Australian Prescriber

AN INDEPENDENT REVIEW

December 2014
Volume 37 Number 6

www.australianprescriber.com

NPS MEDICINEWISE

CONTENTS

ARTICLE

New antiplatelet drugs for acute coronary syndrome

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Key words
aspirin, clopidogrel, prasugrel, ticagrelor

Aust Prescr 2014;37:182–6

SUMMARY

Ticagrelor and prasugrel are antiplatelet drugs that are alternatives to clopidogrel in acute coronary syndrome. Their advantages include reduced rates of ischaemia and stent thrombosis.

The risk of major bleeding is likely to be higher with prasugrel compared to clopidogrel. Intracranial haemorrhage appears to be slightly more common with ticagrelor than with clopidogrel, and it can also cause dyspnoea and ventricular pauses early in treatment.

When patients taking prasugrel or ticagrelor require surgery, perioperative management is challenging. The treating cardiologist should be consulted whenever treatment cessation is considered.

Introduction

Patients presenting with acute coronary syndromes, such as myocardial infarction, are treated with dual antiplatelet therapy to prevent recurrent ischaemia and mortality. After receiving loading doses, patients may undergo either percutaneous or surgical revascularisation. Following percutaneous revascularisation, aspirin is typically continued indefinitely, and another antiplatelet drug, most commonly clopidogrel, is continued for 12 months. While aspirin is also continued indefinitely following coronary artery bypass grafting, the role of a second antiplatelet drug remains unclear, and their use has not been standardised. Data from recently published large randomised trials suggest that prasugrel and ticagrelor may be alternatives to clopidogrel in acute coronary syndrome.[1-3]

Indications for use

Current guidelines published by the Cardiac Society of Australia and New Zealand (CSANZ)[4] recommend that either ticagrelor or prasugrel should be considered as alternative drugs to clopidogrel in patients presenting with ST-elevation myocardial infarction who are at high risk of recurrent ischaemic events, such as those with:

- diabetes mellitus
- stent thrombosis
- recurrent ischaemic events despite clopidogrel therapy
- a high burden of disease on coronary angiography.

The guidelines also recommend the use of either ticagrelor or prasugrel instead of clopidogrel in all patients with high-risk non-ST-elevation acute coronary syndromes who are judged to be of low risk for haemorrhagic events. It should be noted, however, that local hospital protocols may differ from the CSANZ guidelines.

Clinical pharmacology

In acute coronary syndrome, damage to atherosclerotic plaques exposes platelet activating factors such as tissue factor, collagen and von Willebrand factor. The platelets release granules containing adenosine diphosphate. This binds to the $P2Y_{12}$ receptor on the surface of the platelets as the first step of the platelet aggregation pathway.[5] Antagonism at this receptor inhibits platelet aggregation.

From the Editor

The new antiplatelet drugs help to improve the survival of patients with acute coronary syndrome. Praveen Indraratna and Christopher Cao remind us that the drugs also create problems if major surgery is needed. Austin Ng and Leonard Kritharides inform us about the other factors cardiologists consider in their preoperative assessments.

Assessing the patient is also very important when deciding whether to prescribe testosterone. Donald Perry-Keene says the hormone should not be used to manage non-specific symptoms such as reduced energy or poor concentration.

Judicious prescribing is also needed in palliative care. Debra Rowett and David Currow are concerned that adverse effects may be overlooked.

Terminal illness is likely to affect drug disposition. Bruce Charles believes that population pharmacokinetics can help us investigate drugs in patient groups that are difficult to study, including children.

While some children may be prescribed drugs such as imipramine for incontinence, Gail Nankivell and Patrina Caldwell advise that conservative treatment should be tried first.

Clopidogrel and prasugrel are thienopyridines. They bind irreversibly to the $P2Y_{12}$ receptor for the entire lifespan of the platelet (5–9 days). In contrast, ticagrelor binds reversibly, so platelet inhibition is not as prolonged and twice-daily dosing is required to achieve therapeutic concentrations.[5] All three drugs require a loading dose when given in acute coronary syndrome (Table).[6-15]

The time to onset of maximal platelet inhibition after administration of loading doses of antiplatelet drugs is an important consideration, particularly in ST-elevation myocardial infarction, as prompt revascularisation is required. Prasugrel achieves maximal platelet inhibition in approximately 30 minutes, whereas ticagrelor takes two hours. For clopidogrel, the time to maximal platelet inhibition is dose-dependent. A 600 mg dose achieves maximal platelet inhibition within two hours, whereas a dose of 300 mg takes eight hours. For this reason, loading doses of 600 mg have been used for clopidogrel in the acute management of ST-elevation myocardial infarction.

'Clopidogrel resistance' is a poorly defined phenomenon that may affect 4–30% of the population.[7,16] It may be related to a genetic variation of the cytochrome P450 2C19 enzymes that does not appear to affect either prasugrel or ticagrelor.

Prasugrel: safety and efficacy

Prasugrel has been compared to clopidogrel in two separate phase III randomised trials. It has not yet been directly compared to ticagrelor in a randomised clinical trial.

The TRITON-TIMI-38 study randomised patients (n=16 843) undergoing percutaneous coronary intervention to either prasugrel or clopidogrel, in combination with aspirin (75 to 162 mg daily).[1] The efficacy end point (a composite of death due to cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke) was reached by 12.1% of the patients randomised to clopidogrel, compared with 9.9% of the patients taking prasugrel. This significant difference ($p<0.001$) was offset by an increase in major bleeding in the prasugrel group (2.4% vs 1.8%, $p<0.001$) which was sometimes fatal (0.4% vs 0.1%, $p=0.002$). The overall mortality rates for clopidogrel and prasugrel were similar

Table **Pharmacological summary of $P2Y_{12}$ inhibitors**

	Clopidogrel	Prasugrel	Ticagrelor
Loading dose	300 mg or 600 mg	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily	90 mg twice daily
$P2Y_{12}$ receptor binding	Irreversible	Irreversible	Reversible
Hepatic metabolism	Two-step metabolism involving CYP2C19 to convert it to an active metabolite[6] Dysfunction of this enzyme may be the cause of clopidogrel resistance[7]	Rapidly hydrolysed to an intermediate metabolite, and then further metabolised by CYP3A and CYP2B63	Metabolised by CYP3A4[8]
Examples of drug interactions affecting $P2Y_{12}$ inhibitors	CYP2C19 inhibitors will decrease efficacy e.g. clarithromycin, fluconazole, omeprazole	No significant CYP interactions, however data are limited	CYP3A4 inhibitors will increase adverse effects e.g. clarithromycin CYP3A4 inducers will decrease efficacy e.g. carbamazepine, dexamethasone, rifampicin
Examples of $P2Y_{12}$ inhibitors affecting other drugs	–	–	Inhibits CYP3A4 so may increase concentrations of substrates such as simvastatin[9] * Ticagrelor is also a weak P-glycoprotein inhibitor[10] so digoxin concentrations increase and need monitoring[11]
Time to onset of maximal platelet inhibition	8 hours (300 mg)[12] 2 hours (600 mg)[13]	30 minutes[14]	2 hours[12]
Time to recover platelet function after ceasing medication	5 days[15]	7 days[15]	2–3 days[12]

* simvastatin doses of 40 mg or more may be associated with an increased risk of myopathy and other adverse effects
CYP cytochrome

(3.0% vs 3.2%, p=0.64).[1] Subgroup analysis revealed that patients with a history of stroke or transient ischaemic attack experienced poorer outcomes with prasugrel. In patients over 75 years of age or weighing less than 60 kg treated with prasugrel, there was no benefit in relation to the composite end point.

The TRILOGY-ACS study included 7243 patients who did not undergo revascularisation.[2] There was no difference in the combined end point in the prasugrel and clopidogrel groups (13.9% vs 16%, p=0.21) and the risk of haemorrhage was similar.

Prasugrel may be of overall benefit to patients undergoing percutaneous coronary intervention, but it has a higher risk of haemorrhage. It would be better to use clopidogrel for patients with:

- a history of stroke or transient ischaemic attack
- age more than 75 years
- body weight less than 60 kg.

Ticagrelor: safety and efficacy

The PLATO trial compared ticagrelor with clopidogrel, both in combination with aspirin, in 18 624 patients with acute coronary syndrome.[3] Ticagrelor significantly reduced the occurrence of the 12-month composite end point (consisting of death from cardiovascular causes, stroke and myocardial infarction) compared to clopidogrel (9.8% vs 11.7%, p<0.001). The dose of aspirin used in the study was 75–100 mg.

The overall incidence of major bleeding for ticagrelor and clopidogrel was similar (11.6% vs 11.2%, p=0.43), as was the rate of fatal bleeding (0.3% vs 0.3%, p=0.66). Ticagrelor, however, had a higher propensity to cause intracranial haemorrhage (0.3% vs 0.2%, p=0.06). The rate of bleeding related to urgent coronary artery bypass grafting was 7.4% with ticagrelor and 7.9% with clopidogrel.[3]

Dyspnoea was more common with ticagrelor (13.8% vs 7.8%, p<0.001), however this adverse effect was not related to any drug-induced cardiac, metabolic or respiratory dysfunction. The cause of this dyspnoea remains unknown, but ticagrelor inhibits cellular uptake of endogenous adenosine, and dyspnoea is a common adverse effect of adenosine administration.[17] Further studies have found the dyspnoea to be transient,[18] but ticagrelor should be avoided in patients who have chronic shortness of breath, such as those with chronic lung disease or symptomatic left ventricular failure.

In the PLATO study, ventricular pauses longer than three seconds were more common in the first week of therapy with ticagrelor (5.8% vs 3.6%, p=0.01), but this difference resolved after one month of treatment. Uric acid and creatinine also increased slightly in patients taking ticagrelor.

Compliance with ticagrelor has been a concern, given its twice-daily dosing requirement, and more rapid offset time. In the PLATO study, the rates of adherence between clopidogrel and ticagrelor were equal (82.8% in each group), however this may not reflect clinical practice.

Overall, ticagrelor appears to be more effective in preventing ischaemic events, with a similar rate of major bleeding. However, clopidogrel should be preferred over ticagrelor in patients with:

- chronic dyspnoea
- increased risk of intracranial haemorrhage
- bradycardia or a history of ventricular pauses
- a risk of non-compliance due to the twice-daily dosing requirement of ticagrelor.

Prevention of stent thrombosis

In TRITON-TIMI-38, prasugrel was more effective in preventing stent thrombosis than clopidogrel (1.1% vs 2.4%, p<0.001).[1] A post hoc analysis of PLATO found that the rates of stent thrombosis were lower with ticagrelor than with clopidogrel over a period of up to 12 months (2.9% vs 3.8%).[19] Higher rates of stent thrombosis could be expected in patients who do not adhere to the twice-daily regimen of ticagrelor.

Optimum duration and withdrawal of treatment

Current Australian guidelines suggest that following acute coronary syndrome treated with any form of stenting, dual antiplatelet therapy, including aspirin, should be continued for 12 months.[4] After 12 months, the risk of haemorrhage may outweigh potential cardiovascular benefits. Dual antiplatelet therapy may be prescribed for longer than 12 months in patients with drug-eluting stents.

In cases of acute coronary syndrome treated with coronary artery bypass grafting, the data are currently inadequate to make a recommendation for or against dual antiplatelet therapy after surgery.

Opinion is divided as to whether abrupt clopidogrel cessation results in a 'platelet rebound' effect causing thrombotic events. Studies have demonstrated mixed results.[20-22] Clopidogrel tapering has been proposed as a strategy to minimise the risk, but the benefits of this are unclear. The decision to cease or taper antiplatelet therapy should be made at the discretion of the treating cardiologist. Aspirin should be continued indefinitely if tolerated.

Management of bleeding

There are no formal guidelines for the management of bleeding related to $P2Y_{12}$ inhibitors. The most common approach is platelet transfusion, but there are no clinical trials of its efficacy and the number of units required has not been standardised. There are no drugs to reverse the effect. The treating cardiologist should be contacted about the bleeding for advice on whether or not to stop the antiplatelet drug. Given the lack of data and standardised protocols on platelet transfusion, consultation with a haematologist may also be required.

Perioperative management

The antiplatelet drugs prescribed to prevent coronary occlusion also increase the risk of bleeding during surgery. Aspirin should be continued, with the exception of certain high-risk procedures such as neurosurgical, ophthalmological or prostate surgery, which cannot be delayed.[23] $P2Y_{12}$ inhibitors are more difficult to manage.

Elective major surgery

Surgery produces a prothrombotic state where myocardial ischaemia may develop if the $P2Y_{12}$ inhibitor has been ceased, even if aspirin is continued. Current guidelines recommend delaying elective surgery until after the 12-month course of dual antiplatelet therapy is complete.[4]

In some cases, $P2Y_{12}$ inhibitors may be temporarily withheld one month after bare metal stenting or six months after insertion of a drug-eluting stent at the discretion of the treating cardiologist. This period of time correlates to complete re-endothelialisation of the stents in animal models.

While it is generally accepted that clopidogrel should be ceased five days before elective surgery, the timing of discontinuation of prasugrel and ticagrelor is uncertain. There are no randomised trials to guide management, so recommendations have been based on pharmacokinetic data. If appropriate, prasugrel should be ceased seven days before elective surgery, and ticagrelor between 3 and 5 days, depending on the patient's thrombotic risk.[23-25] In light of the lack of conclusive data, the treating cardiologist should be consulted about stopping $P2Y_{12}$ inhibitors before elective surgery.

Emergency surgery

There are no formal guidelines for the management of patients on dual antiplatelet therapy who need emergency surgery. One strategy is perioperative platelet transfusion.

Spinal or epidural anaesthesia

The risk of epidural haematoma following neuraxial blockade is believed to be increased in patients taking dual antiplatelet therapy, although further studies are required. Precautions regarding antiplatelet therapy should be similar to those observed for surgery. In elective circumstances, $P2Y_{12}$ inhibitors should be stopped before the procedure and in the case of an emergency lumbar puncture or neuraxial blockade, platelet transfusion is recommended beforehand to minimise the risk of severe haemorrhage.[26]

Conclusion

Ticagrelor and prasugrel have some advantages over clopidogrel in selected patients. Platelet inhibition is more rapid with prasugrel, and for both drugs the rates of ischaemic events and stent thrombosis are statistically lower. However, the risk of haemorrhage is higher than with clopidogrel.

Perioperative management of patients on dual antiplatelet therapy is a controversial area. The risks of myocardial ischaemia and haemorrhage need to be balanced judiciously for each individual patient. ◀

Conflict of interest: none declared

SELF-TEST QUESTIONS

True or false?

1. Aspirin should not be used at the same time as prasugrel or ticagrelor.
2. Antiplatelet therapy is not required by patients with drug-eluting stents.

Answers on page 219

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Dental note

New antiplatelet drugs

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Dentists should be familiar with clopidogrel, which is commonly used in combination with aspirin following placement of coronary stents to prevent coronary stent thrombosis. Clopidogrel may also be used in patients who are unable to take aspirin. Ticagrelor and prasugrel are new antiplatelet drugs that may be used as alternatives to clopidogrel.

All antiplatelet drugs place patients at an increased risk of bleeding following invasive dental procedures, especially dental extractions or dentoalveolar surgery. In patients who are receiving dual antiplatelet therapy following coronary artery stenting, premature discontinuation of the drugs can increase the risk of stent thrombosis, which may lead to acute myocardial infarction and death.[1]

Australian guidelines[2] recommend that patients requiring dental extractions or dentoalveolar surgery should not cease antiplatelet therapy, either monotherapy with aspirin, or dual therapy where aspirin is combined with other antiplatelet drugs. Patients should be warned of the increased risk of prolonged bleeding and also bruising.

Local measures such as placement of haemostatic materials into sockets and suturing should be used. If patients stop these medicines without substitute anticoagulants or monitoring, there is a risk of significant cardiac events or cerebrovascular accident. Elective extractions or surgery are best delayed if possible, especially in patients taking dual antiplatelet therapy temporarily (usually 12 months following stent placement).

It is important that a thorough medical history, including a medication history, is obtained for all patients. This should be updated at each visit. For patients requiring dental extractions or dentoalveolar surgery, their antiplatelet medication should not be ceased.[2] However, their treating physician should be made aware of the planned procedures. When a dentist lacks experience in the oral surgical management of patients on antiplatelet therapy, the patient should be referred to an oral and maxillofacial surgeon for specialist management.

Conflict of interest: none declared

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Letters to the Editor

Safe use of sodium valproate

Editor, – Your article on the safe use of sodium valproate (Aust Prescr 2014;37:124-7) is an excellent brief summary on the drug's pharmacology and uses. However, the authors have omitted to mention its use in corticosteroid-induced mania.[1] Corticosteroids in high doses are used in many conditions but cause many dysphoric symptoms, including hypomania, panic, confusion and insomnia, all of which are described as unpleasant.[2] In the past, treatment had to be stopped and symptoms controlled by major tranquillisers. Our work describing 20 case studies of steroid-induced mania coming to the attention of a consultation-liaison team have shown that sodium valproate can rapidly reduce manic-like symptoms while treatment with corticosteroids continued. We think that this is a worthwhile point which should be brought to the attention of your readers.

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Ahamed Zawab and John Carmody, the authors of the article, comment:

We thank Drs Roxanas and Hunt for their kind interest in our brief review. Their recent case series addressed the important issue of pharmacological management of corticosteroid-induced psychiatric symptoms. In their study, using a standardised mania rating scale over a four-day period, a statistically significant reduction in mania was attributed to sodium valproate. However, 16 of the 20 patients were simultaneously prescribed a lower dose of corticosteroid. We agree with the authors' conclusion that the findings need to be replicated in a controlled trial. Until then, we would suggest that corticosteroid dose reduction in concert with formal psychiatric review is preferable.

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Valediction

Dr Paul Kubler

Dr Paul Kubler joined the Editorial Executive Committee of *Australian Prescriber* in 2005 to provide expertise in clinical pharmacology. In 2006 he discovered how controversial medical publishing can be. His first editorial, on patents and evergreening, required the distribution of the journal to be delayed pending legal advice.

Fortunately, the rest of Paul's time on the Editorial Executive Committee has been less controversial. In 2012 he was appointed as the chair and was excellent in the role.

Paul has provided consistently good clinical advice, particularly about the increasingly complex new drugs which are featured in *Australian Prescriber*. Appropriately, Paul finished his time with the journal by writing an article on the Janus kinase inhibitors.

Although he will no longer have to get up at 4 am to attend editorial meetings, the Editorial Executive Committee expects Paul will use the time to write letters to the Editor. His sharp wit and intellect will be missed.

Aust Prescr 2014;37:187

DIAGNOSTIC TESTS

Preoperative assessment

A cardiologist's perspective

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Key words
blood tests, electrocardiography, spirometry, surgery

Aust Prescr 2014;37:188–91

SUMMARY

The number of patients having elective surgery in Australia is increasing. Many of these people are elderly with multiple comorbidities.

Medical optimisation before surgery is recommended for all patients, and careful clinical assessment is the foundation of preoperative evaluation.

For elective surgery, the patient's clinical characteristics and the nature of the surgery both influence their perioperative cardiac risk.

For emergency surgery, both the severity of underlying medical conditions and the urgency of surgery need to be considered before undertaking preoperative investigations and treatment, or deferring surgery.

Introduction

In 2010–11, an estimated 2.4 million hospitalisations in Australia involved surgery. Of these 1.9 million were elective admissions.[1] With an ageing population,[2] an increasing proportion of patients undergoing surgery are elderly with multiple comorbidities.[3] Risk assessment before surgery aims to minimise potential perioperative complications.

A recent observational study found that perioperative cardiovascular complications (including acute myocardial infarction, acute pulmonary oedema and arrhythmia) occurred in around 2–3% of older patients undergoing non-cardiac surgery.[4] Other common complications include acute renal failure (6%) and infection (2–7%). Patients who suffered at least one complication had a 30-day mortality rate of 14%.[4]

Elective versus non-elective surgery

For emergency non-elective surgery, preoperative risk assessment uncommonly alters the course or outcome of the operation as the urgency of the surgery takes precedence. However, identifying high-risk conditions such as class IV congestive heart failure, unstable coronary syndromes, or severe valvular heart disease can impact upon perioperative and postoperative management.

In determining the risk for elective procedures, there is an interaction between comorbidity and surgical factors. These include the magnitude and type of operation and its duration, and secondary effects of the surgery on the patient's core body temperature, blood loss and fluid shifts.[5]

As a guide for elective surgery, the 30-day estimated cardiac risk can be classified into low, intermediate or high risk based on the type of procedure being performed (see Box).[6, 7]

Best approach towards preoperative risk assessment

A preoperative risk assessment can be performed using a preadmission protocol with a clearly defined set of investigations, or a patient-orientated approach, assessing the indication for each investigation in each patient according to the type of surgery. A preadmission protocol ensures relevant clinical details and investigations are obtained consistently for all patients.

There is no single best approach towards preoperative risk assessment. Pending further research, we believe best practice should incorporate elements of both approaches – protocol-driven documentation of important clinical history and risk factors, coupled with standardised investigations relevant to the type of surgery.

The clinical assessment should cover the following:

- history of syncope, chest pain at rest and on exertion
- history of cardiac, pulmonary, renal disease or malignancy
- risk factors for ischaemic heart disease
- pacemaker or defibrillator (to plan perioperative management of the device).

The examination should exclude the presence of heart failure, cardiac murmurs and pulmonary wheezes. Blood pressure should be recorded, and the patients

should be checked for rapid or slow heart rate. For patients with at least moderate risk because of their preoperative condition or because of the nature of the surgery, investigations should include a 12-lead ECG, full blood count and blood biochemistry analyses and a recent chest X-ray. Additional investigations will be dictated by the clinical assessment. This approach allows an individualised risk assessment and an opportunity to provide medical treatment and cardiac or pulmonary interventions if required. It will also guide specific anaesthetic techniques to optimise the patient's perioperative condition.

Age and comorbidities

It is recommended that all patients over 70 years of age should undergo a full preoperative risk assessment.[4,8] Age alone, however, confers only a modestly increased risk of complications, with greater risks being associated with the urgency of the surgery and significant comorbidities such as cardiac, pulmonary and renal diseases.[4-6,8] Among these, cardiovascular disease (including coronary artery disease, peripheral arterial and cerebrovascular disease, cardiac arrhythmias and valvular heart disease) and its associated risk factors of hypertension and diabetes are the most prevalent in the elderly. It is particularly important that patients with multiple comorbidities, with known cardiac, pulmonary or renal disease, or a history of malignancy, should undergo a full preoperative risk assessment.[9] Patients with comorbidities are likely to be taking multiple medicines. The effect of these drugs on perioperative risks, such as bleeding, needs to be considered.

Clinical status

Assessing the functional capacity of a patient before surgery is a simple but essential part of preoperative cardiac risk assessment.[7,10,11] A highly functional asymptomatic patient will very likely have a favourable outcome irrespective of comorbid status, and is unlikely to need further cardiopulmonary testing. If a patient has poor functional capacity, is unable to walk two flights of stairs comfortably, is symptomatic with exertional dyspnoea, chest discomfort, presyncope or syncope, or has unknown functional capacity, then a detailed preoperative clinical assessment supplemented with appropriate tests is recommended.

From a cardiac perspective, a number of conditions require identification and stabilisation before surgery.[7] These include:

- acute ST-elevation myocardial infarction
- other unstable coronary syndromes (unstable angina pectoris, non-ST-elevation myocardial infarction)
- decompensated congestive cardiac failure (class IV heart failure symptoms and clinical signs of congestive cardiac failure)
- significant arrhythmias (second or third degree heart block, atrial fibrillation or flutter with ventricular response rate more than 100 beats/minute, sustained supraventricular tachycardia, sustained or newly recognised ventricular tachycardia, severe sinus bradycardia – heart rate less than 40 beats/minute) especially with history of pre-syncope or syncope
- valvular heart disease (particularly severe aortic or mitral stenosis).

Patients suspected of having these conditions need further cardiac evaluation or referral as they may need treatment before their elective surgery.

Some patients may have non-correctable life-threatening cardiovascular conditions which preclude surgery. Conditions which carry a significant adverse prognosis include:

- terminal congestive cardiac failure
- severe pulmonary hypertension
- uncontrolled ventricular tachycardia
- severe left main coronary artery stenosis not suitable for revascularisation
- cardiogenic shock.

Patients with these conditions will rarely undergo elective surgery. The decision to proceed or cancel semi-urgent or urgent surgery, such as for a fractured neck of femur, requires a coordinated review and consultation between the admitting doctor and the patient's GP, attending physician, anaesthetist and surgeon.

Box **Estimated cardiac risk with different types of surgery**

Low risk (<1%)	endoscopic procedures, superficial procedures such as localised skin excisions, dental, cataract, breast and gynaecological surgery, minor orthopaedic (knee) or urologic surgeries
Intermediate risk (1–5%)	intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, neurological/major orthopaedic (hip and spine) surgery, prostate surgery, peripheral arterial angioplasty, endovascular aneurysm repair
High risk (>5%)	aortic and major vascular surgery, peripheral vascular surgery

Blood tests

Biochemical tests and full blood count are unlikely to affect the outcome of low-risk surgery, but are considered routine before intermediate and high-risk elective surgery. Common blood tests include full blood count (haemoglobin and platelet count), serum electrolytes, urea and creatinine to assess renal function.

Identifying anaemia is important in the elderly patient undergoing non-cardiac surgery as it predicts poorer 30-day postoperative outcomes.[12] A low platelet count (<50 x 10^9/L) requires haematological evaluation. The need for platelet transfusion before or after surgery should be assessed.

Where possible, electrolyte disturbances should be corrected before surgery. An estimated glomerular filtration rate <60 mL/min is associated with an increased incidence of cardiovascular complications,[13] and necessitates fastidious monitoring of fluid status during the perioperative and postoperative periods.

The need for additional investigations such as fasting glucose, liver function tests, coagulation studies, and group and hold for blood products will depend on the patient's demographic, clinical status, medical history (including medicines) and type of surgery. For example, patients with a known history of chronic hepatic disorders (e.g. hepatitis B or C, history of autoimmune hepatic disorder or excessive alcohol use) will require consultation with their specialist, as well as evaluation of liver function and coagulation. Similar issues are relevant to patients with cardiac, endocrine, haematological, respiratory and renal illnesses.

Chest X-ray

A routine chest X-ray is rarely indicated before most elective surgery. However, it is helpful to exclude significant pulmonary pathology and congestive heart failure in patients with unexplained cough or dyspnoea, or for patients with an increased risk of postoperative pulmonary complications.[14]

ECG

An ECG is recommended in patients with a history of cardiovascular disease, those with cardiac risk factors (hypertension, renal insufficiency and diabetes), and in all patients undergoing intermediate-risk or high-risk surgery.

A resting 12-lead ECG contains important prognostic information. The presence of Q-waves, strain pattern or left bundle branch block have all been associated with decreased life expectancy,[15] and predict perioperative cardiac events.[16] In addition, unrecognised cardiac arrhythmias are sometimes diagnosed at this point,[17] some of which should trigger further cardiac evaluation or referral as they may need treatment before their elective surgery.

Cardiac functional assessment

Resting left ventricular function assessment by echocardiography is not a consistent predictor of perioperative ischaemic events and it is not routinely recommended.[7] It is reasonable to test patients with dyspnoea of unknown origin, in patients with current or previous heart failure and worsening dyspnoea, or in those with suspected significant valvular heart disease. Although the evidence that echocardiography improves outcomes is limited, accurate diagnosis of congestive heart failure and poor left ventricular function, for example, should prompt preoperative stabilisation which would then confer prognostic advantage.

Preoperative non-invasive cardiac stress testing (stress ECG, stress echocardiography or cardiac sestamibi scan) provides an objective assessment of a patient's functional capacity, haemodynamic response and the presence of cardiac ischaemia and arrhythmias. It is an estimation of perioperative cardiac risk. Stress testing is not indicated in patients without risk factors undergoing low-risk non-cardiac elective surgery and is unlikely to be helpful in intermediate risk surgery in patients with no risk factors.[7,10] Patients at risk of cardiovascular disease or with known cardiac conditions are advised to undergo further cardiac evaluation that may include stress testing.

Spirometry and pulmonary function tests

These tests allow objective pulmonary function assessment in patients with chronic obstructive pulmonary disease or asthma, sleep disordered breathing syndromes or neuromuscular disorders.[18] They may help to establish the severity of a patient's pulmonary disorder and allow treatment optimisation before elective surgery. However, clinical data suggest these tests do not consistently predict postoperative pulmonary complications, and so are currently recommended only for patients with suspected chronic lung disease.[14]

Conclusion

The physician should exercise clinical judgement in order to correctly assess perioperative surgical risks and the need for further evaluation. A protocol-driven approach ensures essential clinical details are collected and investigations are targeted. Effective communication with the patient's doctors before an elective operation will avoid unnecessary delay and potentially reduce perioperative complications. <

Conflict of interest: none declared

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The full list of references is published with the online version of this article at www.australianprescriber.com/magazine/37/6/188/91

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Medicines Australia Code of Conduct: breaches

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

The Table shows the complaints where at least one breach was identified, and more details can be found in the full report.[2]

Key words
Medicines Australia, breaches

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Table **Breaches of the Code of Conduct July 2013 – June 2014**

Company	Brand (generic) name	Material or activity	Sanction
AstraZeneca	Brilinta (ticagrelor)	Promotional material	$10 000 fine
Boehringer Ingelheim	Micardis, Twynsta (telmisartan, telmisartan with amlodipine)	Misleading promotional materials	$50 000 fine
Eli Lilly Australia	Axiron (testosterone)	Promotion to the public	$250 000 fine Corrective letter
FIT BioCeuticals	D50K (unregistered drug)	Promotion to the public on a website	$150 000 fine reduced on appeal to $25 000 Changes to website Compliance audit of all promotional activities
Novartis	Lucentis (ranibizumab)	Email to ophthalmologists	$250 000 fine Materials not to be used again Corrective letter
Roche	Actemra (tocilizumab)	Unapproved products and indications	$15 000 fine Materials not to be used again

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ARTICLE

Paediatric urinary incontinence

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Key words
bedwetting, nocturnal enuresis

Aust Prescr 2014;37:192–5

SUMMARY

Urinary incontinence, both in the day and at night, is common in school-aged children and can be very distressing for children and their families.

An accurate history together with a thorough physical examination is essential for assessing and diagnosing urinary incontinence.

Conservative treatment should be offered to all children. If that fails, treatment with anticholinergic drugs could be tried in those with daytime urinary incontinence and overactive bladder.

After addressing any daytime bladder symptoms, treatment with alarm therapy is recommended for children with nocturnal enuresis. Desmopressin is another option.

Introduction

Urinary incontinence in the day and at night is common in school-aged children. Its causes can be multifactorial. Daytime urinary incontinence occurs in about 17–20% of children[1-3] with a further 6.6% of those having problems at night as well.[2] The prevalence of nocturnal enuresis is 8–20% at five years of age, with a spontaneous remission rate of about 15% per year with persistence of enuresis in 0.5–2% of adults.[4-6] Enuresis is more common in boys.

Urinary incontinence can have a significant negative impact on a child's psychosocial well-being and quality of life.[7] Successful treatment can make a big difference. Assessment and management of these children should be based on recommendations of the International Children's Continence Society and the National Institute for Health and Clinical Excellence guidelines for nocturnal enuresis.[8,9]

Definitions

The terminology used to describe urinary incontinence is based on standards recommended by the International Children's Continence Society.[8] Urinary incontinence is defined as involuntary wetting at an inappropriate time and place in a child aged five years or more. Continuous incontinence is usually associated with neurological or anatomical congenital malformations. Intermittent incontinence can occur during the day and at night.

Physiology of bladder function

The two functions of the bladder are to store and eliminate urine. With growth and maturity, day- and night-time continence is achieved in most children by about four years of age.[10] However, it is normal for children to still have continence problems at this age.

During the day, voiding occurs when children synchronously contract their detrusor muscle and relax their urinary sphincters and pelvic floor muscles (usually in response to the sensation of bladder fullness). This allows the free flow of urine until the bladder is empty. At night, with adequate bladder storage and urine concentration, children usually sleep through the night without needing to urinate, but have the ability to wake up to void when they sense bladder fullness.

Bladder capacity increases with age in children. The normal expected bladder capacity up to the age of 12 is calculated as (age + 1) x 30 mL (with 400 mL being expected for those older than 12 years).[10] Normal daytime voided volumes are usually 65–150% of expected bladder capacity. These measures are the most useful indicator of bladder function.

Usually children produce less urine at night in response to the circadian variation in the amount of arginine vasopressin released by the pituitary gland.[11] Nocturnal polyuria is overnight urine volumes greater than 130% of expected bladder capacity.

Assessment

An accurate history, including family history, together with a thorough physical examination is essential to evaluate children with urinary incontinence and decide on treatment choices. This includes a detailed history of wetting, toileting patterns including voiding frequency, symptoms of urgency, comorbidities and psychosocial factors.[8]

A bladder diary provides objective documentation of bladder function. Recording night-time urine volumes and incontinence episodes over seven nights is helpful to evaluate enuresis. Night-time urine volumes are estimated by adding the net nappy weight and the first morning voided volume. To evaluate daytime

bladder function, a 48-hour chart can be used to measure frequency and volume of fluid intake and urine output during the day. Urine culture and uroflowmetry with abdominal ultrasound to assess post-void residual urine volumes and kidney anatomy can be helpful in children with daytime urinary symptoms, particularly when treatment has failed. Screening questionnaires for behavioural symptoms can help identify emotional and behavioural disorders which may need to be addressed.[7,8]

Daytime urinary incontinence

Children with daytime urinary incontinence may or may not also wet the bed at night. They often experience other lower urinary tract symptoms such as:

- urgency – the sudden and unexpected need to void
- urge incontinence – an inability to suppress voiding with urgency
- increased or decreased voiding frequency
- hesitancy
- straining
- a weak stream
- holding manoeuvres related to postponement of voiding – squatting or crossing legs.

Overactive bladder is a common disorder of urinary storage and commonly presents with urgency, frequency and urge incontinence.[12] These children have small volume voids during the day. Children with infrequent voiding (less than four voids per day) may have voiding postponement. This may present with urgency and holding postures. Some of these children have behavioural problems.[13,14] Dysfunctional voiding occurs when the child habitually contracts the external urethral sphincter during voiding. It is estimated to occur in 4–30% of children and is commonly associated with recurrent urinary tract infections.[15] Risks for daytime urinary incontinence are listed in the Box.[8,9,16]

Nocturnal enuresis

Nocturnal enuresis without other lower urinary tract symptoms (monosymptomatic nocturnal enuresis) is more common than enuresis with lower urinary tract symptoms (non-monosymptomatic nocturnal enuresis). Enuresis is also classified as primary or secondary. Most children have primary enuresis and have never achieved night continence. Those who have previously been dry for at least six months have secondary enuresis.[8]

Enuresis involves poor sleep arousal in response to the sensation of a full bladder, abnormal bladder function or nocturnal polyuria.[17] Known risk factors are listed in the Box.[8,9,16] Constipation and overactive bladder are commonly associated with non-monosymptomatic nocturnal enuresis. Psychological comorbidities are more commonly associated with secondary enuresis.[18]

Treatment

Conservative therapy (also known as 'urotherapy') is non-surgical, non-pharmacological treatment for lower urinary tract symptoms and should be used in all children with urinary incontinence. It includes:

- education and advice about regular voiding and correct voiding posture
- avoiding holding manoeuvres
- encouraging adequate fluid intake
- managing constipation.

Managing constipation is important as there is a close relationship between bladder and bowel function. In one study, treatment of constipated children with a bowel program resolved daytime incontinence in 89% of cases, enuresis in 63% of cases and urinary tract infections in 100% of cases.[19] Sometimes conservative treatment alone can be effective. When it is inadequate for treating the child's urinary incontinence, other therapies could be tried.

Alarm training

Alarm training is the first-line therapy for nocturnal enuresis and the most effective long-term treatment.[9,20] Enuresis alarms are wetness sensors

Box Factors associated with urinary incontinence in children

Daytime incontinence

- family history[16]
- abnormal bladder function
- vesicoureteral reflux
- uropathy (e.g. posterior urethral valves, epispadias)
- urinary tract infection
- constipation and faecal incontinence
- nocturnal enuresis
- neuropsychiatric or behavioural conditions such as attention deficit hyperactivity disorder, anxiety, depressive and conduct disorders
- intellectual disabilities[8,9]

Nocturnal enuresis

- family history[16]
- constipation
- faecal incontinence
- overactive bladder
- sleep apnoea and upper airway obstruction symptoms
- defective sleep arousal
- psychological factors

which sound and wake the child when wet. They are either placed under the bed sheets ('bell and pad' or bed alarms) or worn in the child's underpants ('body worn' or personal alarms). Alarms work by training the child to hold on during sleep when they do not need to void, or to wake to void with a full bladder.[20] Alarm training usually takes a few weeks to start working. It should be continued until 14 consecutive dry nights are achieved. Stopping earlier may result in relapse. Alarm training should be tried for a maximum of three months and can be used more than once. About two-thirds of children become dry during alarm training and nearly half remain dry after stopping.[20] It is relatively inexpensive and potentially curative, but requires motivation and support as it can be quite difficult.[18]

Desmopressin

Desmopressin is considered a first-line drug therapy for enuresis. It is approved for treating nocturnal enuresis in children six years or older. Desmopressin works in about 70% of children, although less than half will become completely dry.[21] It is a synthetic analogue of the pituitary hormone arginine vasopressin, which is an antidiuretic hormone. It reduces urine production overnight by increasing water reabsorption by the collecting tubules. Oral desmopressin (as a tablet or lyophilisate melt) has a lower risk for water intoxication than the nasal formulation. It is well tolerated and adverse effects such as headaches, abdominal pain and emotional disturbances are uncommon. As desmopressin can increase the risk for water intoxication and hyponatraemia, minimising fluid intake after taking the medication at night is essential. Desmopressin works best if nocturnal polyuria is present and daytime bladder function is normal.[18] It is effective for short-term use when a rapid response is required or when alarm training is not suitable or effective. In therapy-resistant enuresis, it can be used in conjunction with other treatments.[21] However, desmopressin has a high relapse rate, with only 18–38% of children remaining dry after stopping the drug.[22]

Anticholinergic drugs

Anticholinergic drugs have an inhibitory effect on the detrusor muscle. They are thought to increase the capacity and compliance of the bladder and reduce unprovoked bladder contractions.[23,24] Children with overactive bladder, reduced bladder capacity and symptoms of urgency may benefit. Anticholinergics are commonly used for daytime incontinence associated with overactive bladder. Although anticholinergic monotherapy is ineffective for enuresis, it can improve a child's response when combined with other therapies (such as alarm or desmopressin) in treatment-resistant enuresis.[25]

Oxybutynin is the most commonly used anticholinergic. It is approved for use in children aged over five years who have overactive bladder. Adverse effects (such as decreased sweating and facial flushing, dry mouth, constipation, urinary hesitancy and retention and nervous system changes) are common and lead to treatment discontinuation in 10% of children.[26] Newer bladder-specific anticholinergics – such as tolterodine and solifenacin – are increasingly being used in children as they have fewer adverse effects. However, evidence supporting paediatric use is limited. Anticholinergic drugs can cause constipation and incomplete bladder emptying so it is important to monitor for this.

Tricyclic antidepressants

Imipramine can be used to treat enuresis in children aged over six years. It is moderately effective, with about one fifth becoming dry on treatment, but most relapse when treatment is ceased.[27] Most children tolerate tricyclics without experiencing adverse effects, with the main complaints being dry mouth, gastrointestinal symptoms and behavioural changes. However, due to the risk of potentially serious adverse effects (cardiac arrhythmias, hypotension, hepatotoxicity, central nervous system depression and interaction with other drugs) and the danger of overdose, tricyclics require close supervision and should be stored in a secure location. They are used only in therapy-resistant enuresis.

Referral

Referral to specialist services should be considered for children with severe daytime symptoms, recurrent urinary tract infections, physical or neurological problems and psychosocial or other comorbidities requiring further management. Referral should also be considered when treatment is not successful after six months.

Conclusion

Daytime urinary incontinence and nocturnal enuresis are common in children, and are frequently encountered in general practice. This stigmatising condition can have a significant impact on a child and their family, and successful treatment can be life-changing. A thorough history and examination is essential for an accurate diagnosis and for determining the best treatment. <

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. The expected bladder capacity of an eight-year-old child is 270 mL.

4. Desmopressin is most effective for children with daytime incontinence.

Answers on page 219

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Top 10 drugs

These tables show the top 10 subsidised drugs for the year July 2013 – June 2014.

Aust Prescr 2014;37:195

Table 1 **Top 10 drugs by DDD/1000 pop/day** *†

	Constituent drug	PBS/RPBS ‡
1.	atorvastatin	69.31
2.	rosuvastatin	41.87
3.	paracetamol	33.65
4.	perindopril	32.73
5.	irbesartan	28.49
6.	amlodipine	26.73
7.	esomeprazole	24.90
8.	candesartan	23.38
9.	ramipril	22.43
10.	simvastatin	17.94

Table 2 **Top 10 drugs by prescription counts** †

	Drug	PBS/RPBS ‡
1.	atorvastatin	8 659 127
2.	rosuvastatin	7 610 977
3.	esomeprazole	6 967 801
4.	paracetamol	6 299 698
5.	pantoprazole	4 179 926
6.	perindopril	3 951 282
7.	metformin hydrochloride	3 539 513
8.	salmeterol and fluticasone	3 168 825
9.	irbesartan	3 032 109
10.	simvastatin	2 974 311

Table 3 **Top 10 drugs by cost to government** †

	Drug	Cost to government (A$)	DDD/1000 pop/day * PBS/RPBS ‡	Prescriptions PBS/RPBS ‡
1.	rosuvastatin	284 269 233	41.87	7 610 977
2.	adalimumab	270 237 753	0.50	152 563
3.	atorvastatin	259 067 466	69.31	8 659 127
4.	esomeprazole	204 253 775	24.90	6 967 801
5.	etanercept	153 005 371	0.29	87 283
6.	insulin glargine	131 811 872	6.94	320 806
7.	tiotropium bromide	131 776 620	7.03	1 993 769
8.	fingolimod	113 531 100	0.16	49 576
9.	olanzapine	109 682 018	3.09	993 826
10.	quetiapine	99 773 937	2.62	978 353

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

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

‡ PBS Pharmaceutical Benefits Scheme, RPBS Repatriation Pharmaceutical Benefits Scheme

Source: Department of Health, 10 October 2014. © Commonwealth of Australia.

The cost figures exclude any patient contributions.

ARTICLE

Low testosterone in men

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Key words
androgen, deficiency, hypogonadism

Aust Prescr 2014;37:196–200

SUMMARY

Male hypogonadism is a clinical syndrome of symptoms and signs confirmed by the presence of low testosterone.

Serum testosterone concentrations decline with age. The symptoms of hypogonadism are often mimicked by non-specific effects of other illness and ageing.

Low concentrations of serum testosterone should be confirmed by a reliable assay and laboratory. Some conditions alter sex hormone binding globulin, so calculating free testosterone is sometimes useful.

Treatment should not be based on serum testosterone alone. Primary and particularly secondary causes of hypogonadism should be identified. Reversible conditions and the adverse effects of other therapies should be excluded before prescribing testosterone.

The benefits and harms of testosterone should be discussed, with a defined plan to stop the drug if the response is unsatisfactory.

When indicated, testosterone therapy is relatively safe in the short term at recommended doses, but long-term placebo-controlled studies of efficacy and safety are required. Recent publications suggest increased cardiovascular events in older men treated with testosterone.

Introduction

Hypogonadism in men refers to decreased function of the testes, in either testosterone or sperm production. A deficiency of testosterone may be due to primary gonadal failure, or be secondary to hypothalamo-pituitary disease. Certain symptoms and signs suggest androgen deficiency in men (Box 1). Others are less specific and can be seen with many comorbidities and their therapies, and with ageing.[1]

Men with the classical clinical features of androgen deficiency and a confirmed low serum total testosterone concentration should be considered for testosterone therapy.[1] Prescribing testosterone for non-specific symptoms or the lower testosterone concentrations associated with ageing is poorly validated and may be harmful.[2-5] Over the last decade the steep rise in the amount of testosterone dispensed in Australia[6] and globally[7,8] suggests that testosterone is being used when true hypogonadism is not proven, and indeed misused for non-specific symptoms in older men.[7,8]

Testosterone physiology

Testosterone in plasma is bound to sex hormone binding globulin, and weakly to albumin. Only non-bound or free testosterone, representing 1–3% of the total concentration, is biologically available.

Testosterone production in the testes is stimulated by luteinising hormone. When total testosterone is low, an elevated luteinising hormone concentration is a sensitive indicator of primary Leydig cell failure. Low testosterone with inappropriately low, normal or minimally elevated luteinising hormone may indicate hypothalamo-pituitary disease that demands investigation. However, this pattern may be seen with ageing, illness and certain drugs (Box 2).[9]

There is a diurnal variation in serum testosterone with a morning peak and mid-afternoon nadir. Cross-sectional and longitudinal studies show declining concentrations[10-13] and a loss of the diurnal rhythm with ageing.[12] Sampling should therefore be done between 8 and 10 am. With ageing there is a significant rise in concentrations of sex hormone binding globulin and this causes a decline in free testosterone.

Measuring testosterone across populations of men produces a range of results depending on the population selected, sampling times, sample storage and assay methods.[10,12-14] The definition of 'normality' is held to be the serum testosterone range found in healthy 20–40-year-old men. Deficiency is a value lower than the 2.5 percentile in morning samples. One could argue that the decline in testosterone concentrations beyond the age of 60 years in healthy populations should lead to the development of age-specific reference ranges.

Assessment

Following a careful history including checking for specific symptoms of androgen deficiency, assess the patient's body hair distribution, testicular size, body habitus, breast size and ask if there is a history of low trauma fracture. If the history and examination suggest androgen deficiency (Box 1)[1] then consider measuring serum total testosterone. Samples are taken on two separate mornings (Fig.).[1]

Serum luteinising hormone and follicle stimulating hormone should be measured in one of the low total testosterone samples to discriminate primary from secondary gonadal failure. Seminal fluid examination will be required if fertility is a problem. A karyotype is indicated to exclude Klinefelter syndrome (47 XXY) if the testes are less than 5 mL in volume.

Secondary gonadal failure should be further evaluated by exclusion of reversible comorbidities including nutritional deficiency, obesity, severe sleep apnoea, diabetes mellitus, and certain drugs (Box 2).[9] Hypothalamo-pituitary disease can be evaluated by careful assessment for possible diabetes insipidus, intracranial mass effect and visual field assessment. If indicated, measure serum prolactin and other pituitary hormones and consider pituitary magnetic resonance imaging.

Certain syndromes causing 'idiopathic' hypogonadotrophic hypogonadism may be suggested by dysmorphic features. Examples are extreme obesity in Prader-Willi syndrome, polydactyly, renal anomalies and anosmia in Kallmann syndrome, and short stature in certain gene deletion syndromes.

Laboratory assays

While the gold standard for measurement of serum total testosterone is gas or liquid chromatography and mass spectrometry, these techniques are labour intensive and expensive. The need for a high volume output and lower costs has resulted in laboratories using automated immunoassays which have variable sensitivity, accuracy and reproducibility.[14,15] There is less accuracy and greater variability for results in the hypogonadal range, with some significant discrepancies. Reference standards and manufacturers' reference ranges are not always well defined.

Given these caveats, defining a reference range, particularly the lower limit of normal, is fraught with difficulty. American consensus statements say above 11.1 nmol/L is normal, below 6.9 nmol/L is diagnostic of hypogonadism, and 6.9–11.1 nmol/L is equivocal.[14] In Europe those figures are respectively 12, 8 and 8–12 nmol/L.[15]

Box 1 Symptoms and signs suggestive of androgen deficiency in men

More specific

- decreased spontaneous erections
- gynaecomastia
- hot flushes
- incomplete sexual development
- loss of body hair, reduced shaving
- low sperm count
- osteoporosis or fragility fracture
- reduced libido and sexual activity
- small (<5 mL) or shrinking testes

Less specific

- decreased energy and motivation
- dysthymia, depression
- increased body mass index and body fat
- normochromic anaemia
- poor concentration, lethargy
- reduced muscle bulk and strength
- reduced physical or mental performance
- sleep disturbance

Adapted from reference 1

Box 2 Drugs associated with low testosterone

Potent analgesics especially opioids

Systemic glucocorticoids

Gonadal steroids

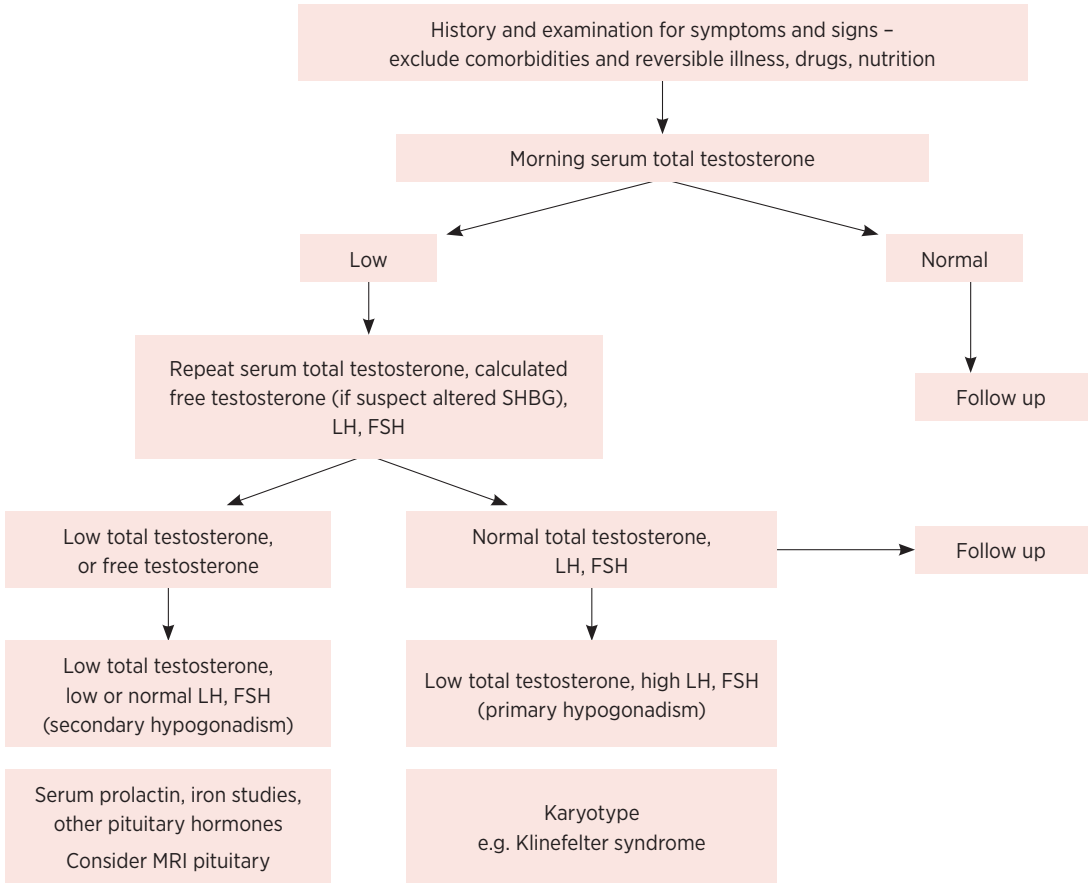
- anabolics
- oestrogenic compounds

Chemotherapy[9]

Gonadotrophin suppressors

A problem in defining a reference range is that most population studies include men with poorly defined health status. An Australian study, in 21–35-year-old men with clearly defined normal health and fertility, used gas chromatography mass spectrometry to measure total testosterone.[16] It reported a reference range of 9.7–34.3 nmol/L with a mean of 18.2 nmol/L. However, there were significant discrepancies between the seven immunoassays assessed. Lower reference values ranged from 6.1 to 11.5 nmol/L, and upper values ranged from 35.1 to 44.9 nmol/L, highlighting the dilemma of defining a normal range with individual assays.

Fig. **Algorithm for assessing adult men with suspected testosterone deficiency**



SHBG sex hormone binding globulin
FSH follicular stimulating hormone
LH luteinising hormone
MRI magnetic resonance imaging
Adapted from reference 1

Measurement of free testosterone, while attractive, is troubled by the poor reliability of such assays and should be abandoned.[1,14,15,17] Calculated free testosterone which depends on measurement of total testosterone, albumin and sex hormone binding globulin bears a close resemblance to the estimate of free testosterone by equilibrium dialysis, but should still be interpreted with caution.[14,15,17,18] These calculations may be useful where variations in sex hormone binding globulin are suspected (Box 3),[1] particularly when total testosterone is low or the patient is old or obese.

Testosterone therapy

There is no argument about testosterone therapy for male hypogonadism due to established testicular disorders, or pituitary disease.[19]

When serum total testosterone is less than 6.9 nmol/L in repeat samples, there is little doubt that true hypogonadism exists. If the results are in the range 6.9–11.1 nmol/L, therapy might be considered if there are symptoms and signs of androgen deficiency.

In Australia, the Pharmaceutical Benefits Scheme subsidises testosterone (Box 4) 'on authority' for males with established pituitary or testicular disease. For men over 40 years old without such disorders the serum total testosterone must be below 8 nmol/L, or below 15 nmol/L in association with concentrations of serum luteinising hormone more than 1.5 times the upper limit of normal. To qualify for subsidised treatment, the patient must have a low testosterone on at least two occasions.

Therapy aims to restore serum testosterone to the mid–normal range and correct symptoms and signs of androgen deficiency.

The amount of circulating testosterone (and indeed oestradiol by aromatisation) that confers physiological effects on body composition, strength and sexual function in males is uncertain. A dose-finding study found that both testosterone and oestradiol are important, and that doses of at least 5 g of testosterone gel or equivalent are required.[20]

The choice of preparation and goals of therapy should be discussed with the patient before starting therapy. Dosing needs to be mindful of the peaks and troughs of plasma concentrations. With the testosterone enanthate product the peak concentrations are often supra-normal at 7–10 days, sometimes with evident behavioural changes such as increased libido and aggression, with a trough 2–3 weeks after the injection.

Monitoring

Monitor the patient by careful clinical review and measuring serum total testosterone. Initial sampling is reasonably performed after two months of therapy (two months after the third injection if testosterone undecanoate is used) then annually.

When defined pituitary or testicular disease is not present, it is important to assess the clinical and symptomatic benefit of therapy after 3–6 months. Withdraw therapy if there is no benefit.

Benefits of therapy

Testosterone therapy for hypogonadal men may improve muscle bulk and strength, libido, sexual function and mood,[21,22] but the evidence is poor, with lack of large placebo-controlled trials.[1,23] Bone density improves[24,25] but there is no current evidence regarding fracture reduction.[24] There is some evidence of improvement in body composition.[25]

For older men with low testosterone, the influences of the age-related decline in testosterone versus effects of other illness are difficult to define.[1,26-28] After correction of any reversible illness or interfering drug therapy and after weight reduction in the obese, it is reasonable to consider a trial of testosterone therapy on a case-by-case basis if the patient has symptoms of androgen deficiency and low testosterone.

Safety and adverse effects

Testosterone should not be given to men with prostate or breast cancer, a haematocrit more than 50%, severe untreated obstructive sleep apnoea or prostatic symptoms. These conditions may be exacerbated by testosterone, so pre-existing prostatic disease, significant obstructive sleep apnoea, and elevated haematocrit should be excluded. A digital rectal examination should be performed and prostate specific antigen measured. In men above age 40 years a prostate specific antigen more than 6 microgram/L should be followed by closer clinical monitoring of the prostate and repeat measurements of prostate specific antigen during therapy.[1,29] In young males with secondary hypogonadism who need fertility, testosterone therapy will suppress spermatogenesis. Gonadotrophin therapy would be the temporary alternative.

Meta-analyses of placebo-controlled trials suggest that testosterone therapy in physiological doses is significantly associated with increased haematocrit, reduced high-density lipoprotein cholesterol and prostatic symptoms.[29,30] If prostate cancer has been excluded, there appears to be no increased risk of induction by testosterone therapy. There is inconsistent evidence regarding the risk of cardiovascular events.[29-31] A recent meta-analysis suggested increased cardiovascular risk and reported publication biases.[32] Long-term safety data are lacking, but recent

Box 3 Variations in sex hormone binding globulin

Causes of increased sex hormone binding globulin

- ageing
- anticonvulsant therapy
- hepatitis and hepatic cirrhosis
- HIV disease
- hyperthyroidism
- oestrogen therapy

Causes of decreased sex hormone binding globulin

- acromegaly
- diabetes mellitus
- glucocorticoids, progestins, androgens
- hypothyroidism
- nephrotic syndrome
- obesity

Adapted from reference 1

Box 4 Testosterone preparations currently subsidised in Australia (2014)

Topical

- testosterone 1% gel 50 mg per 5 g sachet
- testosterone patch either 2.5 mg or 5 mg release in 24 hours
- testosterone 2% axillary dermal spray 30 mg per actuation

Injectable

- testosterone pellets 100 or 200 mg each for deep subcutaneous insertion usually 600–800 mg approximately 6 monthly
- testosterone enanthate 250 mg intramuscular injection every 2–3 weeks
- testosterone undecanoate 1000 mg intramuscular injection every 3 months after initial loading

Oral

- testosterone undecanoate capsule 40 mg (this is a poorly bioavailable androgen and only really suitable for inducing puberty in boys)

Caution is required with some topical preparations to avoid transfer to sexual partners

Other testosterone preparations are available including dermal creams and buccal tablets, but these are not well standardised for absorption and safety

www.pbs.gov.au

reports more strongly suggest an increased risk of cardiovascular events in older men.[3,4] This has prompted the Endocrine Society to issue a warning statement.[5] The results and safety of long-term prospective controlled trials of testosterone therapy are awaited.

Conclusion and recommendations

If a man has symptomatic hypogonadism and proven testosterone deficiency the cause needs to be explored, especially if there is secondary hypogonadism. Serum testosterone is reduced by comorbidities and treatments, which need to be corrected as far as possible before testosterone therapy is considered. Testosterone should not be prescribed for non-specific symptoms.

While a confirmed serum total testosterone less than 8 nmol/L reliably suggests androgen deficiency, values in the range 8–12 nmol/L create uncertainty because of variability in testosterone assays. There is need for standardisation and quality control in testosterone assays.

Short-term studies show benefit with testosterone therapy for androgen deficiency. There are improvements in lean body mass, bone mineral density and strength. Adverse events are erythrocytosis, reduced high-density lipoprotein cholesterol, and some increase in prostatic symptoms. Recent data show a risk of cardiovascular events in men with or at risk of vascular disease. Long-term studies of efficacy and safety are required. <

Conflict of interest: none declared

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Medicines Safety Update

Australian Government
Department of Health
Therapeutic Goods Administration

Volume 5, Number 6, December 2014

In this issue

Epoetin alfa (Eprex) and increased risk of pure red cell aplasia with subcutaneous administration

The Product Information for epoetin alfa has been updated to provide further information regarding an increased risk of pure red cell aplasia with subcutaneous administration, particularly in patients who have chronic renal disease.

Epoetin alfa (marketed in Australia under the brand name Eprex) is a recombinant product that stimulates erythropoiesis and reduces the need for blood transfusions. Among its indications is the treatment of patients with symptomatic or transfusion-requiring anaemia associated with chronic renal failure.

It has been identified that there is an increased risk of pure red cell aplasia with subcutaneous use of epoetin alfa, particularly in patients with chronic renal disease.

The Product Information (PI) had previously stated that pure red cell aplasia was identified post-market as a potential rare adverse event, which could occur after months to years of treatment. However, there was no mention of an association between the development of pure red cell aplasia and either chronic renal disease or the route of administration.

The PI has been updated to advise health professionals that most cases of pure red cell aplasia associated with epoetin alfa occurred in patients with chronic renal failure receiving subcutaneous administration. The subcutaneous route should only be used when intravenous access is not readily available.

Adverse events

From January 2001 to 20 August 2014, the TGA has received 41 reports of pure red cell aplasia associated with epoetin alfa, including 34 cases where it was the sole suspected drug. Of those cases, three resulted in death.

Reports received did not contain sufficient detail to identify how many of those cases involved subcutaneous administration in chronic renal disease patients.

Information for health professionals

When administering epoetin alfa to patients with chronic renal disease, the intravenous route is preferable.

Where intravenous access is not readily available, epoetin alfa can still be administered subcutaneously, but you should be mindful of the increased risk of pure red cell aplasia in these situations.

If pure red cell aplasia is diagnosed, epoetin alfa must be immediately discontinued and testing for erythropoietin antibodies should be considered. If erythropoietin antibodies are detected, patients should not be switched to another erythropoiesis-stimulating agent.

Please report any suspected adverse event associated with epoetin alfa, particularly cases of suspected pure red cell aplasia, to the TGA.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Pregabalin and suicidality

Health professionals are reminded of the risk of suicidality associated with the use of pregabalin for any indication, including off-label use.

Pregabalin is an analogue of the neurotransmitter, gamma-aminobutyric acid. It is indicated for the treatment of neuropathic pain in adults and as adjunctive therapy in adults with partial seizures, with or without secondary generalisation.

The Product Information (PI) for pregabalin includes a precaution that antiepileptic drugs, including this drug, increase the risk of suicidal thoughts or behaviour.

This increased risk applies to patients taking these drugs for any indication, including off-label uses.

Clinical trials

Clinical trial data documented in the PI for pregabalin identify an increased risk of suicidal thoughts or behaviour with antiepileptic drugs as early as one week after starting treatment.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjuvant therapy) of 11 different antiepileptic drugs showed that patients randomised to one of these drugs had approximately twice the risk (adjusted relative risk 1.8; 95% confidence interval 1.2–2.7) of suicidal thoughts or behaviour, compared with patients randomised to placebo treatment.

In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27 863 antiepileptic drug-treated patients was 0.43% compared with 0.24% among 16 029 placebo-treated patients. This represented an increase of approximately one case for every 530 patients treated.

It should be noted that epilepsy and some other illnesses for which pregabalin may be prescribed are themselves associated with an increased risk of suicidal thoughts or behaviour.

Adverse events

From April 2005 to 20 August 2014, the TGA has received two reports of suicide in which pregabalin was being taken and was the sole suspected drug. In the same time period, there were also two cases of attempted suicide, seven cases of suicidal behaviour, and 57 cases of suicidal thoughts reported to the TGA. In all but one case of attempted suicide and three cases of suicidal thoughts, pregabalin was the sole suspected drug.

Information for health professionals

Patients being treated with pregabalin, including those prescribed it off-label, should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviours and/or any unusual changes in mood or behaviour.

Advise patients and caregivers of the risk of suicidality and educate them regarding the associated symptoms and the need to contact you if they experience any.

If symptoms of suicidal thoughts or behaviour are identified, consider whether they are related to treatment with pregabalin or could be related to the illness being treated. The risks of treatment with pregabalin should be weighed against the risks of the untreated illness.

Online reporting form for consumers

Health professionals are encouraged to advise consumers of a new web-based service that makes it easier for them to report adverse events involving medicines and vaccines.

While consumers are still able to report adverse events to their health professional, who can then report on their behalf, the online form is designed to help improve the number and quality of reports the TGA receives directly from consumers.

Each year the TGA receives more than 17 000 reports of suspected adverse events involving medicines and vaccines. In 2013, about 3% of these reports came directly from consumers, compared with 55% coming via sponsors, 17% from state and territory health departments (predominantly vaccines), 10% from hospitals and hospital pharmacists, and the remainder from community pharmacists and general practitioners.

The form can be accessed at www.tga.gov.au. Click on ‘Report a problem’ and follow the links.

MEDICINES SAFETY UPDATE

Topiramate and visual field defects

The sponsor of topiramate, in consultation with the TGA, has issued a Dear Healthcare Professional letter advising that a precaution for visual field defects has been added to the Product Information.

Topiramate is a sulfamate substituted monosaccharide. It is indicated in adults and children aged two years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome.

Topiramate is also indicated for the prophylaxis of migraine headache in adults.

New information

A precaution regarding visual field defects has been added to the Product Information (PI) for topiramate.

Visual field defects have been reported in patients being treated with topiramate independent of elevated intraocular pressure.

In clinical trials, most of these adverse events were reversible after topiramate was discontinued. However, some cases were not.

In a large proportion of postmarket reports, reversibility was unknown. In cases where an outcome was reported, most were reversible.

The TGA recommends that you advise patients and caregivers of this issue and educate them regarding the signs and symptoms of visual field defects. Instruct them to seek immediate medical attention if any problems are suspected.

If a patient receiving topiramate experiences visual problems, consider discontinuing treatment with this drug.

What to report? You don't need to be certain, just suspicious!

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

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

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

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

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ARTICLE

Pharmacovigilance in palliative care

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Key words
adverse effects, opioids

Aust Prescr 2014;37:204–9

CPD FOR PHARMACISTS

This article has a continuing professional development activity for pharmacists available at www.australianprescriber.com/continuing-professional-development

SUMMARY

Patients receiving palliative care are at high risk of adverse effects from drugs. As these effects can be difficult to distinguish from the symptoms of the terminal illness, harm from medicines is often not recognised.

Adverse effects can contribute to the burden of symptoms, at a time when good control of symptoms is paramount. Adding another drug to treat the adverse effects can compound the problem.

Patients should be asked about their symptoms as they may not volunteer the information or recognise the link with their medicines. Reviewing their treatment may prompt a change in dose, drug or lead to some treatments being stopped.

Introduction

In Australia over 140 000 people die each year including 100 000 whose deaths are expected because of a terminal condition.[1,2] The increasing number of deaths related to organ failure and physical and cognitive frailty mean that many patients now have longer periods between diagnosis and death. A prolonged deteriorating phase will therefore require longer periods of drug therapy to reduce symptoms.

Prescribing medicines to relieve suffering and distress is a cornerstone of palliative care. However, there is limited evidence about the efficacy and safety of many drugs in palliative care. Currently most of this evidence comes from patients with cancer rather than those with other terminal chronic diseases.

Palliative care requires the balancing of many considerations, including a judicious appraisal of the benefits and harms of both pharmacological and non-pharmacological treatments. Pharmacovigilance, the process of monitoring, evaluating and improving the safety of medicines, is essential if palliative care is to maximise the benefits from medicines and minimise the harms. Pharmacovigilance data have not been systematically collected in palliative care.

Balancing harm and benefit

Palliative care is not just about the last days of life. It now includes care for weeks, months, and for some people, years reflecting the different disease trajectories for cancer, organ failure and dementia. The balance between the benefit and harm of drugs will fluctuate depending on whether the patient's condition is stable, unstable, deteriorating or terminal.[3] The patient's needs and choices will also change as the disease progresses.

Little is known about the prevalence of adverse drug events in palliative care. These patients have a high risk of adverse events because they are often elderly with multiple concomitant drug therapies, both for symptom control and for management of the terminal disease and other chronic conditions. They may experience significant weight loss, diminished oral intake, and altered organ function each of which can change a drug's pharmacokinetics and pharmacodynamics. The burden of advancing disease and multiple morbidities often results in progressive increases in the number of drugs prescribed.[4] Many patients will also be using non-prescribed treatments, including over-the-counter and complementary medicines, increasing the risk of interactions.

The adverse effects of drugs may have significant functional consequences for patients and their families. There are also associated burdens for patients, carers and families in managing the cost and complexity of medication regimens.

Balancing benefit and harm becomes increasingly challenging because of the difficulty in differentiating the pathology of the underlying progressive, life-limiting illness from emerging and fluctuating adverse drug effects. Symptoms may easily be misattributed because clinicians, patients and their families know that dying often brings with it a collection of worsening symptoms.

Decision making

Information from the patient, their families and carers about their goals and values is vital for informing decisions about treatment.[5]

Adverse effects may be weighed differently by patients and their families. Patients may have a

strong preference for having an opportunity to gain a sense of completion in their lives, of being able to say goodbye, resolve unfinished business and complete last tasks.[6] While good pain control is essential, in one study physicians considered mental awareness to be much less important than pain control in contrast with patients who strongly valued being mentally aware. This study suggests that patients may be less willing to sacrifice lucidity for analgesia than doctors think.[6]

Treatments should be altered as symptoms change with time, reflecting changes in the patient's condition. The expected benefits may diminish and the likely harms increase so the original therapeutic goals will need to be reset.[7]

Chronic diseases should be managed differently in patients who have little life remaining. The number needed to treat for one patient to benefit will tend to increase as death approaches because of the shortened prognosis, and the number needed to harm will fall as adverse effects become more frequent. The focus of prescribing should be on improving the quality of life while preventing avoidable harms.[4,8] For example, there is little point in continuing a lipid-lowering drug in someone who is dying.

Symptom cascades

Drugs play an important role in relieving common symptoms, but there is a need to be vigilant for the 'symptom cascades' that result from adverse effects.

Some of these symptom cascades are expected, such as constipation in patients starting opioids. Other examples of symptoms resulting from adverse effects are shown in Table 1.[9]

Common symptoms

There can be a tenfold difference between the number of symptoms volunteered by patients and those identified using systematic assessment.[10] A study revealed that 69% of severe symptoms and 79% of distressing symptoms were not volunteered. This makes it difficult to identify symptoms that may be drug-related or exacerbated by drugs. Symptom assessment by nurses or other proxies only modestly correlates with the patient's assessment and can significantly under-represent the patient's actual symptom burden.[11]

Drugs may be either the primary cause, or exacerbate an underlying cause, of many common symptoms. Medicines that are used to treat a particular symptom may also cause that symptom, for example antipsychotics and benzodiazepines can trigger delirium.[9]

Table 1 **Common drug-related symptoms in palliative care** [9]

Symptom	Drugs which may cause, contribute to or exacerbate these symptoms
fatigue	chemotherapy, opioids (chronic), anticonvulsants (carbamazepine, gabapentin)
anxiety	corticosteroids, withdrawal of benzodiazepines, opioids or antidepressants
dry mouth	opioids, anticholinergics, antidepressants, antipsychotics, antihistamines, benzodiazepines, diuretics, anticonvulsants (carbamazepine, pregabalin, gabapentin), proton pump inhibitors
depression	corticosteroids
hiccups	corticosteroids (dexamethasone), benzodiazepines, antipsychotics
delirium	opioids, benzodiazepines, antipsychotics, anticonvulsants, anticholinergics, corticosteroids
insomnia	corticosteroids
constipation	opioids, tricyclic antidepressants, anticholinergics, anticonvulsants (pregabalin), antipsychotics, benzodiazepines, diuretics, iron, calcium channel blockers (verapamil, diltiazem), antacids containing calcium and aluminium, calcium supplements, $5HT_3$ receptor antagonists (ondansetron, granisetron, dolasetron)
drowsiness	opioids, antipsychotics, anticonvulsants, anticholinergics, benzodiazepines
restlessness	metoclopramide, antipsychotics, opioids
diarrhoea	laxatives, cholinesterase inhibitors, antibiotics, chemotherapy
sweating	antidepressants, cholinesterase inhibitors, opioids, sialogogues (pilocarpine), tramadol
nausea	opioids, anticonvulsants, antibiotics, antidepressants, antipsychotics, corticosteroids, non-steroidal anti-inflammatory drugs, tramadol, chemotherapy
vomiting	opioids, chemotherapy, anticonvulsants (carbamazepine, sodium valproate, phenytoin), antibiotics, antifungals

Drug-induced symptoms are usually a diagnosis of exclusion of other causes, but this is not always possible in palliative care. Some symptoms are also discontinuation effects when a drug is not taken, such as when agitation results from missed antidepressant doses.

Delirium

Delirium is a common neuropsychiatric complication in palliative care. It can result from a combination of predisposing baseline risk factors and superimposed precipitating factors.[12] The prevalence is 26–62% for palliative care inpatients and up to 88% in the last days and hours of life.[12]

Many drugs used for symptom control in palliative care (for example, benzodiazepines, corticosteroids, anticholinergics, opioids, antipsychotics) can exacerbate or cause neuropsychiatric adverse effects, including delirium. Opioids can cause delirium, but so can uncontrolled pain.

There are many similarities between the clinical presentation observed in terminal restlessness and delirium. This has led to the suggestion that terminal restlessness may actually be a potentially reversible acute delirium.[13] A study of the occurrence, precipitating factors, and reversibility of delirium in patients with advanced cancer found that it was reversible in 49% of episodes.[14]

Management options

An individualised approach is required which takes account of the level of investigation needed to identify reversible causes and the intensity of the therapeutic intervention to control delirium.

Initial management includes the identification of reversible causes. Many cases can be reversed if the delirium was precipitated by drugs, electrolyte abnormalities (which may also be drug induced) or infection.[12] Non-drug strategies such as maintaining calm and quiet surroundings may be appropriate in some circumstances. Antipsychotics, specifically haloperidol, are widely used although there is limited evidence in palliative care. Benzodiazepines lack evidence to support their use for delirium in palliative care. Importantly, both antipsychotics and benzodiazepines can also cause delirium.

Constipation

Altered bowel habit is very common during palliative care. There are likely to be numerous concurrent risk factors, but opioids are often responsible. The relative contribution of different factors will change over time and it is often difficult to attribute constipation to opioids alone. For example, the catabolic state of cachexia, decreasing mobility and oral intake, and drugs with anticholinergic adverse effects are all likely to contribute.[15] Opioids and other drugs may simply 'tip the balance'.

Observational studies report that up to 60% of patients admitted to palliative care units are already receiving laxatives with the majority taking more than one type of laxative.[16] However, constipation is still often underdiagnosed and undertreated in palliative care.[17]

The consequences of constipation (see Box)[18] can contribute significantly to the patient's symptom burden. This may result in prescribing cascades to treat the complications, with further potential for drug-related adverse effects. This includes the potential for harm from laxatives, such as the salt and water retention associated with some macrogol formulations which have a high sodium content, or pain associated with stimulant laxatives in people who have hard or impacted stools. Bowel perforation is a rare but important severe adverse effect.

Management options

In addition to addressing and modifying reversible causes of constipation, including drugs, laxatives are usually required. Current clinical guidelines such as Therapeutic Guidelines: Palliative Care[19] recommends that, if it is safe to do so, the initial prescription should be an oral stool softener and a stimulant laxative. Rectal interventions may also be necessary when impaction has occurred, particularly if myopathy or neuropathy is contributing to the problem. After excluding bowel obstruction, methylnaltrexone can be tried in opioid-induced constipation which has failed to respond to laxatives.

Box Potential consequences of drug-induced constipation

Gastrointestinal

Impaction, obstruction, megacolon, faecal incontinence, rectal prolapse, haemorrhoids, bloating, anorexia and vomiting

Cardiac and vascular

Arrhythmias, vasovagal episodes, angina

Urological

Retention, incontinence, urinary infection

Other

Delirium, anxiety, analgesic failure (opioid dose-limiting constipation), worsening pain, impaired quality of life

Adapted from reference 18

Urinary symptoms

Many medicines can contribute to urinary symptoms (see Table 2).[20–22] Anticholinergic effects contribute to and worsen urinary symptoms particularly urinary retention and overflow incontinence. Complementary medicines can also cause problems. For example, St John's wort has been associated with voiding difficulty, and guarana or large amounts of caffeine can increase diuresis, aggravate detrusor instability and worsen urge incontinence.

Many patients experience urinary symptoms, but often do not disclose them. If they are not asked directly, urinary incontinence may go unrecognised by clinicians. The causes are likely to be multifactorial and fluctuate so the contribution to symptom burden will vary. Urinary incontinence and faecal incontinence can sometimes be the 'last straw' for managing a person at home.

Urinary incontinence can impair participation in daily activities, physical functioning, psychological well-being, and overall quality of life. Patients with urge incontinence are almost twice as likely to fall than other patients.[23] Incontinence can also put patients at increased risk of skin and urinary tract infections. Drug-related urinary retention is potentially reversible. Agitation and restlessness may be the result of a full

Table 2 **Drugs that can cause or exacerbate urinary incontinence** [20–22]

Drug	Effect	Type of incontinence caused
ACE inhibitors	cough	stress
Diuretics	diuresis (polyuria)	urge
Verapamil	impaired emptying (retention), voiding difficulty, constipation, dependent oedema (nocturnal polyuria)	overflow, urge
Alpha adrenergic agonists (pseudoephedrine)	increase urethral and prostate capsule smooth muscle tone (obstruction and retention)	overflow
Alpha adrenergic antagonists (prazosin, tamsulosin, terazosin)	sphincter relaxation	stress
Anticholinergics (oxybutynin, solifenacin, tolterodine) Some antihistamines, tiotropium	reduce detrusor activity (retention), bladder outlet obstruction, constipation, sedation, dry mouth (polydipsia), blurred vision, confusion, delirium	overflow, functional, urge
Antidepressants		
selective serotonin reuptake inhibitors	increase detrusor activity, sedation	urge, functional
tricyclic antidepressants	anticholinergic effect, sedation, confusion	overflow, functional
Antipsychotics	anticholinergic effect, sedation, confusion, impaired mobility, parkinsonism, constipation	overflow, functional, stress
Benzodiazepines	sedation, confusion, impaired mobility	functional
Opioids (oxycodone, morphine, fentanyl, codeine, tramadol)	impair voiding reflex (retention), reduce detrusor activity, constipation, sedation, confusion	overflow, functional
Alcohol	diuresis (polyuria), lowers central inhibition	urge, functional
Caffeine	diuresis (polyuria)	urge
Beta agonists	impair emptying (retention)	overflow
Cholinergics (donepezil, galantamine, rivastigmine, bethanecol)	increase detrusor activity	urge
Gabapentin	dependent oedema (nocturnal polyuria)	urge
Rosiglitazone, pioglitazone	dependent oedema (nocturnal polyuria)	urge
Lithium	polydipsia (polyuria)	urge
Non-steroidal anti-inflammatory drugs	dependent oedema (nocturnal polyuria)	urge

and distended bladder and resolution of the problem can bring much relief.

Management options

Management of incontinence and urinary retention includes assessment of underlying causes. It may not be possible to change or alter effective drugs, for example analgesics, but careful review may identify drugs which are exacerbating incontinence and contributing to symptom burden. Some can be stopped or have their adverse effects managed, for example improved management of constipation may relieve urinary retention. A trial of simple catheterisation, repeated if necessary or leading to a permanent indwelling catheter, may be appropriate depending on the underlying aetiology of the urinary symptoms.[19]

Dry mouth

A dry mouth may be caused by underlying disease, surgery, radiotherapy, fluid restriction and many drugs. It is a common symptom, but patients do not often complain about it. A study of 200 patients revealed that dry mouth was only volunteered by 1.5% of them, however when systematically assessed 65.5% had the symptom.[10] It can result in a very painful, sore mouth which impacts on the ability to eat, drink, take medicines or talk.

A hospice study found that dry mouth can contribute to the risk of falls as patients may struggle to get water to quench their thirst, particularly marginally ambulant patients who feel uneasy about asking for help or losing independence.[24]

Commonly used medicines for symptoms such as pain, nausea, agitation, delirium and confusion may contribute to dry mouth. Many medicines for comorbid conditions also contribute to a cumulative anticholinergic burden.[25,26]

Fluid intake for some patients needs to be carefully balanced, for example in heart failure, while for others increasing fluid intake to relieve dry mouth can contribute to increased urinary frequency. Moving more frequently to the toilet may exacerbate painful movements and trigger other symptom cascades for which additional drugs may be prescribed. If movement is not possible, additional toileting can increase the burden on patients and carers.[27]

Management options

Carmellose spray and hypromellose gel for dry mouth and benzydamine for painful mouth are available through the palliative care section of the Pharmaceutical Benefits Scheme.[28] A few treatment options advocated for dry mouth can worsen or exacerbate painful mouths in some people, for example lemon and glycerine mouth swabs. It is important to individualise treatment and monitor outcomes to enable timely changes in management.

Pharmacovigilance and research

There are very few studies of adverse drug events in palliative care.[29] In addition, the impact of adverse effects, such as urinary and faecal incontinence, anorexia, confusion, restlessness and agitation, on patients and their carers has not been well studied.

There is a need to be aware that drugs may contribute to symptom clusters or cascades in palliative care. Identifying an adverse drug event presents an opportunity to effect a 'cure' by lowering the dose, stopping the drug or changing to a less 'toxic' treatment.[30] Stopping treatment is an integral part of good prescribing and should be reflected in conversations with the patients and their carers.

The discipline of palliative care aims to improve its evidence base for clinical prescribing. In Australia randomised controlled trials of drugs in palliative care are being conducted as part of the Palliative Care Clinical Studies Collaborative (PaCCSC).[28,31,32] A need to encourage the reporting of adverse drug events has prompted the development of the PaCCSC Rapid Pharmacovigilance studies, with more than 90 centres in 18 countries now participating.[33] Adverse events should be reported to the Office of Product Review of the Therapeutic Goods Administration.

Conclusion

The increasing use of drugs for chronic disease and symptom management in palliative care increases the risk of adverse effects. There is a need to review the patient's symptoms to see if they are caused or exacerbated by drugs. Unnecessary medicines should be stopped safely and non-pharmacological options should be considered.

As patients often do not volunteer their symptoms, ask about problems which may be adverse effects of treatment. Pharmacovigilance does not end when palliative care begins.

Conflict of interest: none declared

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The full list of references and further reading is published with the online version of this article at www.australianprescriber.com/magazine/37/6/204/9

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Dental note

Managing the adverse effects of drugs used in palliative care

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On behalf of the Dental Therapeutics Committee
Australian Dental Association

Very few patients actually complain of oral dryness (1.5%), yet on questioning, this is the second highest reported symptom of concern (67%) in patients receiving palliative care.[1] A study assessing end-of-life care found that of the 96 patients with an estimated life expectancy under three months, mouth pain was reported by 67%, problems with food intake by 56%, and dry mouth by 78%.[2] What is disappointing is that 78% of these patients said that they had received no information about oral adverse effects of cancer treatment.[2]

In an interview-focused study of 14 palliative care patients, from a mid-sized hospital in regional Australia, it was found that a range of oral problems significantly impacted on their physical, social and psychological well-being to varying degrees, sometimes over extended periods of time.[3] The participants reported a lack of oral assessment and virtually no input from dental experts to assist with palliating oral problems.[3]

These problems are not new. In the 1990s many terminally ill patients were found to have oral problems resulting from therapy and poor oral care during lengthy illnesses. It was suggested that by including a dentist in the palliative care team, the dental needs of dying patients would be likely to be managed more effectively.[4]

Dental assessments may well identify dental disease, to not only reduce the microbial load, but also decrease the risk of oral pain and infection.[5] Including a dentist in the multidisciplinary approach to palliative care may also improve the patient's ability to speak, eat or swallow.[5]

Unfortunately, there is no single panacea for oral palliative care. There have been many suggested strategies, based on the limited clinical trial data available.[6] Simple mouthwashes using bicarbonate[7] may well be as effective as complex, over-the-counter and expensive topical products. These simple mouthwashes will not alleviate pain from dental disease, such as oral candidiasis, periodontal disease, tooth pain or abscesses, however dentists are excellent at dealing with specific physical curative treatment, that often has almost instantaneous results. Examples are the repair of a fractured tooth, the removal of an infected tooth, or the perfection of a smile with dental aesthetics.

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ARTICLE

Population pharmacokinetics: an overview

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Key words
modelling, population pharmacokinetics, variability

Aust Prescr 2014;37:210–3

SUMMARY

The pharmacokinetics of a drug refers to how it is handled by the body. This includes absorption, distribution, metabolism and elimination.

Pharmacokinetic studies have usually been carried out in small numbers of people, often healthy volunteers. In population pharmacokinetics opportunistic samples are collected from actual patients taking a drug.

Population pharmacokinetic studies aim to identify and quantify sources of variability in drug concentration in the patient population. Associations between patient characteristics and differences in pharmacokinetics can then be used to customise pharmacotherapy, such as the safe use of metformin in patients with renal impairment.

As multiple samples from one person are not required, a population approach is useful for investigating patient groups that are difficult to study, such as premature infants.

Population pharmacokinetics is being increasingly used in drug development. It is particularly useful when it is suspected that the pharmacokinetics of the drug will vary between subgroups of the population.

Introduction

The fundamentals of pharmacokinetics are crucial to understanding the biological fate of drugs. They are a cornerstone for good prescribing and drug development.[1]

Pharmacokinetics is concerned with the time-course of drug movement through the body. This involves the absorption, distribution, metabolism and elimination of drugs and their metabolites. These processes are described by mathematical models, which in many instances have been used in other disciplines such as biological chemistry (enzyme kinetics) and nuclear physics (exponential decay).

The study of pharmacokinetics has benefited immensely from advances in computer science and analytical chemistry. Pharmacokinetics can now be studied in populations of patients who are taking a drug. Studying a population enables the analysis of the variability in pharmacokinetics that occurs within and between patients. An example would be the variations in drug concentration which will occur with renal impairment when the patient is taking a drug excreted in the urine.

Origins and development of population pharmacokinetics

It is routine practice to measure the concentration of drugs such as gentamicin. The population pharmacokinetic approach developed from the notion that improved prescribing could be achieved by the analysis of drug concentration-time data, typically produced from routine therapeutic drug monitoring. Population-derived pharmacokinetic parameters such as clearance could then be used to guide prescribing for individual patients.[2] Most importantly, this individualisation of therapy required the identification and quantification of various sources of pharmacokinetic variability such as weight, age, renal function and significant drug interactions.

Traditional pharmacokinetic studies usually involve multiple samples taken at fixed intervals from healthy volunteers. In contrast, population pharmacokinetic data are obtained from patients being treated with a drug. These patients are often taking different doses and have blood samples at different times. This unstructured and unbalanced dosage and blood sampling produces sparse response data (for example 2–4 samples per patient). A review of the various methods used in population pharmacokinetic analyses is provided elsewhere,[3] but the advantages and disadvantages of non-population and population methods are summarised in Boxes 1 and 2.

Models and methods

Pharmacokinetic modelling is a mathematical method for predicting how a drug will be handled by the body. The term population pharmacokinetics almost always refers to 'mixed-effects' modelling. This is a mixture of fixed and random effects.

Fixed (structural model) effects are parameters such as clearance and factors that significantly influence clearance (for example weight, age). Random effects (variance model) parameters include the intersubject variability, and the variability which remains unexplained after fitting the model to the data.

Non-population methods (Box 1)

In traditional pharmacokinetics studies, small numbers of people are intensively sampled over a given post-dose period using a fixed design. This is the so-called 'two-stage' approach. It is still widely used, for example in comparative bioavailability trials[4] and in clinical pharmacokinetics.[5]

In the first stage the values of the pharmacokinetic parameters (for example clearance) in each individual are calculated. The second stage involves estimation of descriptive statistics, usually the mean or geometric mean and standard deviation for each parameter. For example, the mean renal clearance of metformin is 510 +/– 130 mL/minute.

There are deficiencies with traditional studies, including the inability to handle sparse data and to identify which covariates, such as age and weight, are important sources of pharmacokinetic variability. The imprecision in estimating the parameter values is also unidentified when fitting the model to the data. This uncertainty leads to the interindividual variability being overestimated.

Another traditional method is the 'naïve pooled data' approach in which data from all participants are pooled as if they had been collected from one 'super-subject'. However, this approach ignores the sources of variability within and between individuals. It is not recommended even if there are numerous participants and the interindividual pharmacokinetic variability is relatively small.

Population methods (Box 2)

A population pharmacokinetic method deals with modelling in a cohort which has many participants (usually more than 40). The population is studied rather than the individuals in it. Samples can be collected from patients taking different doses over different periods of time (see Fig.).

In population pharmacokinetics one may be interested, for example, in estimating a typical value of drug clearance or oral bioavailability. The typical parameter value is usually the mode (most frequently occurring value). This approaches the population mean value as the number of patients increases. However, the individuality of the information supplied by each patient to the population analysis is not lost, but is used to estimate the most likely value of a parameter for each patient. The reliability of these individual estimates is predicated on the amount of data contributed by each patient and by how much their estimated parameter value varies from the typical population value. In a sense, each patient lends information to the population model, but borrows information back from the population model to obtain an estimate of their own pharmacokinetic parameters.

There is a misconception that population pharmacokinetics is a fallback method for when there are only very sparse data, and that the ultimate aim should be to build models with as many covariates as possible. Neither of these views is valid. First, there is no substitute for data and while a population approach can handle sparse

Box 1 Non-population pharmacokinetics

Advantages

- relatively small numbers of people are required (typically 8–16)
- sampling design is often fixed and therefore similar in all participants, so there is less potential for sampling errors
- pharmacostatistical concepts are familiar and may require only simple calculations

Disadvantages

- often performed in people who are not representative of the patient population
- infrequently performed in children
- multiple blood samples are required (typically >10 samples per person)
- pharmacokinetic variability between individuals is confounded with variability in the estimates of parameters such as clearance
- often cannot screen and quantify effects of covariates, such as weight, on pharmacokinetic response

Box 2 Population pharmacokinetics

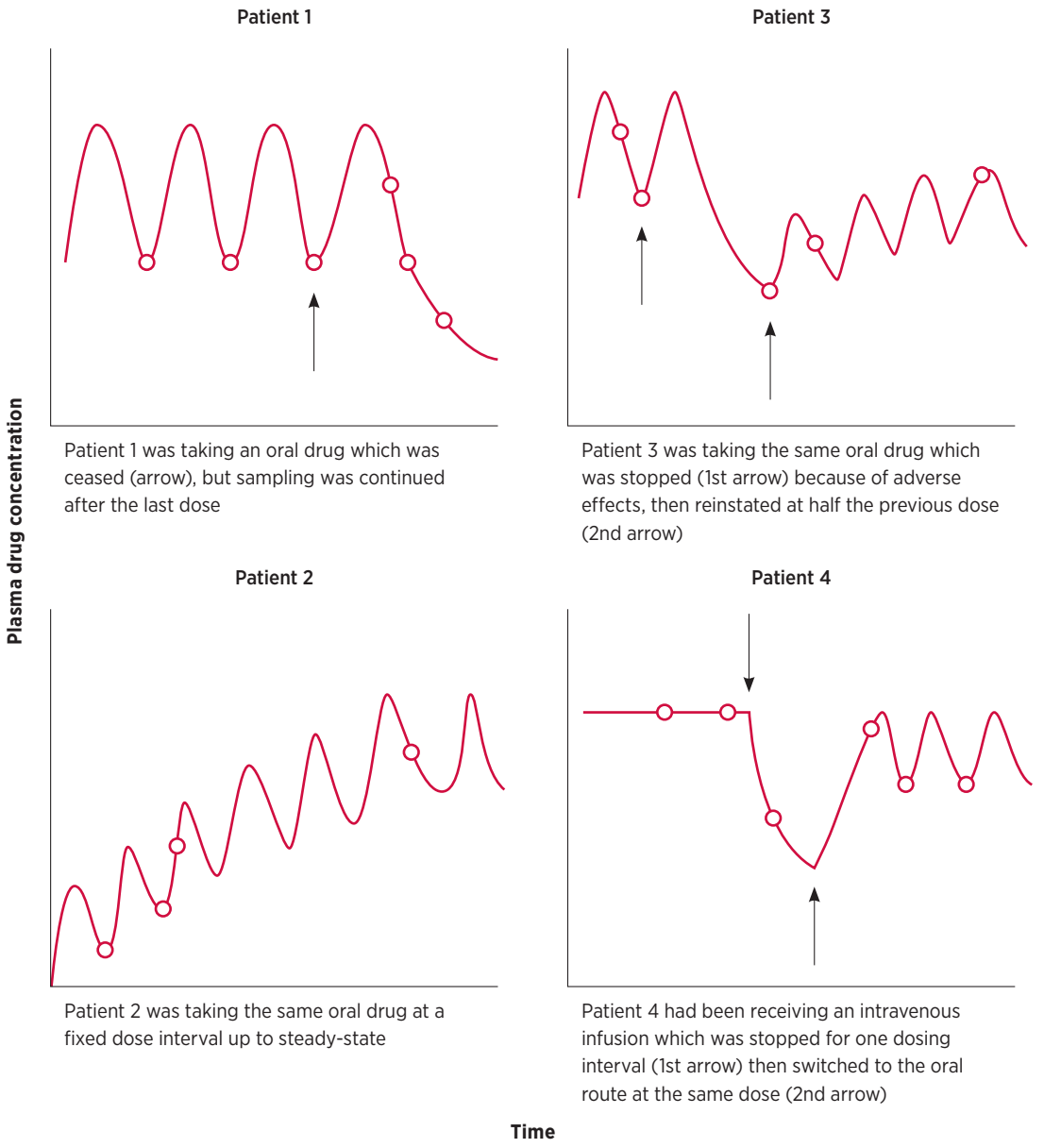
Advantages

- pharmacokinetic analysis is usually conducted in patients taking the drug
- can accommodate flexible study designs which occur during treatment
- only a few samples are needed from each patient
- opportunistic sampling has the potential to be cost-effective
- screening and quantification of covariates for explaining variability
- can distinguish between interindividual and intraindividual variability
- modelling software is widely available (e.g. NONMEM)

Disadvantages

- relatively large numbers of patients are required (typically >40)
- complex pharmacostatistical analyses
- requires collection, compilation and verification of large amounts of data
- model building may be tedious, labour intensive and time-consuming
- model diagnostics are often complex and time-consuming
- difficulties with handling missing data (e.g. all covariates in all patients)

Fig. **Examples of sparse blood sampling**



The figure shows four theoretical drug concentration time plots for different patients taking the same drug. It shows sparse blood sampling typically encountered in a population pharmacokinetic analysis. These profiles frequently involve different dosage regimens and different routes of administration (e.g. oral, intravenous) often with unheralded switching between routes in an unstructured and unbalanced pattern as clinical circumstances dictate.

observational data, there are limitations. For example, there should be more than one data point per patient, otherwise the interindividual variability becomes confounded (unidentified). Second, in the clinical context, it can be argued that a covariate should earn its place in a model only if its inclusion reduces the pharmacokinetic variability enough to warrant a change in prescribing. For example, renal function should be included when modelling the pharmacokinetics of gentamicin. Besides the problem of masking – in which two or more correlated covariates, for example weight and sex, can overlap in explaining a source of variability – complex models are harder to implement clinically and may increase the risk of prescribing errors.

Application of population pharmacokinetic models

Population pharmacokinetic modelling is a complex activity.[6] It is also labour intensive and time consuming.

Like all mathematical models, a population pharmacokinetic model only provides estimates of the true (but unknown) pharmacokinetic parameter values. Fitting a model to the data results in some uncertainty in the true value of the estimated parameter, therefore plasma concentrations predicted by a model also have a degree of uncertainty attached to them. There is an oft-quoted adage that 'all models are wrong, but some are useful'. Population analyses have numerous useful clinical applications, especially in patients who otherwise may be difficult to recruit for a traditional pharmacokinetic study, for example young children or patients in intensive care.

Population pharmacokinetics is a much underused resource in Australia which could potentially improve clinical outcomes by informing individualised prescribing.[7] One example is the use of population pharmacokinetics to develop a dosage nomogram for caffeine in the treatment of infants with apnoea of prematurity.[8]

Another example is safely prescribing metformin for patients with impaired renal function. Using data from patients with various stages of renal dysfunction, a model was developed to identify and quantify the covariates, such as weight, which influence the pharmacokinetics of metformin. It then simulated dosage scenarios that could be used at various levels of renal dysfunction without the plasma concentration of metformin reaching a level which would result in adverse effects.[9] This work is valuable because it provided guidelines for using metformin in patients with renal impairment in whom the drug was previously contraindicated.

Population pharmacokinetic methods are an emerging and important part of drug development including preclinical studies, clinical trials and postmarketing surveillance. There are excellent reviews from the pharmaceutical industry[10] and regulatory perspectives,[11] and web-based guidelines from regulatory agencies.[12,13]

Studies have involved research and clinical applications in a wide variety of patients and conditions including diabetes,[9] clotting disorders,[14] malignancy,[15] serious infection,[16] apnoea of prematurity,[8,17] pregnancy,[18] organ transplantation,[19] self-poisoning[20] and arthritis.[21]

Conclusion

The population pharmacokinetics approach is a powerful pharmacostatistical methodology for studying drug disposition under clinical conditions. It has major advantages over traditional methods of pharmacokinetics modelling, in that it can handle sparse data collected from unstructured and unbalanced dosing and sampling while facilitating a means of screening and quantifying sources of pharmacokinetic variability. Clinically, it has the potential to help the selection of the optimum dose for an individual patient. ◀

Conflict of interest: none declared

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NEW DRUGS

New drugs

Bendamustine

Approved indication: chronic lymphocytic leukaemia, non-Hodgkin lymphoma

Ribomustin (Janssen-Cilag)

vials containing 25 mg and 100 mg powder for injection

Australian Medicines Handbook section 14.1.1

Bendamustine hydrochloride is a cytotoxic anticancer drug. It is an alkylating agent similar to chlorambucil and cyclophosphamide and is thought to interfere with cell replication by cross-linking single- and double-stranded DNA.

Bendamustine has been approved for a number of different indications in Australia:

- chronic lymphocytic leukaemia (first-line)
- in combination with rituximab for previously untreated CD20-positive indolent non-Hodgkin lymphoma and mantle cell lymphoma (in patients ineligible for autologous stem cell transplant)
- relapsed or refractory indolent non-Hodgkin lymphoma.

Chronic lymphocytic leukaemia

An open-label study randomised people, up to 75 years of age, with previously untreated chronic lymphocytic leukaemia to bendamustine or chlorambucil. To be included in the trial, patients needed to have Binet stage B (≥3 affected lymph nodes and hepatomegaly and splenomegaly) or Binet stage C (anaemia, thrombocytopenia or both regardless of the number of lymph nodes affected). After a median of six treatment cycles, progression-free survival was longer with bendamustine than with chlorambucil (see Table).[1] There were more complete responses to bendamustine than to chlorambucil (31% vs 2%). Median overall survival was not reached in the bendamustine group. However, overall survival rates were not significantly different after 84 months (see Table).[2]

Severe haematological toxicities (such as neutropenia, thrombocytopenia and anaemia) were significantly more common with bendamustine than with chlorambucil (40% vs 19%). Serious infections were also more frequent (8% vs 3%).[1]

Table **Efficacy of bendamustine in pivotal trials**

Previously untreated chronic lymphocytic leukaemia [1,2]		
	Bendamustine 100 mg/m² IV on days 1 and 2 of a 4-week cycle	**Chlorambucil orally 0.8 mg/kg on days 1 and 15 of a 4-week cycle**
Overall response[1]	68% (110/162)	31% (48/157)
Median progression-free survival[1]	21.6 months	8.3 months
Overall survival at 84 months[2]	51.3%	42.6%
Previously untreated advanced indolent non-Hodgkin or mantle cell lymphoma [3]		
	Bendamustine plus rituximab every 4 weeks‡	**Cyclophosphamide-containing regimen plus rituximab every 3 weeks§**
Overall response	93% (242/261) (104 complete responses)	91% (231/253) (76 complete responses)
Median progression-free survival	69.5 months	31.2 months
Relapsed or refractory non-Hodgkin lymphoma [4]		
	Bendamustine 120 mg/m² IV on days 1 and 2 of a 3-week cycle (up to 8 cycles)	
Overall response	75% (75/100) (17 complete responses)	
Median progression-free survival	9.3 months	

‡ bendamustine 90 mg/m² IV on days 1 and 2 and rituximab 375 mg/m² on day 1 of a 4-week cycle for up to 6 cycles

§ cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and rituximab 375 mg/m² on day 1 of a 3-week cycle for up to 6 cycles. Prednisolone 100 mg/day given for 5 days of each cycle.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Indolent and mantle cell lymphoma

Bendamustine has also been investigated in patients with advanced indolent lymphoma and elderly patients with mantle cell lymphoma. A non-inferiority, open-label trial randomised participants to bendamustine plus rituximab or a cyclophosphamide/doxorubicin/vincristine/prednisolone combination plus rituximab. After a maximum of six treatment cycles, median progression-free survival was significantly longer with bendamustine than with the comparator (see Table).[3] Overall responses were similar but complete responses were more common with bendamustine. Median overall survival was not reached but the number of deaths was similar in both treatments (43/261 with bendamustine, 45/253 with comparator).[3]

Haematological toxicities were less common with bendamustine and rituximab than with the cyclophosphamide regimen (30% vs 68%), as were infections (37% vs 50%), peripheral neuropathy (7% vs 29%) and stomatitis (6% vs 19%). Conversely erythmatous skin reactions were more frequent in people receiving bendamustine.[3] Bendamustine did not cause hair loss.

Relapsed or refractory indolent lymphoma

Currently there is no standard treatment for patients with relapsed or refractory indolent lymphoma. A single-arm trial enrolled patients who were not responding to rituximab or whose disease had progressed. After a median of six treatment cycles, three-quarters of the patients had responded to bendamustine (see Table).[4] However, response rates were better in patients who had been sensitive to their last treatment compared to those with refractory disease (88% vs 64%), as was progression-free survival (11.8 vs 7.5 months).[4]

In the trial, anaemia, thrombocytopenia and neutropenia were the most common adverse events with bendamustine and occurred in most patients. Of the non-haematological events, nausea (77%), infection (69%), fatigue (64%), diarrhoea (42%), vomiting (40%), fever (36%), constipation (31%), anorexia (24%), headache (21%) and stomatitis (21%) were the most common. The most frequently occurring infections included urinary tract infections, pneumonia and sinusitis. There were five cases of cytomegalovirus infection. Two patients had a secondary malignancy – myelodysplastic syndrome and squamous cell carcinoma. Seven patients died as a result of a serious adverse event – causes included cytomegalovirus pneumonia, pneumonia with diffuse intra-alveolar haemorrhage and thrombocytopenia, pneumonia with sepsis, respiratory failure, chronic obstructive pulmonary disease with neutropenia, and cardiopulmonary arrest.[4]

Precautions

As myelosuppression is so common with bendamustine, blood counts should be monitored at least weekly. Treatment is contraindicated with low blood counts (leukocyte $<3 \times 10^9$/L or platelets $<75 \times 10^9$/L). Patients should be warned about the risk of infections, including respiratory problems, and advised to seek medical attention if symptoms develop. Infections, particularly those involving leukocytopenia, are a contraindication to treatment.

Skin reactions with bendamustine are common and treatment should be stopped if reactions progress. Serum potassium should be closely monitored in patients with cardiac disorders. Supplementation and an ECG are needed if serum potassium falls below 3.5 mmol/L.

Tumour lysis syndrome has been reported with bendamustine, usually within two days of treatment, so monitoring is important. Adequate hydration and close monitoring of serum potassium and uric acid are recommended as prophylactic measures. Allopurinol can be prescribed during the first two weeks but has occasionally been associated with Stevens-Johnson syndrome and toxic necrolysis.

Infusion reactions such as fever, chills and rash can occur with bendamustine, and antihistamines, antipyretics and corticosteroids are recommended. Anaphylaxis, although rare, has been reported and hypersensitivity to bendamustine is a contraindication to treatment. Other contraindications include major surgery in the previous month, yellow fever vaccination and breastfeeding.

Bendamustine is a category D pregnancy drug. There are no data in women but the drug was toxic and teratogenic in animals. Contraception is recommended in women and men being treated. Like other alkylating agents, irreversible infertility may occur in men.

After an intravenous infusion over 30–60 minutes, bendamustine is rapidly cleared by hydrolysis, and conjugation with glutathione. The elimination half-life is around 30 minutes with half the dose recovered in urine and a quarter in faeces. Bendamustine is contraindicated in people with severe hepatic impairment (serum bilirubin 51.3 micromol/L) or those with jaundice.

Hepatic metabolism of bendamustine involves cytochrome P450 (CYP) 1A2 so there is a potential for drug interactions with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine. Based on in vitro data, inhibitors of transporters such as P-glycoprotein may increase exposure to bendamustine.

Conclusion

Bendamustine as monotherapy, or in combination with rituximab, seems to improve disease control in people with slow-growing B cell malignancies. However, it has not so far been found to improve overall survival. Bendamustine causes more adverse effects than chlorambucil but fewer than a cyclophosphamide/doxorubicin/vincristine/prednisolone regimen. Myelosuppression and infections are common and are likely to limit treatment in some patients.

T manufacturer provided the product information

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First published online 24 September 2014

Eribulin

Approved indication: metastatic breast cancer
Halaven (Eisai)
vials containing 1 mg/2 mL solution for injection
Australian Medicines Handbook Appendix A

Eribulin mesilate is a synthetic analogue of halichondrin B, a product derived from a marine sponge. It inhibits the division of proliferating cells. By binding to tubulin, eribulin blocks the formation of microtubules and cells cannot undergo mitosis.

Eribulin is indicated as a monotherapy for women whose breast cancer has progressed despite previous chemotherapy (including an anthracycline and a taxane). After showing some benefit in phase II trials,[1,2] an open-label randomised phase III trial (EMBRACE) compared eribulin to other treatments chosen by the doctor (including vinorelbine, gemcitabine, capecitabine, taxanes, anthracyclines, hormone treatment).[3] The trial enrolled 762 women with heavily pre-treated (median of 4 chemotherapies) locally recurrent or metastatic disease. Treatment was continued until the disease progressed or serious toxicities occurred (median of 3.9 months for eribulin and 2.1 months for the comparators). Median overall survival was longer with eribulin than with the comparator treatments (13.1 vs 10.6 months, p=0.041). However, progression-free survival was not significantly different (3.7 vs 2.2 months, p=0.137), as determined by an independent review.[3]

The most common adverse reactions to eribulin are neutropenia (82% of patients), anaemia (58%), weakness or fatigue (54%), alopecia (45%), peripheral neuropathy (35%), nausea (35%) and constipation (25%). Other common events (≥18% of people) included headache, fever, diarrhoea, vomiting, joint and muscle pain, reduced appetite and weight loss. Abnormal liver function tests were found in 18% of women. Peripheral neuropathy was the most common reason for discontinuing treatment, with 4% of women stopping treatment because of it.

In the phase III trial, grades 3 and 4 neutropenia, leucopenia and peripheral neuropathy were more common with eribulin than with the other treatments. Febrile neutropenia occurred in 5% of women. Five women in the eribulin arm died of treatment-related adverse events which included febrile neutropenia and lung infection.[3]

As haematological toxicities are common, it is important to monitor blood counts before treatment starts and then before each dose as dose delay or reduction may be necessary. The dose should not be increased again after a reduction. Women taking anticoagulants were excluded from the phase III trial.

In a group of 26 patients, eribulin was found to prolong the QTc interval by 11 milliseconds on day 8 of treatment. ECG monitoring is therefore recommended in patients with heart failure, bradycardia (<60 beats/min), electrolyte abnormalities or those taking other drugs that prolong the QT interval.

After intravenous administration, unchanged eribulin is eliminated in the faeces (82%) and urine (9%) with an elimination half-life of about 40 hours. The recommended dose is 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. Lower doses are recommended in people with liver impairment (Child-Pugh A or B) or moderate renal impairment (glomerular filtration rate 30–59 mL/min).

Eribulin was teratogenic in rats and is not recommended in pregnancy. It is also contraindicated in breastfeeding.

This new cytotoxic drug offers another option for women with treatment-refractory breast cancer. Although eribulin appears to extend life by a median of 2.5 months over other chemotherapies, toxicities are likely to limit treatment in some patients.

† manufacturer declined to supply data

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First published online 13 October 2014

Olodaterol

Approved indication: chronic obstructive pulmonary disease

Striverdi Respimat (Boehringer Ingelheim)

inhaler cartridge containing 2.5 microgram per actuation

Australian Medicines Handbook section 19.1.1

If a patient with chronic obstructive pulmonary disease remains symptomatic despite the appropriate use of a short-acting bronchodilator, a long-acting bronchodilator can be added. Eformoterol, indacaterol and salmeterol are already available, so olodaterol adds to the choice of long-acting beta$_2$ agonists for maintenance treatment.

The olodaterol inhaler contains a solution of olodaterol hydrochloride. Two puffs of the inhaler deliver a dose of 5 microgram olodaterol. The peak plasma concentration is reached 10–20 minutes after inhalation. The duration of bronchodilation is at least 24 hours so the recommended dose is 5 microgram once daily. No dose adjustment is needed in patients with moderate liver impairment or severe renal impairment. (There are no data in patients with severe hepatic impairment.) Most of the absorbed dose is metabolised and excreted in the faeces. The terminal half-life following inhalation is around 45 hours.

At the time of writing most of the major clinical trials of olodaterol had not been published. Approximately 2000 people were treated at the recommended dose with trials lasting from 6 to 48 weeks. The patients had moderate to very severe chronic obstructive pulmonary disease and a smoking history of at least 10 pack-years.

Two placebo-controlled trials of olodaterol studied patients for 48 weeks, but used lung function at 12 weeks as the primary end point for efficacy. After 12 weeks the difference in the mean forced expiratory volume in one second, measured before the next dose (trough FEV$_1$), between olodaterol 5 microgram and placebo was 91 mL in one study and 47 mL in the other. After 24 weeks the differences were 86 mL and 69 mL more than placebo and the differences were statistically significant throughout the 48 weeks of the trials. Patients taking olodaterol had a significantly reduced need for 'rescue' bronchodilator treatment.

Two other controlled trials included eformoterol (12 microgram twice daily) as well as placebo. Although they were also 48-week studies, efficacy was assessed after 24 weeks. At that time the patients taking olodaterol had mean trough FEV$_1$ values that were 53 mL and 78 mL more than placebo. The differences between eformoterol and placebo were 42 mL and 54 mL. For most of the 48 weeks, the differences in trough FEV$_1$ between the active drugs and placebo were statistically significant.

The potential adverse effects of olodaterol are similar to those of other inhaled beta$_2$ agonists. These include increased pulse and blood pressure and hypokalaemia. Some patients with cardiovascular disease were excluded from the clinical trials. Adverse events caused 7.2% of the patients to stop olodaterol compared with 8.8% of the placebo group.

While olodaterol only needs to be given once a day it does not have any clear advantage over other long-acting beta$_2$ agonists. It significantly improves trough FEV$_1$, but only by a modest amount. This effect may not be significant if the patient is already being treated with tiotropium. In studies of exercise endurance patients given olodaterol for six weeks could exercise for an extra 42–52 seconds compared to patients given a placebo. Olodaterol has no significant effects on exacerbations of chronic obstructive pulmonary disease. Although a bronchodilator effect can be detected five minutes after an inhalation of olodaterol, it is not approved for treating acute bronchospasm or asthma.

T T T manufacturer provided clinical evaluation

REFERENCES *A

(none)

First published online 24 September 2014

Trametinib

Approved indication: melanoma

Mekinist (GlaxoSmithKline)

0.5 mg and 2 mg tablets

Australian Medicines Handbook section 14.2.4

In 40–60% of melanomas there is a genetic mutation which results in an abnormal serine-threonine protein kinase (BRAF). This kinase is involved in

the activation of mitogen-activated extracellular signal regulated kinases (MEK1 and 2) which are part of a pathway which regulates cell proliferation. Trametinib is a kinase inhibitor which reversibly blocks MEK1 and MEK2 in melanoma cells with the BRAF mutation. It therefore acts at a different point in the pathway from the BRAF inhibitors – vemurafenib (Aust Prescr 2012;35:128-35) and dabrafenib (Aust Prescr 2014;37:32-5).

A phase II trial studied trametinib in patients with metastatic melanoma. There were 40 patients who had previously been treated with a BRAF inhibitor (cohort A) and 57 who had received chemotherapy or immunotherapy (cohort B). Cohort A took 2 mg trametinib daily for a median of 56 days while cohort B took the drug for a median of 120 days. None of the patients in cohort A had a clinical response, but 25% of cohort B responded to treatment. The median progression-free survival was 1.8 months in cohort A and 4 months in cohort B.[1]

An open-label phase III trial compared trametinib against chemotherapy with dacarbazine or paclitaxel. The 326 patients in the trial had metastatic or stage IIIc melanomas containing BRAF mutations. Only 11 patients had a history of brain metastases and they were excluded from the primary efficacy analysis. There was a response to treatment in 47 of the 214 (22%) patients given trametinib and 9 of the 108 (8%) of those given chemotherapy. Progression-free survival was 4.8 months with trametinib and 1.5 months with chemotherapy. By the end of the study 16% of the trametinib group and 27% of the chemotherapy group had died (see Table).[2]

The results for cohort A in the phase II trial suggested that patients who have been previously treated with a BRAF inhibitor develop a resistance to treatment with trametinib.[1] This led to another study which combined trametinib and dabrafenib for metastatic melanoma. After the pharmacokinetics of the combination had been assessed, 162 patients were randomised to take dabrafenib 150 mg twice daily as monotherapy, or in combination with trametinib 1 mg or 2 mg. After a median follow-up of 14.1 months, monotherapy had produced a response in 54% of patients while 50% of the trametinib 1 mg group and 76% of the trametinib 2 mg group responded. Progression-free survival was a median of 5.8 months with monotherapy, 9.2 months with the 1 mg combination and 9.4 months with the 2 mg combination. After one year 41% of the patients taking the 2 mg combination were alive and free of progression compared to just 9% of the monotherapy group.[3]

Adverse reactions to trametinib are common and may require the dose to be reduced or stopped. In the comparative study with chemotherapy 27% of patients had to reduce the dose of trametinib and 35% had to interrupt their treatment.[2] Adverse effects which require dose interruptions include rashes, reduced left ventricular function and retinal pigment epithelial detachment. Interstitial lung disease, congestive heart failure and retinal vein occlusion are indications for stopping trametinib. The most common adverse effects, which are more frequent with trametinib than with chemotherapy, are rashes (57% of patients), diarrhoea (43%) and peripheral oedema (26%).[2]

Patients taking trametinib in combination with dabrafenib will experience adverse effects from both drugs. Among the patients who took trametinib 2 mg with dabrafenib, common adverse events were fever (71%), chills (58%), fatigue (53%), nausea (44%) and vomiting (40%). Squamous cell carcinoma developed in 7% of these patients, but this was less than the 19% of patients affected by dabrafenib monotherapy.[3] The combination increases the risk of bleeding and fatal haemorrhages have occurred.

Trametinib is embryotoxic. If a woman of childbearing age is treated with this drug, pregnancy must be avoided.

Although trametinib is mainly metabolised there have been no studies of patients with moderate or severe hepatic impairment. As less than 20% of the dose is excreted in the urine, mild or moderate renal impairment is unlikely to affect the pharmacokinetics of trametinib. There are no studies in severe renal impairment. As the absorption of trametinib is reduced by food, it should not be taken with meals.

Table **Comparison of trametinib and chemotherapy for BRAF-mutated advanced melanoma** [2]

	Trametinib	Chemotherapy
Patients	214	108
Response rate	22%	8%
Progression-free survival	4.8 months	1.5 months
Overall survival rate at 6 months	81%	67%

The overall five-year survival of patients with metastatic melanoma is 7–19%. While trametinib can increase progression-free survival, its effects on long-term survival are currently uncertain. The six-month overall survival rate was 81% with trametinib and 67% with chemotherapy.[2] Trametinib monotherapy is not effective if the melanoma has progressed despite treatment with a BRAF inhibitor.

[X] manufacturer did not supply data

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First published online 24 September 2014

The Transparency score ([T]) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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.ema.europa.eu)

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

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Funded by the Australian Government Department of Health.