there are some interactions with prescribed psychotropic drugs.[5] These would be most significant following inadvertent intravenous administration of the vasoconstrictor.

Much has been made in the literature of the potential for interaction between local sympathomimetic vasoconstrictors and tricyclic antidepressants, but this is probably most significant with levonordefrine and with noradrenaline (neither in common use in Australia). The antidepressants may potentiate the action of adrenaline and possibly increase the patient's blood pressure. If adrenaline is necessary, consider using about one-third of the normal amount.

Some conjecture exists about the potential for an interaction between monoamine oxidase inhibitors and dental sympathomimetic vasoconstrictors to cause severe hypertensive reactions. Insufficient evidence has been produced to substantiate this interaction and the combination would generally be regarded as safe. It has also been claimed that some antipsychotics can adversely interact with sympathomimetic vasoconstrictors through their alpha-blocking activity. The consequent unopposed beta activity of the sympathomimetic might lead to peripheral vasodilation resulting in prolonged bleeding, hypotension and reflex tachycardia. The evidence in dental practice has not borne this out sufficiently to warrant serious concern where adrenaline is used for its local effect.[5]

Interactions can occur when patients taking non-selective beta blockers are given local anaesthetics containing adrenaline. A lower dose is advised with extra care to avoid intravascular injection.[5]

If there is concern about interactions with sympathomimetic vasoconstrictors, felypressin may be an alternative. Interactions have not been reported with this non-sympathomimetic vasoconstrictor.

Table 2

Examples of interactions between drugs used in dentistry and psychotropic drugs [2]

Dental drugs	Interacting drug(s)	Details of interaction
Non-steroidal anti-inflammatory drugs	Lithium	NSAIDs (including COX-2 selective) all have the capacity to decrease renal lithium excretion, potentially resulting in lithium toxicity
	SSRIs	Increased risk of pathological or surgery-related bleeding when combined with NSAIDs
	Sodium valproate	Combination with aspirin may have a synergistic effect on bleeding time
Opioids and tramadol	Antidepressants	Most antidepressants have the potential to cause serotonin syndrome when combined with tramadol. This effect is not necessarily dose dependent and is unpredictable and the combination should be avoided. Monoamine oxidase inhibitors are contraindicated in combination with tramadol and pethidine due to hypertensive and other autonomic reactions.
	Antipsychotics or tricyclic antidepressants	Tramadol may lower the seizure threshold unpredictably and should not be used.
Antibiotics	Lithium	Metronidazole has the potential to increase lithium concentrations via a decrease in renal excretion. Avoid combination.
	Carbamazepine	Macrolides increase carbamazepine concentration by CYP3A4 inhibition. Avoid combination. Carbamazepine decreases doxycycline half-life by up to 50%. Use alternative antibiotic.
	Sodium valproate	Macrolides increase valproate concentration via CYP3A4 inhibition. Avoid combination.
	Some antipsychotics, tricyclic antidepressants, fluoxetine or venlafaxine	Combination with macrolides can potentiate QT prolongation. Avoid combination.

NSAIDs non-steroidal anti-inflammatory drugs
COX cyclo-oxygenase
SSRIs selective serotonin reuptake inhibitors
CYP cytochrome P450

Post-operative prescribing

Patients who need pain relief after dental treatment should not be denied analgesia because they are taking psychotropic drugs. There are important interactions and some combinations should not be used (Table 2). For example, dextropropoxyphene should not be used in combination with carbamazepine or monoamine oxidase inhibitors, and tramadol or pethidine should generally not be used in combination with antidepressants due to the risk of serotonin syndrome. Alternatives are usually available and paracetamol with codeine is often effective.[6]

Patient participation in preventive dentistry

Patients with a mental illness may be less likely than others to follow oral hygiene advice, but can do so if carefully instructed.[3] Close liaison with other health professionals involved in the patient's general medical and psychiatric management may result in more favourable outcomes.

Pharmacological management of the anxious dental patient

Anyone may suffer anxiety of a severity necessitating pharmacological management in order to facilitate dental treatment. Benzodiazepines and nitrous oxide are the most frequently used drugs. When considering the use of conscious sedation, the 'Guidelines on conscious sedation for dental procedures'[7] should be referred to and all appropriate safety measures taken.

Benzodiazepines

Benzodiazepines alleviate anxiety, and cause sedation, anterograde amnesia and muscle relaxation. Each of these

effects may be of value in treating the anxious patient. These drugs have a wide margin of safety in most patients and differ from one another clinically mainly in their onset and duration of action.

Of the oral benzodiazepines, a reasonable choice is temazepam due to its moderate duration of activity and lower propensity for drug interactions.

Benzodiazepines should be used with caution in patients taking other central nervous system depressant drugs. Drug interactions may also increase or decrease effects of benzodiazepines in patients taking other medication. Benzodiazepines should be avoided in pregnancy wherever possible.[2,8]

Patients who have taken a benzodiazepine should be escorted after treatment and advised not to drive or undertake any other potentially hazardous activities for the rest of the day, even if the benzodiazepine has a short half-life. The duration of action of any benzodiazepine can vary from patient to patient.

Nitrous oxide

Nitrous oxide is a useful and inexpensive inhaled sedative with which many dentists are familiar. It is relatively safe to use provided that appropriate monitoring and procedures for initiation and termination of sedation are followed. Its various advantages include a lack of propensity for drug interactions and rapid 'on-off' activity. If nitrous oxide is being considered for a pregnant patient consult the patient's obstetrician, although it is considered relatively safe with short-term use. Some respiratory illnesses warrant caution, but most other medical conditions pose little problem. It has good anxiolytic and analgesic properties. Adverse effects are uncommon when lower concentrations and shorter durations are used. Nausea and vomiting are occasional problems during recovery. Many patients recover quickly enough to be able to drive home after a short period of observation. Brief psychomotor evaluation tests may be useful in assessing the patient's ability to leave the practice unescorted.[8]

Conclusion

The patients encountered in dental practice are increasingly likely to be taking psychotropic medication due to increased recognition of mental illnesses in the community. It is therefore important for dentists to be familiar with the oral health implications of these drugs. Additionally, dentists frequently use conscious sedation as a useful means of managing the anxious patient and should be well versed in the appropriate use of sedation techniques to ensure safe and effective treatment.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 111)

5. Patients taking antidepressants should not be given local anaesthetics in combination with a vasoconstrictor.
6. Anticholinergic drugs reduce the severity of the xerostomia caused by psychotropic drugs.

Correction

Managing chronic obstructive pulmonary disease
(Aust Prescr 2007;30:64-7)

The combination of fluticasone and salmeterol is approved for use in severe chronic obstructive pulmonary disease. It was included on the Pharmaceutical Benefits Schedule on 1 August 2007 for patients with FEV_1 less than 50% of the predicted normal, and a history of repeated exacerbations, who have significant symptoms despite regular $beta_2$-agonist treatment.[1]

Reference

1. Fluticasone with salmeterol (Seretide) for chronic obstructive pulmonary disease. RADAR 2007 Aug 1. National Prescribing Service.www.npsradar.org.au

Abnormal laboratory results

Magnesium: the forgotten electrolyte

Joyce Wu, Registrar, and Andrew Carter, Director, Department of Chemical Pathology, Queensland Health Pathology Service, Brisbane

Summary

Magnesium is important for the proper functioning of various metabolic pathways and ion channels so disturbances in magnesium concentration can cause clinical problems. Hypomagnesaemia has many renal and extra-renal causes whereas hypermagnesaemia is usually due to renal insufficiency. Magnesium should be monitored in conditions such as arrythmia and when other electrolytes are abnormal.

Key words: hypermagnesaemia, hypomagnesaemia.

(Aust Prescr 2007;30:102–5)

Introduction

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation after potassium. Dietary sources of magnesium include whole grain cereals, green leafy vegetables, legumes, soybeans, nuts, dried fruit, animal protein and seafood.[1,2,3] The minimum recommended daily intake of magnesium for adults is 0.25 mmol (6 mg)/kg body weight.[4]

The total body magnesium of an adult male is approximately 1 mol (24 g).[1] Approximately 66% is distributed in bone, 33% in muscle and soft tissues, and less than 1% in blood. In blood 55% of the magnesium is free (ionised) and physiologically active, 30% is bound to proteins (primarily albumin), and 15% is complexed to anions.[5]

Magnesium homeostasis

Under normal conditions the body maintains constant circulating concentrations of magnesium in the blood. Homeostasis depends on the balance between intestinal absorption and renal excretion, with kidney tubules having primary control.[4]

The main site of absorption is the small intestine with smaller amounts absorbed in the colon.[4] Absorption can range from 24% of ingested magnesium in magnesium replete states to 76% in deficient states. Approximately 1 mmol is lost in gastrointestinal secretions daily.[1]

The kidney's handling of magnesium is more complicated. There is a circadian excretory rhythm with more magnesium excretion occurring at night.[3,6] Ionised and complexed magnesium are freely filtered at the glomerulus (70% of circulating magnesium). To maintain homeostasis, the nephrons normally reabsorb more than 96% of the filtered magnesium.[1,4] The amount reabsorbed can vary, however, from nearly zero to 99.5% depending on the individual's magnesium balance.[1]

Most reabsorption occurs in the thick ascending limb of the loop of Henle where 65–75% of filtered magnesium is reabsorbed passively down an electrochemical gradient which is actively maintained.[1,4] The amount reabsorbed is inversely related to tubular flow. Situations that abolish the positive luminal charge (for example loop diuretics, hypercalcaemia) will reduce the reabsorption of magnesium. The reabsorption of magnesium and calcium parallel each other in this segment, but the hormonal regulation of magnesium homeostasis is incompletely understood.[1]

Function

Magnesium is involved in over 300 enzymatic reactions. It is needed in energy metabolism, glucose utilisation, protein synthesis, fatty acid synthesis and breakdown, muscle contraction, all ATPase functions, for almost all hormonal reactions, and in the maintenance of cellular ionic balance.[2]

Magnesium is needed for the proper functioning of the Na^+/K^+–ATPase pump, so a deficiency causes an increase in intracellular sodium and allows potassium to leak out of cells.[2] Loss of intracellular potassium also occurs in the renal tubules.[1] This can lead to a hypokalaemia which only responds to magnesium replacement.[2]

Magnesium also affects calcium homeostasis through two mechanisms. Firstly, many calcium channels are dependent on magnesium. When the intracellular magnesium concentration is high, calcium transport into the cell and from the sarcoplasmic reticulum is inhibited. In magnesium deficiency the inverse occurs and consequently the intracellular concentration of calcium rises.[2] Secondly, magnesium is needed for the release and action of parathyroid hormone.[2] Magnesium's relationship with calcium means that patients with hypomagnesaemia may have a low plasma calcium that remains refractory to calcium supplementation until the magnesium deficiency is corrected.[2]

Laboratory tests

Most laboratories measure total magnesium; measurement of ionised magnesium is not standard practice. The normal range for total magnesium is 0.7–1.0 mmol/L. Caution should be taken in interpreting results from patients who have low total magnesium and low albumin, as they may have normal concentrations of ionised magnesium. Blood levels may not reflect total body stores.[5] One reason for this is that in acidosis magnesium shifts from the intracellular to the extracellular space, whereas in alkalosis the reverse occurs.[2] This can cause a dilemma particularly in determining the presence or absence of hypomagnesaemia.

Hypomagnesaemia

Due to magnesium's wide-ranging functions, magnesium deficiency may be the cause of numerous serious pathologies.[1,2,3,7,8]

As total blood magnesium concentrations do not always reflect total body stores, a high index of suspicion is needed particularly in patients at high risk of magnesium deficiency (see Table 1). Magnesium is often not included in routine electrolyte testing, so it is important that clinicians remember to order and monitor it. Changes in magnesium concentrations for an individual might be significant, even if they remain within the normal range.[2] Occasionally the magnesium-loading test is required to confirm magnesium deficiency.[2,4]

Causes

The causes of hypomagnesaemia are extra-renal or renal (Table 1). A 24-hour urine collection can be used to determine the presence or absence of renal magnesium wasting. In the presence of hypomagnesaemia, a 24-hour urine total magnesium less than 0.5 mmol is evidence of an intact renal response to hypomagnesaemia. A value greater than 1.0 mmol indicates abnormal renal wasting. Alternatively, the fractional excretion of magnesium (FE_{Mg}) on a random urine specimen can be used. In the presence of hypomagnesaemia, FE_{Mg} less than 2% indicates appropriate response to hypomagnesaemia while FE_{Mg} greater than 2% indicates renal wasting.[1]

Extra-renal causes

Conditions that cause malabsorption may lead to decreased gastrointestinal absorption of magnesium. These conditions include inflammatory bowel disease, chronic pancreatitis and alcoholism. In alcoholics, increased urinary magnesium wasting may also contribute to hypomagnesaemia. As magnesium is present in gastric secretions, vomiting and nasogastric suction are recognised (rare) causes of hypomagnesaemia. Skin loss of magnesium can be significant in burns patients. 'Hungry bone' syndrome which can occur following parathyroidectomy can also drop blood calcium, magnesium and potassium concentrations.[1]

Renal causes

There are two classic congenital magnesium wasting syndromes – Bartter's syndrome and Gitelman's syndrome. Both groups of patients have hypomagnesaemia, hypokalaemia, metabolic alkalosis and normal blood pressure. The main difference between the two syndromes is that urinary calcium is elevated in Bartter's syndrome and decreased in Gitelman's syndrome.[1,4]

Table 1

Causes of hypomagnesaemia*

Extra-renal		**Renal losses**	
Gastrointestinal	diarrhoea steatorrhoea alcoholism inflammatory bowel disease vomiting short bowel syndrome sprue chronic pancreatitis enteral nutrition gastric suction intestinal bypass for obesity protein calorie malnutrition (rare)	Drugs	aminoglycoside toxicity pentamidine toxicity amphotericin B toxicity thiazide and loop diuretics calcineurin inhibitors e.g. cyclosporin, tacrolimus foscarnet cisplatin alcohol
		Loop of Henle	hypercalcaemia
		Increased tubular flow	osmotic diuresis diabetes mellitus type I and II hyperaldosteronism volume expansion diabetic ketoacidosis
Skin	burns toxic epidermal necrolysis		
Bone	'hungry bone' syndrome		
		Tubular dysfunction	recovery from acute tubular necrosis recovery from obstruction
		Congenital renal magnesium wasting	

* adapted from reference 1

Drugs can cause renal wasting of magnesium. They either cause tubular toxicity (for example amphotericin B, aminoglycosides) or block renal reabsorption (for example loop diuretics).[1]

Hypercalcaemia can block renal reabsorption of magnesium, resulting in hypomagnesaemia. However, when hypercalcaemia is due to hyperparathyroidism, patients are usually normomagnesaemic because parathyroid hormone stimulates magnesium reabsorption.[1]

Effects

Hypomagnesaemia can cause hypokalaemia and hypocalcaemia. It is also associated with hyponatraemia and hypophosphataemia.[1]

Magnesium's usual role in the sodium-potassium ATPase pump and calcium-blocking activity is impaired by hypomagnesaemia leading to membrane destabilisation and hyperexcitability.[7] Patients can develop Trousseau's and Chvostek's signs even in the presence of a normal ionised serum calcium concentration.[1] With severe hypomagnesaemia, patients can have tetany and seizures (Table 2).

The effect on the myocardium is an increase in atrial and ventricular arrhythmias. Some ventricular arrhythmias caused by hypomagnesaemia only respond to treatment with magnesium.[1]

Table 2

Clinical findings associated with altered magnesium concentrations *†

Total magnesium concentration (mmol/L)	Findings
<0.5	tetany seizures arrhythmias
0.5–0.7	neuromuscular irritability
0.7–1.0	normal range
1.0–2.1	typically asymptomatic
2.1–2.9	lethargy drowsiness flushing nausea and vomiting diminished deep tendon reflexes
2.9–5.0	somnolence loss of deep tendon reflexes hypotension ECG changes
>5.0	complete heart block cardiac arrest apnoea paralysis coma

* adapted from reference 1
† when magnesium concentrations are altered, also check calcium and potassium

Treatment

An attempt should be made to identify the underlying cause for the hypomagnesaemia. In asymptomatic hypomagnesaemic or magnesium-deficient patients, oral magnesium supplements are used. Recommended dosages vary. Commonly, magnesium aspartate (1.65 mmol magnesium ion per tablet) is prescribed at 2–4 tablets per day, given in divided doses.[9] As higher doses have a laxative effect, dosage will be limited by diarrhoea.[2,4]

Symptomatic or severe (< 0.4 mmol/L) hypomagnesaemia should be treated with intravenous magnesium, as correcting magnesium deficiency takes six times longer with oral supplementation – six weeks versus seven days.[8] Intravenous magnesium sulfate is the formulation commonly used. One 5 mL ampoule of magnesium sulfate contains 10 mmol of magnesium ions. 10–20 mmol of magnesium ions can be given in 100 mL of 0.9% sodium chloride over 1–2 hours. Sulfate anions however may bind calcium and aggravate existing hypocalcaemia. Calcium should thus be administered as well.[9,10] Patients with renal insufficiency should have their doses decreased appropriately, be monitored closely for decreased deep tendon reflexes, and have their magnesium concentrations checked regularly.[1,7]

Hypermagnesaemia

Causes

The most common cause of hypermagnesaemia is decreased renal excretion of magnesium with increased intake being the second major cause (Table 3).

Table 3

Causes of hypermagnesaemia *

Renal insufficiency		
Excess magnesium intake	parenteral	dosing error treatment of specific conditions e.g. eclampsia, torsades de pointes
	oral	damage to the intestinal epithelium may increase magnesium absorption magnesium-containing antacids Epsom salts ($MgSO_4$) and other magnesium-containing cathartics magnesium-containing enemas aspiration
	other	theophylline toxicity familial hypocalciuric hypercalcaemia acute rhabdomyolysis[8] lithium ingestion[8]

* adapted from reference 1

Effects

Magnesium can block synaptic transmission of nerve impulses causing loss of deep tendon reflexes. More severe toxicity can cause flaccid paralysis and apnoea. The effect on smooth muscle results in ileus and urinary retention. Through its effect on calcium and potassium channels, hypermagnesaemia can cause bradycardia and hypotension (Table 2). Hypermagnesaemia can also cause hypocalcaemia, possibly by inhibiting the release of parathyroid hormone. Hyperkalaemia has also been associated with hypermagnesaemia.[1]

Treatment

Hypermagnesaemia can be prevented by not using magnesium containing antacids or cathartics in patients with renal insufficiency. Patients with normal renal function will usually recover after the infusion or oral intake of magnesium-containing compounds stops. Intravenous calcium can be used as an antidote for hypotension and respiratory depression. In patients with severe renal dysfunction, dialysis may be required.[1]

Conclusion

Disturbances in magnesium homeostasis can lead to serious conditions some of which are only amenable to treatment with magnesium. Doctors must remember to measure magnesium especially in patients who are at risk. Patients with hypocalcaemia and hypokalaemia who are magnesium deficient should be treated with magnesium. Hypermagnesaemia can be prevented by not using magnesium-containing compounds in patients with renal insufficiency.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 111)

7. Hypermagnesaemia results in increased deep tendon reflexes.
8. Patients with hypomagnesaemia and a low albumin may have normal concentrations of ionised magnesium.

Book review

Disputes and Dilemmas in Health Law. Freckleton I, Petersen K, editors.

Sydney: The Federation Press; 2006. 698 pages. Price $125

Cate Howell, General Practitioner, Primary Care Mental Health Unit, Discipline of General Practice, Adelaide

Disputes and Dilemmas in Health Law is an Australian book which explains that health law is significant because it reflects on fundamental issues that impact on the beginning, end and quality of life. The book is divided into sections on health law and ethical dilemmas, human rights, public health, reproductive technologies, the end of life, litigation and liabilities, and privacy and confidentiality. The contributors include many eminent Australian legal and medical experts.

There is discussion about the 'ethics of care', and the relationship between ethics and law is explored. Law deals with practical issues, such as resolving disputes, and focuses on facts, but has limitations in dealing with moral issues. The ethical and legal issues related to advance directives, and competency to consent are explained, and information is provided about legislation in different Australian states.

Public health law covers environmental health issues and the control of disease and drugs. It is a critical area for prevention of many illnesses and dealing with epidemics. International issues such as the impact of trade agreements on health and practice are explored.

Issues related to the end of life are covered, including legislation in relation to the coroner, organ donation and end-of-life decisions. Legal cases concerning the insistence of families that life-sustaining treatment be continued in situations of overwhelming illness are discussed.

The section on litigation and liability covers medical negligence law. The question of whether a doctor has breached duty of care is discussed and the Bolam principle described. This principle was rejected in an Australian case, however, a modified form has been introduced as part of a review of tort reforms in Australia. 'A professional does not incur a liability in negligence... if it is established that [they] acted in a manner that… was widely accepted by peer professional opinion as competent professional practice'.

The final section looks at privacy and confidentiality. Disputes about confidentiality are only a recent phenomenon. Much discussion relates to HIV infection, in which a balance is sought between protecting the individual from discrimination and ensuring public safety. The obligations relating to privacy of information and allowing access to records are reviewed. The impact of legislative changes on records is discussed as well as issues relating to the electronic transfer of information.

Disputes and Dilemmas in Health Law is presented in a clear and readable manner. One can focus on topics of particular relevance, but it is likely that the reader will find the text engaging enough to read much more broadly. It contains important information for all practitioners, and there are many topics directly relevant to general practitioners. The book achieves its aims by providing clear and comprehensive information, and by provoking thought about ethical and legal aspects of health care.

Book review

Therapeutic Guidelines: Oral and Dental. Version 1.

Melbourne: Therapeutic Guidelines Limited; 2007. 235 pages. Price $39, students $30, plus postage

Camile S Farah, Consultant Oral Pathologist and Senior Lecturer in Oral Medicine and Pathology, School of Dentistry, University of Queensland, Brisbane

The new Therapeutic Guidelines: Oral and Dental is a long overdue but very welcome addition to the family of pocket-sized user-friendly reference guides to therapeutics. This first edition is a collaborative effort between the Therapeutic Guidelines Limited and the Australian Dental Association.

'Oral and Dental' aims to assist the general dental practitioner in their day-to-day practice and provides sound advice in situations where a prescription may be required. In an age of polypharmacy, the dentist is continuously challenged with patients taking multiple therapeutic preparations. The chapters on 'Dental management of patients taking medications' and 'Medical emergencies' are succinct and will prove very useful in daily dental practice.

This book is well laid out, although it would perhaps have been better to move chapters on 'Antibiotic prophylaxis' and 'Acute odontogenic infections' further up the contents table, and move chapters on 'Halitosis' and 'Oral mucosal disease' further down. In addition, the chapters on 'Getting to know your drugs' and 'Dental management of patients taking medications' could have been further subdivided in the table of contents for ease of reference, due to their length. Nonetheless, the extensive use of tables throughout the book compensates for this.

Therapeutic Guidelines: Oral and Dental is a single reference that brings together information usually obtained from multiple sources, and is packed with useful data based on clinical evidence, which will see it become an integral part of the armamentarium of every practising dentist. It is also a very valuable learning guide for both undergraduate and postgraduate dental students, and other practitioners who deal with oral disease. This guide comes with my strongest recommendation as a useful resource for all practitioners involved in the assessment and management of dental and oral disease.

New drugs

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

Carbetocin

Duratocin (Ferring)

ampoules containing 100 microgram/mL

Approved indication: prevention of uterine atony after Caesarian section

Australian Medicines Handbook section 17.7.1

Oxytocin is a hormone released from the posterior pituitary. As it stimulates rhythmic contractions of uterine smooth muscle, synthetic preparations can be used to induce or augment labour. Oxytocin can also be used to prevent postpartum haemorrhage.

Carbetocin is a synthetic analogue of oxytocin, with a longer half-life (41 minutes after intravenous injection vs 1–5 minutes). It stimulates a prolonged uterine response lasting about an hour.

The approved indications reflect the largest published trial of carbetocin. This involved 694 women who were having elective Caesarian sections under regional anaesthesia. The women were randomised to receive, after delivery, a bolus dose of oxytocin followed by an infusion, or a bolus dose of carbetocin followed by an infusion of placebo. In the oxytocin group, 10% of the women needed additional treatment to maintain the uterine contraction in the 48 hours after delivery. Only 6.3% of the women given carbetocin needed additional treatment.[1]

The adverse effects of carbetocin resemble those of oxytocin. They include abdominal pain, nausea, flushing and headache. Nearly half the patients may complain of itching.

While a single dose of carbetocin may be preferable to an infusion of oxytocin, after Caesarian section, it may not reduce blood loss more than oxytocin. In the main trial, the fall in postoperative haemoglobin was similar in both groups. Two women in each group had a postpartum haemorrhage.[1]

Carbetocin has not been studied after vaginal delivery or in women with a high risk of postpartum haemorrhage after Caesarian section. More research, including patient safety and economic evaluations, will therefore be needed before it can replace oxytocin as the first drug to use in the active management of the third stage of labour.

T T T manufacturer provided all requested data

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Fulvestrant

Faslodex (AstraZeneca)

pre-filled syringes containing 250 mg/5 mL

Approved indication: advanced breast cancer

Australian Medicines Handbook section 14.4.2

Women with breast cancer that is hormone receptor positive are often given an anti-oestrogen, such as tamoxifen, as part of their treatment. Despite this treatment the cancer can still advance and metastasise. When this occurs the woman may be treated with an aromatase inhibitor such as anastrozole to further reduce the circulating oestrogen concentrations.

Fulvestrant offers another option for postmenopausal women with hormone receptor positive, locally advanced or metastatic breast cancer whose disease has progressed despite taking tamoxifen. It competitively binds to oestrogen receptors and leads to their down-regulation. Unlike tamoxifen, fulvestrant has no agonist activity at the oestrogen receptor.

Fulvestrant is formulated as an oily solution. There is a slow absorption after intramuscular injection so the peak plasma concentration is not reached for a week. Absorption continues for over a month and a steady state is reached after six injections at one-month intervals. The half-life is approximately 50 days. As fulvestrant is a steroid molecule it is mainly eliminated by metabolism. Less than 1% of the dose is excreted in the urine.

A double-blind trial compared fulvestrant and tamoxifen in 587 postmenopausal women with locally advanced or metastatic breast cancer. Their cancers were hormone receptor positive (or of unknown status) and they had not been recently treated with hormonal therapy. Approximately 33% of the women responded to treatment with a median time to progression of the cancer of 6.8 months with fulvestrant and 8.3 months with tamoxifen. After 31 months of follow-up, 48% of the fulvestrant group were dead compared to 43% of the tamoxifen group. Although the overall results favoured tamoxifen there was less difference in outcomes in women with hormone-receptor positive tumours.[1]

Two studies have compared monthly injections of fulvestrant with daily oral anastrozole in women with breast cancer that had progressed despite hormonal therapy. One of these studies was an open label trial which included some Australians among the 451 participants. After a median follow-up of 14.4 months the cancer had progressed in 82.4% of the women taking fulvestrant and in 83.4% of those taking anastrozole.[2] The other

study was a double-blind American trial involving 400 women. After a median follow-up of 16.8 months the cancer had progressed in 83.5% of the women taking fulvestrant and in 86.1% of those taking anastrozole.[3]

When the results of the two trials[2,3] were combined the median time to progression was calculated to be 5.5 months with fulvestrant and 4.1 months with anastrozole. After a median follow-up of 27 months 74.5% of the fulvestrant group and 76.1% of the anastrozole group were dead. There was no significant difference in the median overall survival (27–28 months).[4]

The frequency of adverse reactions to fulvestrant and anastrozole is similar[2,3] and neither drug has a greater effect than the other on the patient's quality of life. Commonly reported adverse events with fulvestrant include hot flushes, injection-site reactions, gastrointestinal upsets, bone pain and rashes. Thromboembolism has been reported, but as the risk of thrombosis may be increased in patients with breast cancer the association with fulvestrant is uncertain. The effect of fulvestrant on bone is unknown. It is also unknown if fulvestrant will be of benefit to women with an advanced cancer which has previously been treated with tamoxifen and has not responded to an aromatase inhibitor.

manufacturer declined to supply data

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Natalizumab

Tysabri (Biogen-Idec)

glass vials containing 300 mg antibody in 15 mL liquid

Approved indication: monotherapy for relapsing-remitting multiple sclerosis

Australian Medicines Handbook section 14.1.4

Multiple sclerosis is characterised by the development of inflammatory lesions in the brain and spinal cord resulting in progressive disability for the patient. This process is mediated by immune cells that cross into the central nervous system. In most patients, the disease initially follows a relapsing-remitting course but eventually develops into a secondary progressive phase.

In Australia, there are currently two treatments for this disease, interferon beta and glatiramer, which act by modulating the immune system. Both of these drugs have been shown to reduce relapse rates by approximately 30% and retard disease progression by 12–18 months.[1]

Natalizumab, a humanised mouse monoclonal antibody, acts by binding to integrins present on the surface of leucocytes. This interaction stops the leucocytes from migrating into the central nervous system. Natalizumab may also suppress ongoing inflammation by preventing leucocytes from binding to ligands within the extracellular matrix.

Following the repeat intravenous administration of a 300 mg dose of natalizumab every four weeks, the serum concentration reaches a steady state after 24 weeks. The mean half-life of the drug is 11 days but clearance increases with body weight. After discontinuation, natalizumab stays in the blood for about 12 weeks, therefore a washout period may be appropriate before starting other treatments.

There have been three phase II trials and one phase III trial investigating natalizumab as a monotherapy for multiple sclerosis. In a placebo-controlled phase II trial, natalizumab (3 mg or 6 mg/kg) was given intravenously every four weeks for six months to patients with relapsing-remitting disease or secondary progressive multiple sclerosis. In the placebo group, 15 of 71 (21.1%) patients had at least one relapse compared with only 3 of 68 (4.4%) patients given natalizumab 3 mg/kg and 8 of 74 (10.8%) patients given natalizumab 6 mg/kg.[2]

Two other phase II trials also assessed natalizumab in patients with relapsing-remitting disease or secondary progressive multiple sclerosis. In the larger trial of 180 patients, a single dose of natalizumab (1 or 3 mg/kg) did not significantly improve the clinical course of acute relapses. Although natalizumab reduced the gadolinium-enhancing lesion volume in patients (observed by MRI) at 1 and 3 weeks after the beginning of treatment, by 14 weeks there were no differences in lesion volume between the treatment and placebo groups.[3]

In the other phase II trial of 72 patients, the number of new gadolinium-enhancing lesions was less in the treatment group

(two doses of natalizumab 3 mg/kg four weeks apart) compared to the placebo group over the first 12 weeks. However, in the second 12-week period there were no significant differences in the number of new lesions between the two groups.[4]

A phase III trial enrolled only patients with relapsing-remitting disease who had had a documented relapse in the previous 12 months. They received either a 300 mg dose of natalizumab or placebo every four weeks for up to 116 weeks. Of the 627 patients randomised to receive natalizumab, 72% remained relapse-free after two years compared with 46% of 315 patients randomised to the placebo group. Similarly after an MRI evaluation, no new or enlarging hyper-intense lesions were detected in 57% of patients in the natalizumab group compared with 15% of patients in the placebo group.[5]

During the phase III trial, 6% of natalizumab patients and 4% of placebo patients discontinued the study because of adverse effects. Infusion reactions occurred in 148 patients in the natalizumab group compared with 55 patients in the control group. Hypersensitivity reactions, which included urticaria, allergic dermatitis and anaphylaxis, were reported by 25 patients receiving natalizumab. There were five cases of cancer reported in the treatment group compared to one in the placebo group. Two deaths occurred during the trial. Both were in the natalizumab group; one was from malignant melanoma and the other was from alcohol intoxication.[5]

Persistent antibodies to natalizumab developed in 37 patients who also had an increase in infusion-related adverse events and loss of efficacy of the study drug.[5] It is known that the presence of such antibodies increases the clearance of natalizumab three-fold.

In 2005 natalizumab was voluntarily withdrawn in the USA following reports of progressive multifocal leukoencephalopathy, a serious viral infection of the brain, in approximately 1 in 1000 patients taking the drug. After confirming that there were no additional cases of the infection, natalizumab was re-released in the USA through a restricted prescribing program. The drug also comes with a warning to doctors and patients that it increases the risk of progressive multifocal leukoencephalopathy.

Natalizumab is contraindicated for patients who have an increased risk of opportunistic infections. It should not be given in combination with other drugs that modulate the immune system.

The safety and efficacy of natalizumab beyond two years is unknown. During treatment there is a possibility that patients will develop antibodies to this drug that may reduce its efficacy and cause a hypersensitivity reaction.

Natalizumab should only be given by a neurologist who has timely access to MRI facilities. Patients should be evaluated three and six months after the first infusion and then every six months. If there is no sign of clinical benefit after six months, consider discontinuing treatment.

T manufacturer provided only the product information

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Pentastarch

Voluven (Pharmatel Fresenius Kabi)

6% solution for intravenous infusion

Approved indication: hypovolaemia

The optimum solution for expanding plasma volume is uncertain. There is debate about whether patients given colloid solutions, such as albumin, have worse outcomes than patients given crystalloid solutions.[1] To address some of the concerns synthetic colloids have been developed.

Pentastarch is derived from amylopectin. To slow down its metabolism by amylase, hydroxyethyl groups are added to the molecule. After this formulation is infused the expansion in intravascular volume lasts for 4–6 hours.

This formulation has been compared with other colloids in relatively small numbers of patients. Some of these comparisons have been with similar products containing a different ratio of hydroxyethyl groups.

In cardiac surgery there was no difference in efficacy between the new formulation and a similar product with a higher molecular weight.[2] A study in orthopaedic surgery had a similar result and found that the new formulation may have less effect on some coagulation factors.[3]

Patients may develop hypersensitivity reactions, including anaphylaxis, to pentastarch. Itching is common. There may be confusion about pancreatitis as amylase concentrations rise in patients given pentastarch.

While pentastarch is effective, many factors including cost and physicians' opinions will determine whether it is used in preference to other volume expanders.[1]

T manufacturer provided only the product information

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Perflutren

Definity (Bristol-Myers Squibb)

vials containing 6.52 mg/mL

Approved indications: echocardiography, ultrasound of liver and kidney

Ultrasound studies, such as echocardiography, are not always clear. To improve image quality it may be necessary to use a contrast medium.

Perflutren is a gas so it will produce echoes which are distinct from those of the surrounding tissues. To transport this inert gas to the heart, it has to be enveloped in a microsphere. A vial containing perflutren and liquid lipid is shaken by a machine for 45 seconds. This creates a suspension containing perflutren within lipid microspheres. The activated substance is then slowly injected intravenously or given as an infusion, depending on the investigation. Its half-life is less than two minutes with the gas being eliminated through the lungs.

Perflutren has been compared with saline in 211 patients, who had previously had a suboptimal echocardiography, in a double-blind trial. Depending on the dose, perflutren enhanced the imaging of the left ventricle in 87–91% of patients. There was no enhancement with saline.[1] In addition to opacifying the cardiac chambers, perflutren can be used in regional wall motion studies. After administration of perflutren the agreement with magnetic resonance imaging of wall motion increased, however it did not improve the accuracy of measurements of the ejection fraction. Although there have been fewer trials, perflutren has also been approved for use in characterising focal lesions in the liver and kidney.

Injecting patients with gas bubbles is not without risk, particularly in patients who may have a cardiac shunt or compromised pulmonary vessels. Patients with congestive heart failure also have a higher incidence of adverse effects. While headache is the most frequent adverse reaction, there have been serious hypersensitivity reactions and seizures. This has prompted a revision of the product information in the USA.

T T T manufacturer provided clinical evaluation

Reference * †

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Tipranavir

Aptivus (Boehringer Ingelheim)

250 mg capsules

Approved indication: HIV

Australian Medicines Handbook section 5.4.3

Protease inhibitors can be used as components in combination regimens for HIV infection (see 'New developments in antiretroviral therapy for HIV infection', Aust Prescr 2005;28:146–9). As the virus can develop resistance there is a need to find treatments which work when these regimens fail. There are already eight protease inhibitors available in Australia, so tipranavir is reserved for patients who have viral replication with HIV strains that are resistant to multiple protease inhibitors.

Although tipranavir inhibits HIV production in the same way as other protease inhibitors it is not a peptide. *In vitro* it retains antiviral activity against strains that have decreased susceptibility to protease inhibitors.

Tipranavir is poorly absorbed so several doses would be needed to reach effective concentrations. However, a twice-daily dose is possible if ritonavir is also taken. Ritonavir inhibits cytochrome P450 3A and the P-glycoprotein pump, significantly increasing the plasma concentrations of tipranavir. In the presence of ritonavir there is very little metabolism of tipranavir and most of the dose is excreted in the faeces. The elimination half-life is approximately six hours.

In a dose-response study 31 untreated patients were randomised to take different doses of tipranavir, with or without ritonavir, for 14 days. All three regimens reduced viral RNA concentrations, but the greatest effect was in the two regimens containing ritonavir.[1]

Two open-label studies have assessed regimens including tipranavir and ritonavir in patients who had previously been treated with at least two protease inhibitors. Although the studies were not complete, tipranavir was approved on the basis of the results of 24 weeks treatment. A total of 1177 patients were randomised to take tipranavir with ritonavir or another protease inhibitor with ritonavir, in addition to other antiviral drugs. At 24 weeks 34% of the tipranavir group and 15% of the comparator group had less than 400 viral copies/mL. While only 9% of the comparator group had less than 50 copies/mL, 24% of the tipranavir group had reached this concentration. There was an increase of 34 CD4 cells/mm^3 with tipranavir but only 4 cells/mm^3 with the comparator drugs.

Although more patients responded to tipranavir it also caused more people (8% vs 4%) to discontinue treatment because of adverse events. The most common adverse reactions are diarrhoea, nausea, vomiting, fever, fatigue and headache. Altered liver function and dyslipidaemia are more frequent than with other protease inhibitors. Tipranavir is contraindicated if there is impaired liver function so frequent monitoring is needed. Patients should not be given drugs, such as midazolam, which are cleared by cytochrome P450 3A. There are many other drugs which may interact with tipranavir, particularly as it will be used in combination with ritonavir.

Preliminary data suggest that tipranavir will have a role in treating patients with resistant HIV. To define this role genotypic testing is recommended. At present the data about which mutations may have increased resistance to tipranavir are unclear.

[T] manufacturer provided only the product information

Reference * †

1. McCallister S, Valdez H, Curry K, MacGregor T, Borin M, Freimuth W, et al. A 14-day dose-response study of the efficacy, safety, and pharmacokinetics of the nonpeptidic protease inhibitor tipranavir in treatment-naive HIV-1-infected patients. J Acquir Immune Defic Syndr 2004;35:376-82.

The T-score ([T]) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.europa.eu).

Answers to self-test questions

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

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Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica.

Typesetting
Barnes Desktopping and Design

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

Published by the
National Prescribing Service Limited (NPS), an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing

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INTERNATIONAL SOCIETY OF DRUG BULLETINS

Print Post Approved PP349181/00151 • ISSN 0312-8008